MEDICINAL PLANTS FOR LONGEVITY

Evidence-based Approach for Geriatric Care in Unani Medicine

CENTRAL COUNCIL FOR RESEARCH IN UNANI MEDICINE

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Ministry of AYUSH, Government of India

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Preface

The world is experiencing the later stages of a long-standing demographic transition from a predominant high mortality/high fertility pattern to a low mortality/low fertility pattern. The global increase in life expectancy and sharp decline in fertility rates underlie the current, rapid age-specific population growth. The social and economic impacts of this transition in dependency ratios will be enormous.

India is also in a phase of demographic transition. There has been a sharp increase in the number of elderly persons during recent times and it is projected that by the year 2050, the percentage of elderly people would rise to about 20%. India has thus acquired the label of "an ageing nation" with growing number in the population above 60 years of age. The demographic transition is attributed to the decreasing fertility and mortality rates due to the availability of better health care services. Over the past decades, India's health program and policies have been focusing on issues like population stabilization, maternal and child health, and disease control. There is a need to highlight the medical and socio-economic problems that are being faced by the elderly people in India and strategies for bringing improvement in their quality of life also need to be explored. The elderly people suffer from dual medical problems, i.e., both communicable as well as non–communicable diseases. This is further compounded by impairment of special sensory functions like vision and hearing. A decline in immunity as well as age-related physiologic changes leads to an increased burden of communicable diseases in the elderly. The chronic illnesses usually include hypertension, coronary heart disease, respiratory disorders, diabetes, osteoarthritis and cancer. Nutritional deficiencies, metabolic disorders and urinary complaints are also common among elderly population. Obesity and its related complications due to a sedentary lifestyle and decreased physical activity also accounts to deterioration in overall health of aged people. Furthermore, elderly people are highly prone to mental morbidities due to ageing of the brain, problems associated with physical health, cerebral pathology, socio-economic factors and decrease in economic independence. The mental disorders that are frequently encountered include anxiety disorders, mood disorders and dementia.

The degeneration continues in the human body with increasing age. The resultant effects, though, cannot be overcome but by the help of certain measures, the ageing process can be slowed down and the diseases of old age can either be prevented or treated.

Unani Medicine, being a complete system of medicine, discusses different states of human body in health and disease in various phases of life. The physiology of individuals belonging to recognized four stages of human life is different from each other as per the requirement of a particular stage. In Unani Medicine, the *Quwwat Mudabbira-i Badan* (medicatrix naturae) has been given primary importance in different states of health and disease. The immune system is the direct instrument responsible for prevention and control of hazardous extrinsic and intrinsic factors influencing human health and wellbeing. Ageing is predominantly tantamount to the weakness of *Quwwat Mudabbira-i Badan* and the physician tries to strengthen this *Quwwat* through different measures of dietotherapy, regimenal therapy and pharmacotherapy.

Unani physicians have described various dietary articles, regimens and drugs, single as well as compound, for promotion of longevity and healthy ageing. A good number of Unani single drugs of plant origin have scientifically been proved for having anti-ageing activity, anti-oxidant activity, immunomodulatory activity, besides having effects in prevention and treatment of various diseases prevalent in elderly people.

The present document comprises description on medicinal plants used for longevity and healthy ageing in Unani Medicine since long. The information also include references of scientific studies carried out for establishing effects of Unani single drugs in various age related conditions.

I hope, the book will highlight the strength of Unani Medicine in the field of geriatrics and will be helpful for general public as well. I am sure it will also pave the way for further research in the field.

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Contents

Transliteration Table

The following Arabic letters have been transliterated with diacritical marks as mentioned against each:

ا	*a*	ر	*r*	ف	*f*
ب	*b*	ز	*z*	ق	*q*
ت	*t*	س	*s*	ک	*k*
ث	*th*	ش	*sh*	ل	*l*
ج	*j*	ص	*ṣ*	م	*m*
ح	*ḥ*	ض	*ḍ*	ن	*n*
خ	*kh*	ط	*ṭ*	ہ	*h*
د	*d*	ظ	*ẓ*	ی	*y*
ذ	*dh*	غ	*gh*		

The following Persian letters have been transliterated with diacritical marks as expressed against each:

پ	*p*	گ	*g*	ٹھ	*th*
ٹ	*t*	ں	*n*	چھ	*ch*
چ	*ch*	بھ	*bh*	دھ	*dh*
ڈ	*d*	پھ	*ph*	کھ	*kh*
ڑ	*r*	تھ	*th*	گھ	*gh*

- ء/أ has been transliterated with elevated coma (’) if used in the mid or end of word followed by relevant vowel and this elevated coma is not expressed at the beginning and only related vowel has been used directly.
- Letter ع is transliterated as elevated inverted coma (‘).
- Letter و as Arabic letter is transliterated as *w* and as Persian/Urdu letter is transliterated as *v*.
- ۃ and ہ are not expressed in both pause and construct forms.
- Article ال is transliterated as *al-* (*’l-* in construct form) whether followed by a moon or a sun letter.
- و as a Persian/Urdu conjunction is transliterated as (*o*) and as an Arabic conjunction is transliterated as *wa-*.
- Short vowel (ـِ) in Persian/Urdu passive or in conjunction form is transliterated as (*-i*).
- Double letters have been expressed as following:

  وّ = *uww*

  یّ = *iyy*

- Short & long vowels and diphthongs are used in the following form:

Short vowels	Long vowels	Diphthongs
ـَ = *a*	ا = *ā*	ـَو = *aw*
ـِ = *i*	آ = *ā*	ـَی = *ay*
ـُ = **u**	و = *ū*	
	ی = *ī*	

Introduction

Ever since antiquity man has been interested in finding favorable conditions for living and avoiding hazardous things to his life and health. The man explored the nature for two major needs; food for survival and herbs for relieving pain and disease. The ancient civilizations used herbs as primary remedial measure for their different sufferings.

Unani Medicine uses only natural products as drugs. Although, the system made great advancements in the chemical processing of drugs, i.e. distillation, sublimation, etc., it does not disturb the basic natural character of drugs, which is one of the fundamental reasons for the safety of Unani drugs. Unani drugs, according to their origin, have been classified into *Adwiya Nabātiyya* (drugs of plant origin), *Adwiya Maʿdaniyya* (drugs of mineral origin) and *Adwiya Haywāniyya* (drugs of animal origin). However the major chunk of drugs are derived from plants only. The drugs obtained from all three sources are, preferably used singly, and also in the form of a compound of various drugs. Unani Medicine also possesses a unique concept of *Dawā' Ghidhā'ī* (food medicine) and *Ghidhā' Dawā'ī* (medicinal food). Substances used primarily for their medicinal properties but also having nutritional value are called *Dawā' Ghidhā'ī* e.g. Almond, Fig etc. Therefore, they not only treat a disease but also nourish the individual. The substances which are used primarily as food but also have some medicinal properties are known as *Ghidhā' Dawā'ī e.g.* Egg, Bengal gram etc. The general character of a drug is described in terms of its temperament which when correlated with the temperament of the disease helps achieve holistic treatment.

Unani Medicine, though advocates the non-drug factors for promotion of health and treatment of disease, the use of drugs for promotive, preventive and curative purposes is no less important. The use of longevity promoting agents, tonics for innate heat, organ-specific tonics, exhilarants, and immunomodulatory drugs, etc. are some unique features of the system. Likewise, Unani Medicine offer various measures, regimens and drugs for individuals of different age groups for their age related health issues.

In Unani Medicine, the lifespan of the man is divided into four stages:

- *Sinn-i-Numū'* (growing age): The stage of growth that extends from the birth up to the age of 30 years
- *Sinn-i-Waqūf* (adulthood): The stage of stability, which extends from 30-40 years
- *Sinn-i-Kuhūlat* (age of decline): The stage when *Quwā* (body faculties) start to decline, but some strength persists. This stage extends from 40-60 years.
- *Sinn-ī-Shaykhūkhat* (age of elderly): The stage, in which decline occurs and ultimately leads to death, applies to people above 60 years of age. Such people are considered as *Mashāikh* (elderly). It is the period of decline associated with general weakness and lack of vigour.

As conceptualized in Unani Medicine, health is maintained by equilibrium of *Akhlāṭ-i Arbʿa* i.e. *Dam* (Sanguinous humour), *Balgham* (Phlegmatic humour), *Ṣafrā'* (bilious humour), *Sawdā'* (atrabilious humour). As long as these humours remain in equilibrium, health is maintained and derangement, either quantitative or qualitative, leads to different diseases. Since the equilibrium mechanism becomes weak as the age advances it leads to various age related disorders and lifestyle diseases in elderly. Unani scholars were well aware about the ageing process and a separate chapter has been dedicated to it in the Unani classical literature under the heading of *Tadābīr-i Mashāikh*. The process of ageing is attributed to depletion of *Ruṭūbat-i- Gharīziyya* (innate humour) and *Ḥarārat-i-Gharīziyya* (innate heat) of the body. *Ruṭūbat-i- Gharīziyya* is essential for maintaining health of vital organs and its depletion marks the onset of senility. Healthy ageing can be achieved by safeguarding *Ruṭūbat-i- Gharīziyya* from too rapid dissipation and by maintaining it.

There has always been an effort by Unani physicians to nurture a state of health that allows maximal active life expectancy while maintaining high levels of function. The physician's role in promoting such a state of health is disease prevention and the control of chronic diseases.

The contribution of Unani Medicine in this dimension of care is notably strong, as this system has rich potential to promote health of elderly along with the scope of rejuvenation and promotion of longevity. Many documents containing information on promoting longevity and healthy ageing can easily be traced within this system

of medicine. The treatises such as *Firdaws al-Ḥikma, Kitāb al-Manṣūrī, Kāmil al-Sanaʻa al-Tibbiyya, Al-Qānūn fi'l Ṭibb, Kitāb al-Mukhtarāt fi'l Ṭibb, Kitāb al-Kulliyyāt, Zakhīra Khwārzam Shāhī* and *A'yn-al-Ḥyāt,* etc. authored by scholars of Unani Medicine, deal with the subject in detail. Unani scholars categorized the elderly as *Abdān-i Ḍaʻīfa*', i.e., persons having debility without disease. It is believed that people within this age group have a cold and dry temperament that easily changes by extrinsic and intrinsic factors. The quantity of *Ruṭūbat-i- Gharīziyya* decreases with advancement of age and results in weakening of *Ḥarārat-i-Gharīziyya* leading to deficient nutrition further resulting in decreased formation of *Akhlāṭ*. The *Mizāj* is also modified towards cold with a decrease in *Ḥarārat-i-Gharīziyya* resulting in decline of *Quwā* (body faculties), thereby affecting the *Afʻāl* (functions) of the body.

Promotion of longevity and ensuring healthy ageing mainly include preservation of *Ruṭūbat-i-Gharīziyya* and *Ḥarārat-i-Gharīziyya* as long as possible. Checking the production of *Ruṭūbat-i-Gharība* that is responsible for conversion of *Mizāj* from *Ḥār Raṭab* to *Bārid Yābis* in elderly, elimination of body wastes and protection of the body from hazardous extrinsic factors are also important. The preservation of *Ruṭūbat-i-Gharīziyya* is performed by various regimens of *'Ilāj bi'l-Ghiḍhā* (dietotherapy), *'Ilāj bi'l-Tadbīr* (regimenal therapy) and *'Ilāj bi'l-Dawā'* (pharmacotherapy).

Under pharmacotherapy section, the medicament for promotion of longevity and healthy ageing based on three primary sources of drugs; plant, animal and minerals has been described. It is interesting to mention here that while describing various pharmacological actions of drugs, the Unani scholars introduced many unique terms that not only have correlation with the philosophy of Unani Medicine but also have contemporary scientific relevance. The terms of *Mu'ammir* (longevity promoting agents), *Muqawwī-i-Ḥarārat Gharīziyya* (tonic for innate heat), *Muqawwī-i-Aʻḍā' Raʼīsa* (tonic for vital organs) and *Mufarriḥ* (exhilarant) bring about a whole new understanding to the pharmacological actions of Unani drugs that may be of immense interest for those working in the fields of geriatrics and gerontology. Such drugs, may help delay ageing process, strengthen body faculties, prevent and control chronic diseases and thus ensure longevity and healthy ageing.

The "*Medicinal plants for longevity: evidence based geriatric care approach of Unani Medicine*" comprises description of 35 medicinal plants used in Unani Medicine for their actions related to promotion of longevity, healthy ageing and prevention

and treatment of chronic diseases. The selection of the plants included in the text has been made meticulously. The plants that are commonly found within the rich repository of flora and fauna of the country, have been included in this book. The information related to each plant has been described under the heads; name of the drug including scientific name, introduction, vernacular name, temperament, chemical constituents, Pharmacological actions, therapeutic uses, important formulations, evidence based pharmacological /clinical studies. These plants, with a very few exceptions, possess hot temperament that help preserve *Ruṭūbat-i-Gharīziyya* and *Ḥarārat-i-Gharīziyya,* the key approach in promotion of longevity.

Standard classical books of Unani Medicine such as *Al-Qānūn fi'l Ṭibb* by *Ibn Sīnā* (980-1037 AD), *Al-Jāmi'li-Mufradāt al-Adwiya wal-Aghdhiya* (Urdu translation) by *Ibn Bayṭār* (1197-1248 AD), *A'yn-al-Ḥyāt* by *Muḥammad bin Yūsuf al-Ḥarawi* (d. 1542 AD), *Muhīṭ-i-A'zam* by *Muḥammad A'zam Khān* (d. 1902 AD) and *Khazain al-Adwiya* by *Najmul Ghani* have been primarily referred to for the compilation of traditional knowledge. These references encompass not only the inputs of authors, but reflect the whole research work undertaken by the scholars on Unani medicinal plants during the Greek, Roman, Arabian, Persian and Indian periods.

The Unani Pharmacopoeia of India and research studies published in various scientific journals were referred for gathering information related to Chemical Constituents and research evidences in particular. The published studies have been presented in a manner that they could provide evidence for their activities in relation to longevity and healthy ageing. For the purpose, the studies, pharmacological as well as clinical, have been categorized according to their findings; anti-ageing activity, immunomodulatory, anti-oxidant, cardio-protective, CNS protective, Hepato-protective, nephro-protective, gastro-protective, anti-depressant, antianxiety, anti-nociceptive, anti-diabetic, anti-hypertensive, anti-hyperglycemic, anti-inflammatory, analgesic, anti-microbial, anti-viral, anti-obesity, anti-cancer and aphrodisiac activities. The references in support of furnished information have been provided at the end of the description of each plant.

It is hoped that the document would not only be appreciated by the academician, researchers and students of Unani Medicine but would get recognition among scientific community and general people as well.

Āmla
(Fruit)
Phyllanthus emblica L.

Introduction

Āmla consists of pericarp of mature fruits of *Phyllanthus emblica* L. Syn. *Emblica officinalis* Gaertn. (Family-Phyllanthaceae). *Āmla* is mostly collected in winter season after ripening and in Kashmir in summer. Drug yielding plant is a small or medium sized tree, found both in natural state in mixed deciduous forests of the country ascending to 1300 m on hills, cultivated in garden, home yards or grown as a road side tree. (Anonymous, 2007a)

Fig. *Āmla*

Vernacular Names

English: Embolic Myrobalan; Hindi: *Āmla, Āonla, Amlikā*; Urdu: *Āmla, Āmlaj*; Arabic: *Āmlaj*; Persian: *Āmla* (Khān, 2012; Ibn Sīnā, 1987; *Ibn Baytār*, 1985; Ghani, YNM; Anonymous, 2007a)

Temperament

Bārid (Cold)[1] *Yābis* (Dry)[2] (Khān, 2012; Ibn Sīnā, 1987)

Chemical Constituents

Hydrolysable Tannins	Emblicanin A and B, Punigluconin, Pedunculagin, Chebulinic acid (Ellagitannin), Chebulagic acid (Benzopyran tannin), Corilagin (Ellagitannin), Geraniin (Dehydroellagitannin), Ellagotannin
Alkaloids	Phyllantine, Phyllembein, Phyllantidine

Phenolic compounds	Gallic acid, Methyl gallate, Ellagic acid, Trigallayl glucose
Amino acids	Glutamic acid, Proline, Aspartic acid, Alanine, Cystine, Lysine
Carbohydrates	Pectin
Vitamins	Ascorbic acid
Flavonoids	Quercetin, Kaempferol
Organic acids	Citric acid

(Kulkarni & Ghurghure, 2018)

Pharmacological Actions

- *Mu'mmir* (Longevity promoting agent)
- *Muqawwī-i-Ḥarārat Gharīziyya* (Tonic for innate heat)
- *Muqawwī-i-'Ām* (General tonic)
- *Muqawwī-i-Dimagh* (Brain tonic)
- *Muqawwī-i-Qalb* (Cardio tonic)
- *Mufarriḥ* (Exhilarant)
- *Muqawwī-i-Baṣar* (Eye tonic)
- *Muqawwī-i-Mi'da* (Stomachic)
- *Muqawwī-i-Sha'r* (Hair tonic)
- *Mu'addil-i- Ṣafrā'* (Normalizing yellow bile)

  (Khān, 2012; Ibn Sīnā, 1987; *Ibn Baytār*, 1985; Al-Harawi, 2002; Ghani, YNM; Anonymous, 2007a; *Kabīruddīn*, 2000)

Therapeutic Uses

- *Ḍu'f-i-Ḥarārat Gharīziyya* (Innate heat insufficiency)
- *Ḍu'f-i-'Ām* (General debility)
- *Ḍu'f-i-Dimāgh* (Cerebrasthenia)
- *Ḍu'f-i-Qalb* (Cardiac insufficiency)
- *Khafaqān* (Palpitation)
- *Ḍu'f-i-Baṣar* (Poor eyesight)
- *Nisyān* (Forgetfulness)
- *Ḍu'f-i- Mi'da* (Gastric debility)

- *Qarḥa'-i-Mi'da* (Gastric ulcer)
- *Humūḍat-i-Mi'da* (Hyperacidity)
- *Ḍu'f-i-Kabid* (Hepatic insufficiency)
- *Ishāl* (Diarrhoea)

(Khān, 2012; Ibn Sīnā, 1987; *Ibn Baytār*, 1985; Al-Harawi, 2002; Ghani, YNM; Anonymous, 2007a; *Kabīruddīn*, 2000)

Important Formulations

Murabbā Āmla, Jawārish-i-Āmla Sāda, Anoshdārū, Jawārish Shāhī, Safūf-i-Āmla, Safūf-i-Hāḍim Kalān, Dawā-ul-Misk Mu'tadil Sāda and Mostly all Iṭrīfalāt (like Iṭrīfal Saghīr, Iṭrīfal Zamāni, Iṭrīfal Ustūkhūdūs). (Anonymous, 2007a; *Kabīruddīn*, 2000)

Pharmacological / Clinical studies (Evidence based studies)

Anti-oxidant and free radical scavenging activity

- Prakash *et al.,* 2012 showed that Gallic acid equivalent as total phenolic content from fruit of E. officinalis has excellent Anti-oxidant properties and play an important role as free radical scavengers required in the maintenance of 'redox homeostasis' responsible for diverse degenerative diseases. (Hasan *et al.,* 2016)

- Methanolic extract of fruit pulp of *E. officinalis* showed in various studies that it has potent anti-oxidant and free radical scavenging activities. (Hasan *et al.,* 2016; Jamwal *et al.,* 2011; Mehrotra *et al.,* 2011; Liu *et al.,* 2008a; Liu *et al.,* 2008b, Hazra *et al.,* 2010; Majumdar *et al.,* 2010)

- A study carried out with aqueous extract of *E. officinalis* fruit prepared according to Thai Herbal Pharmacopoeia for free radical scavenging activity, the result showed that it has a strong potential for free radical scavenging, ferric reducing as well as inhibiting ROS (reactive oxygen species) production. (Charoenteeraboon *et al.,* 2010).

Anti-oxidant and anti-cancer activity

- *Āmla* is one of the richest sources of vitamin-C and low molecular weight hydrolysable tannins which makes it a good anti-oxidant. The tannins of *Āmla* like emblicanin-A (37%), emblicanin-B (33%), punigluconin and pedunculagin are reported to provide protection against oxygen radical

included haemolysis of rat peripheral blood erythrocytes. Emblicanin A & B of *Āmla* fruit are reported to possess strong anti-oxidant and anti-cancer activities. (Ghosal *et al.,* 1996)

- The mechanism behind anti-oxidant activity is due to the recycling of sugar moiety and conversion of the polyphenol into medium and high molecular weight tannins. The powerful anti-oxidant ellagic acid, present in *Āmla*, can inhibit mutations in genes and repair the chromosomal abnormalities. (Bhattacharya *et al.,* 1999; Kulkarni & Ghurghure, 2018)
- *Āmla* inhibits the growth and spread of various cancers like breast, uterus, pancreas, stomach and liver cancers. It can prevent and/or reduce the side effects of chemotherapy and radiotherapy. (Kulkarni & Ghurghure, 2018)
- More than 18 compounds were identified in *Āmla* fruit which can exert anti-proliferative activity on gastric and uterine cancer cells. The main mechanism behind its activity is by enhancing Natural Killer (NK) cell activity in various tumor cells. (Kulkarni & Ghurghure, 2018).

Immunomodulatory activity

- A study was carried out with aqueous extract of dried *Emblica officinalis* fruit pulp powder for its immunomodulatory effect on male Swiss Albino mice. The result showed that there was significant dose dependent increase in haemagglutination antibody titre, sheep red blood cells induced delayed type of hypersensitivity reaction, macrophage migration index, respiratory burst activity of the peritoneal macrophages, total leukocyte count, percentage lymphocyte distribution, serum globulin and relative lymphoid organ weight in *Emblica* treated mice indicating its ability to stimulate humoral as well as cell mediated immunity along with macrophage phagocyte. (Suja *et al.,* 2009)
- A study carried out with fruit extracts of *Emblica officinalis* for Immunomodulatory properties was evaluated by utilizing chromium (VI) as an immunosuppressive agent. It additionally inhibited apoptosis and DNA fragmentation and relieved the immunosuppressive effects of chromium (Cr) on lymphocyte proliferation. (Jain *et al.,* 2016)

Anti-ageing activity

- A study carried out with methanolic, ethyl acetate, n-butanol and aqueous extracts of *Emblica officinalis* fruit pulp for anti-oxidant, anti-collagenase, anti-

elastase and anti-hyaluronidase activities. *Emblica officinalis* of methanolic extracts showed significant anti-oxidant, anti-collagenase, anti-elastase and anti-hyaluronidase activities. The study also revealed that *Emblica officinalis* may serve as a potent anti-aging agent. These results suggested that *Emblica officinalis* could be used as an effective ingredient in cosmetics since it provides protection against various aging enzymes and can be beneficial for skin aging particularly photo aging. (Garg and Garg, 2018)

- *Emblica officinalis* (EO) has been used extensively as a nutraceutical in several diseases since it is known to boost immunity and offers numerous health benefits such as anti-oxidant, and anti-aging effects. A study carried out with extract of *Emblica officinalis* on AMD RPE trans mitochondrial cell lines created by fusing mitochondria DNA-deficient APRE-19 (Rho 0) cells with platelets isolated from AMD patients, and therefore had identical nuclei but differed in mitochondrial DNA content. These AMD RPE cells were treated with EO extract followed by characterization of effects of EO using cellular and molecular assays. EO significantly improved live cell number and mitochondrial membrane potential, reduced apoptosis and oxidative stress, down regulated VEGF, and up regulated PGC-1α. Hence the result showed that EO improved cellular and mitochondrial health, thereby playing a key cyto-protective role in AMD *in-vitro* . (Nashine *et al.*, 2019)

- The effects of EO on the lipid metabolism and protein expression involved in oxidative stress during the ageing process. Sun *Āmla* or ethyl acetate (Et Ac) extract of *Āmla*, a polyphenol-wealthy fraction, was administered at a dose of 40 or 10 mg/kg physique weight per day for 100 days to younger rats aged 2 months and aged rats aged 10 months. The lipid levels, corresponding to cholesterol and TGs, in serum and liver had been markedly extended in aged manage rats, and at the same time, they had been enormously decreased by way of the administration of EO (*Āmla*). The peroxisome proliferator activated receptor alpha (PPA Ralpha) is famous to control the transcription of genes involved in lipid and cholesterol metabolism. The PPAR alpha protein stage in liver was reduced in aged manage rats. Nonetheless, the oral administration of *Āmla* vastly accelerated the hepatic PPAR alpha protein degree. In addition, oral administration of *Āmla* drastically inhibited the serum and hepatic mitochondrial thio barbituric acid (TBA)-reactive substance levels in aged rats. The elevated expression stage of bax used to be drastically reduced after the oral administration of EO (*Āmla*) while the level of bcl-2 ended

in a massive broaden. In addition, the expressions of hepatic nuclear factor (NF)-kappa B, inducible NO synthase (iNOS) and cyclo-oxygenase-2 (COX-2) protein levels have been also elevated with aging. Nonetheless, EO (*Āmla*) extract decreased the iNOS and COX-2 expression phases through inhibiting NF-kappa B activation in aged rats. These results point out that EO (*Āmla*) could preclude age-related hyperlipidemia via attenuating oxidative stress within the growing older system. (Yokozawa *et al,* 2007)

Additional activities

- The fruit of *Phyllanthus emblica* L. has also been reported to possess gastro-protective, hepato-protective, cardio-protective, nephro-protective, anti-ulcer, anti-diarrheal, spasmolytic, anti-microbial, anti-bacterial, anti-viral, anti-diabetic, anti-hypercholesteraemic/ hypo-lipidemic/ anti-atherogenic, hair growth promotion, anti-biotic, anti-amnesiac, anti-inflammatory, wound healing, ophthacare and memory enhancer activities. (Dasaroju & Gottumukkala, 2014; Kulkarni & Ghurghure, 2018; Nashine *et al.,* 2019; Hasan *et al.,* 2016; Garg & Garg, 2018)

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Anjīr
(Fruits/ Fleshy receptacles)
Ficus carica L.

Introduction

The drug *Anjīr* consists of dried fleshy receptacles/ fruits of *Ficus carica* L. (Family- Moraceae). The tree is a native of Asia Minor and cultivated in many parts of the Northern India, Andhra Pradesh, Karnataka and Maharashtra. Receptacles occur during January to April and ripe fruits (fig) from June to October. (Anonymous, 2007b)

Fig. *Anjīr*

Vernacular Names

English: Fig; Urdu; *Anjīr*; Arabic: *Tīn*; Persian: *Anjīr*; Hindi: *Anjīr*. (Khān, 2012; Ibn Sīnā, 1987; *Ibn Baytār*, 1985; Anonymous, 2007b; Ghani, YNM; *Kabīruddīn*, 2000)

Temperament

Ḥār (Hot)[1] *Raṭb* (Moist)[2] (Khān, 2012; Ibn Sīnā, 1987; *Kabīruddīn*, 2000)

Chemical Constituents

Glycosides, proteins/amino acids, resins, reducing sugar, steroids/triterpenes, tannins, fixed oils, potassium, calcium, magnesium, iron, copper, phosphorus in phosphate and chlorine in chloride forms, Protease, amino acid, tyrosin, cravin lipase, protease, carotene. (Chawla *et al.*, 2012; Anonymous, 2007b; Shamkant et al., 2014)

Pharmacological Actions

- *Muqawwī-i-Ḥarārat Gharīziyya* (Tonic for innate heat)
- *Mughadhdhī* (Nutritive)
- *Musammin-i-Badan* (Body weight enhancer)
- *Muqawwī-i Bāh* (Aphrodisiac)
- *Muḥallil-i-Awrām* (Resolvent)
- *Mulayyin* (Laxative)
- *Mulaṭṭif* (Demulcent)
- *Mufattiḥ-i-Sudad* (Deobstruent)

  (Khān, 2012; Ibn Sīnā, 1987; *Ibn Baytār*, 1985; Al-Harawi, 2002; Anonymous, 2007b; Ghani, YNM; *Kabīruddīn*, 2000)

Therapeutic Uses

- *Ḍu'f-i-Ḥarārat Gharīziyya* (Innate heat insufficiency)
- *Ḍu'f-i-'Ām* (General debility)
- *Ḍu'f-i-Bāh* (Sexual debility)
- *Qabḍ* (Constipation)
- *Ḍīq al-Nafas* (Bronchial asthma)
- *Ṣar'* (Epilepsy)
- *Bawāsīr* (Heamorrhoids)

  (Khān, 2012; Ibn Sīnā, 1987; *Ibn Baytār*, 1985; Al-Harawi, 2002; Anonymous, 2007b; Ghani, YNM; *Kabīruddīn*, 2000)

Important Formulations

Safūf-i-Baraṣ (Anonymous, 2007b)

Pharmacological / Clinical studies (evidence based)

Anti-oxidant activity

- Vinson et al. 1999, reported significant anti-oxidant activity in dried fruits of *Ficus carica* L. Study results suggested that dried fruits of *Ficus carica* should be a greater part of diet, as they are dense in phenol anti-oxidants, nutrients and fibres. (Chawla *et al.*, 2012)

- *F. carica* contains phenolic compounds that play many physiological roles in plants. Some of them are also favourable to human health, since they are able to act as an anti-oxidant by different ways: reducing agents, hydrogen donators, free radical scavengers, singlet oxygen quenchers, and so forth. Fig fruits of *F. carica* were studied with six commercial fig varieties with different colours (black, red, yellow, and green) for total polyphenols, total flavonoids, Anti-oxidant capacity, and profile of anthocyanins. The anti-oxidant properties were determined by ferric reducing anti-oxidant method. Fruits contained the highest levels of polyphenols, flavonoids, and anthocyanins and exhibited the highest anti-oxidant capacity. (Chawla *et al.,* 2012)

- Fig fruits of *F. carica* were analysed for total flavonoids, anti-oxidant capacity, and profile of anthocyanins. Using RP-LC, various concentrations of anthocyanins but similar profiles have been found in all varieties studied. Cyanidin was confirmed as the major aglycone in several studies. NMR data confirmed that cyanidin-3-*O*-rutinoside (C3R) was the main anthocyanin in all fruits. Colour appearance of the fig extract correlated well with total polyphenols, flavonoids, anthocyanins, and anti-oxidant capacity. C3R contributed 92% of the total anti-oxidant capacity of the anthocyanin fraction, and fruits contained highest levels of polyphenols; flavonoids and anthocyanins exhibited the highest anti-oxidant capacity. (Chawla *et al.,* 2012)

Immunomodulatory activity

- Patil et al, 2010 reported the immunomodulatory effect of ethanolic extract of *Ficus carica* (Moraceae) which was investigated in mice. The study was carried out by various haematological and serological tests. Administration of extract remarkably ameliorated both cellular and humoral antibody response. (Chawla *et al.,* 2012)

Free radical scavenging activity

- Run-ya et al, 2010 designed the method to study the ultrasonic-assisted extraction of total flavonoids of *Ficus carica* Linn. and their scavenging activities against hydroxyl and superoxide anion free radicals. The optimum conditions for extracting total flavonoids of *Ficus carica* Linn. were found to be: ethanol concentration 40%, material-to-liquid ratio 1:60 (g/mL), extraction temperature 60 °C and length of ultrasonic treatment of 50 min.

Under these optimum conditions, the extraction efficiency of total flavonoids reached as high as 25.04 mg/g. The total flavonoids extract had marked scavenging effects on both hydroxyl and superoxide anion free radicals in a concentration-dependent fashion. (Chawla *et al.,* 2012)

Cytotoxic activity

- Khodarahmi *et al.,* 2011 reported that extracts of different species of *Ficus* are cytotoxic to some human cancerous cell lines. Therefore, fruit, leaf, with ethyl acetate and dichloromethane and latex extracts were prepared through percolation and after 24 h incubation at 37°C, the cells were treated with different concentrations of the extracts or latex. The viability of the cells was determined by the reduction of 3-(4, 5- dimethylthiazol- 2-yl)-2, 5-diphenyl tetrazolium bromide (MTT) from formazan following 48 h incubation and the latex and different extracts of *Ficus carica* values of the ethanolic, ethyl acetate and dichloromethane extracts of the leaves and fruits. (Chawla *et al.,* 2012).

Additional activities

- The fruit of *Ficus carica* has also been reported to possess activities like anti-inflammatory, anti-microbial, anti-fungal, hepato-protective, hypo-triglyceridaemic, anti-angiogenic, erythropoeitic, anti-spasmodic, anthelmintic, anti-viral, anti-constipation and hypolipidimic. (Shamkant et al., 2014; Chawla *et al.,* 2012)

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Āqarqarḥa
(Root)
Anacyclus pyrethrum (L.) Lag.

Introduction

The drug of *Āqarqarḥa* consists of dried root of *Anacyclus pyrethrum* (L.) Lag. (Family-Asteraceae). A perennial, procumbent herb. The plant is indigenous to North Africa and occurs throughout the year. Flowering and fruiting take place during winter season. (Anonymous, 2007b)

Fig. *Āqarqarḥa*

Vernacular Names

English: Pellitory, Pyrethrum Root; Hindi: *Akarakara*; Urdu: *Āqarqarḥa*; Arabic: *Āqarqarḥa*, *'Ūd al-Qaraḥ*; Persian: *Bekh-e-Tarkhun Kohī*, *Kākrah, Kālū*. (Khān, 2014; Ibn Sīnā, 1987; *Ibn Baytār*, 1999; Anonymous, 2007b)

Temperament

Ḥār (Hot)[3] *Yābis* (Dry)[3] (Khān, 2014; Ibn Sīnā, 1987; Anonymous, 2007b)

Chemical Constituents

Anacyclin, pellitorine, enetriyne alcohol, hydrocarolin, inulin, protein, sugar, trace of volatile oil and sesamin, also contains tyramine amides corresponding to isobutylamides, polyacetylenic compounds and a trace of essential oil. (Anonymous, 2007b; Tauheed *et al.,* 2017)

Pharmacological Actions

- *Muqawwī-i-'Ām* (General tonic)
- *Mukhrij-i-Balgham* (Expellant of phlegm)
- *Muḥallil* (Resolvent)

- *Musakkin-i-Alam* (Analgesic)
- *Muqawwī-i-Bāh* (Aphrodisiac)
- *Mumsik-i-Manī* (Retentive of semen)
- *Muḥammir* (Rubefacient)
- *Mukhaddir-i- Maqāmi* (Local anaesthetic)
- *Mudirr-i-Laban* (Galactagogue)
- *Mufattiḥ-i- Sudad* (Deobstruent)

(Khān, 2014; Ibn Sīnā, 1987; *Ibn Baytār*, 1999; Ghani, YNM; *Kabīruddīn*, 2000; Anonymous, 2007b; Tauheed *et al.*, 2017)

Therapeutic Uses

- *Ḍu'f-i-'Ām* (General debility)
- *Amrāḍ-i-Bārida Balghamiyya* (Cold phlegmatic diseases; such as *Laqwa* (Bell's palsy), *Istirkhā'* (Atony or flaccidity), *Ri'sha* (Tremor) etc.
- *Fālij* (Hemiplegia)
- *Ṣar'* (Epilepsy)
- *Ḍu'f-i-Bāh* (Sexual debility)
- *Istirkhā'–i-Qaḍīb* (Penile flaccidity)
- *Sur'at-i-Inzāl* (Premature ejaculation)
- *Waja' al-Mafāṣil* (Polyarthritis)
- *'Irq al-Nasā* (Sciatica)
- *Istisqā'* (Ascites)
- *Khasham* (Anosmia)
- *Waja' al-Asnān* (Toothache)

(Khān, 2014; Ibn Sīnā, 1987; *Ibn Baytār*, 1999; Ghani, YNM; *Kabīruddīn*, 2000; Anonymous, 2007b; Tauheed *et al.*, 2017)

Important Formulations

Falūniya Rūmī Tarsūsī, Falūniya Fārsī, Ma'jūn Fīroznosh, Barsha'sha, Tiryāq-i-Aqrab, Jawārish-i-QaiṢar, Jawārish Zar'ūnī, Jawārish-i- Zar'ūnī'Ambarī Ba Nuskha-i-Kalān, Jawārish Za'frān, Jawārish Lu'luwī, Anqaroya Kabīr, Labūb Ṣaghīr, Ma'jūn Balādur, Ma'jūn Sa'lab, Roghan-i-Sudāb, Sanūn-i-Mulūk, Ḥabb-i- Fālij Mulayyin, Ḥabb-i-Mumsik Qawī, Ma'jūn Zabīb, Roghan-i-Qust, Sanūn-i-Mujallī, Qayrūṭī Ārad-i-Karsana (*Kabīruddīn*, 2000; Tauheed *et al.*, 2017)

Pharmacological / Clinical studies (evidence based)

Anti-oxidant activity

- The ethanolic extract of *Anacyclus pyrethrum* was evaluated for *in vivo* and ex-vivo anti-oxidant activities by using different experimental models at different concentration 25, 50, 100, 200, 400 microgram/ml. Anti-oxidant potential of *A. pyrethrum* root may be due to its phytochemical constituents such as Phenol, Flavonoids, Alkaloids, Tannins (Sujith *et al.,* 2012; Tauheed *et al.,* 2017)

Immunostimulating activity

- Hot water polysaccharide extracts of *Anacyclus pyrethrum* were tested for their immune stimulating activity in mice. The fractions from *Anacyclus pyrethrum* and *Alpinia galanga* showed a marked stimulating activity on the reticulo-endothelial system(RES) and increased the number of peritoneal exudates cells (PEC), and spleen cells of mice. In this case, the optimum doses were 50 and 25 mg/kg for the 2 fractions, respectively. On the other hand, the polysaccharide extracts of both *Anacyclus pyrethrum* and *Alpinia galangal* markedly increased the production of the murine spleen cells *in-vitro* using two tests (*in-vitro* and *in-vivo* effect). The results of the *in vivo* effect at a doses of 50 and 25 mg/kg, showed an encouragement index better than obtained with the *in vitro* effect at 50 and 25 mg/ml for *Anacyclus pyrethrum* and *Alpinia galanga*, respectively. While the extract of *Citrullus colocynthis* showed much weaker and changeable immunostimulating activity. (Tauheed *et al.,* 2017; Bendjeddou et al., 2003)

- Immunomodulatory activity of petroleum ether extract of *Anacyclus pyrethrum*. Sharma et al. (2010) investigated that the PEE-treated rats were able to overcome cyclophosphamide-induced myelo suppression as evidenced by the normalization of blood parameters. Survival rate of albino rats was improved in Candida albicans-infected animals by treatment with the extract ($p < 0.05$). An increase in delayed type hypersensitivity response (DTH), percentage neutrophil adhesion, and in vivo phagocytosis by carbon clearance method was observed after treatment.

Memory enhancing activity

- Darwin et al. studied on memory enhancing activity of *Anacyclus pyrethrum*. (Tauheed *et al.,* 2017)

- Ethanolic extract of *A. pyrethrum* has been demonstrated to improve cognitive processes by enhancing memory in different experimental paradigms such as passive avoidance paradigms, elevated plus maze and social learning task when administered orally Brain cholinesterase level was measured to assess central cholinergic activity. The treatment with drugs, which increase cholinergic neurotransmission, causes an improvement in cognitive deficits. The study suggest that ethanolic extract of *A. pyrethrum* increased brain cholinesterase level and hence it possess memory enhancing activity in scopolamine induced amnesia model by enhancing central cholinergic neurotransmission. (Sujith *et al.,* 2012)

- Memory enhancing effects of *Anacyclus pyrethrum* at three doses 50, 100, 200 mg/kg in Albino wistar rats (Ronald et al., 2012). Central cholinergic system is considered as the most important neurotransmitter involved in regulation of cognitive functions (Levander et al., 2009). Impaired cognitive functions are the major characters of Alzheimer diseases (AD) (Iriti et al., 2010). Loss of cholinergic neurons in nucleus basalis magno cellular is one of the most important features of AD, primarily accounting for memory loss (Patel et al., 2011). The treatment with drugs, which augment cholinergic neurotransmission, causes an improvement in cognitive deficits in AD (Pattewar et al., 2011; Usmani et al., 2016).

Anti-convulsant activity

- Electro-convulsive shock, inducing Hind limb tonic Extension (HLTE) in 99% of the animals, was determined. Corneal electrode were used for bilateral delivery of electrical motivation Electro-convulsive alarm (50mA for 0.2 sec) to induce HLTE phase in mice. The electrical stimulus was functionalized by using a stimulator apparatus for five groups. (Gautam, 2011). Group I served as control (vehicle treated) (i.p.); Group II served as standard (received phenytoin sodium 25 mg/kg body weight, i.p.)Group III, IV, V were treated with ethanolic extract as 200, 400, and 600mg/kg body weight, i.p. respectively. The current was delivered after 30 min of intraperitonial insertion of control and standard. The incidence and duration of HLTE was noted. It shows that the extract significantly decreased the duration of HLTE phase in maximum electroshock induced seizures. The MES test is considered to be a predictor of likely therapeutic efficacy generalized tonic-clonic seizures (Loscher & Schmidt, 1998).

- MES induced tonic seizures can be prevented either by drugs that inhibit voltage dependent Na ion channels, such as phenytoin, valproate and lamotrigine or by drugs that block glutamatergic excitation mediated by the N-Methyl – D asparatate (NMDA) receptor such as felbamate. The ethanolic extract from roots of AP can inhibit voltage dependent sodium ion channels as phenytoin in MES induced tonic seizures. The effect on motor co-ordination was evaluated using rota rod apparatus. Pre-selected mice were placed on the horizontal rotating bar.The test was conducted on five groups of 6 mice each , 30 min after the administration of ethanolic extract (200, 400, 600 mg/kg i.p) and diazepam (1 mg/kg i.p) and normal saline (Mandgary and Sayyah, 2003). A significant dose dependent muscle relaxant activity of AP was observed in rota rod apparatus compared to that produced by diazepam. (Fielding et al., 1995; Usmani et al., 2016).

Anti-depressant activity

- An experiment was planned by different method such as locomotor activity, haloperidol induced catalepsy, forced swimming test (FST), tail suspension test (TST), clonidine induced hypothermia & Reserpine-induced hypothermia on Swiss male albino mice. Root extract of *Anacyclus pyrethrum* showed an increase in ambulatory behaviour indicating a stimulant effect of the photoactometer. *A. pyrethrum* root extract produces a significant anti-depressant effect in both forced swim test and tail suspension test as they reduced the immobility.(Badhe *et al.,* 2010)

Additional activities

- The root of *Anacyclus pyrethrum* has also been reported to possess aphrodisiac, spermatogenic, anti-diabetic, anti-depressant, anti-convulsant, myrorelaxation, insecticidal, anti-cancer and hepato-protective activities. (Tauheed et al, 2017)

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Asgand
(Root)
Withania somnifera (L.) Dunal

Introduction

Asgand consists of dried mature root of *Withania somnifera* (L.) Dunal (family - Solanaceae), Drug yielding plant is perennial shrub, found in waste land, cultivated in fields and open grounds throughout India; widely cultivated in certain areas of Madhya Pradesh and Rajashtan, roots are collected in winter, washed and cut into short pieces. (Anonymous, 2007a)

Fig. *Asgand*

Vernacular Names

English: Withania Root, Winter Cherry; Hindi: *Asgandh*, : Urdu; *Asgand*, *Asgand Nāgori*; Arabic: *Kāknaj Hindī*; Persian: *Asgandh Nāgori*, *Kāknaj Hindī* (Khān, 2012; Anonymous, 2007a)

Temperament

Ḥār (Hot)^3 *Yābis* (Dry)^3 (Khān, 2012; Ghani, YNM; *Kabīruddīn*, 2000)

Chemical Constituents

Alkaloids	Withanine, Withananine, Withananinine, Pseudo-Withanine, Somnine, Somniferine, Somniferinine
Amino acids	Aspartic Acid, Glycine, Tyrosine, Alanine, Proline, Tryptophan, Glutamic Acid, Cystine
Steroidal alkaloids	Withanolides; Withaferin A and Withanolide D
In addition to above , the root also contains starch, resin, fat, potassium nitrate, phytosterol, reducing sugars, hentriacontane glycosides, dulcitol, withaniol, stearic, palmatic, linoleic, withanic acids, ipuranol and somnirol	

(Imtiyaz *et al.*, 2013; Saiyed *et al.*, 2016; Qamar Uddin *et al.*, 2012)

Pharmacological Actions

- *Muqawwī-i-ʻĀm* (General tonic)
- *Muqawwī -i-Aʻṣāb* (Nervine tonic)
- *Muqawwī-i Bāh* (Aphrodisiac)
- *Muwallid-i-Mani* (Spermatogogue)
- *Munawwim* (Hypnotic)
- *Muḥallil-i-Waram* (Anti-inflammatory)
- *Mufattiḥ-i- Sudad* (Deobstruent)
- *Muqawwī-i-Miʻda* (Stomachic)
- *Muqawwī-i-Raḥim* (Uterine tonic)
- *Mufattit-i-Hasāt* (Lithotriptic)

(Khān, 2012; Anonymous, 2007a; Ghani, YNM; *Kabīruddīn*, 2000)

Therapeutic Uses

- *Ḍuʻf-i-ʻĀm* (General debility)
- *Ḍuʻf-i-Aʻṣāb* (Nervine weakness)
- *Nisyān* (Forgetfulness)
- *Ḍuʻf-i-Bāh* (Sexual debility)
- *Jiryān* (Spermatorrhoea)
- *Qillat-i-Mani* (Oligospermia)
- *Ḍuʻf-i- Miʻda* (Gastric debility)
- *Waja' al-Mafāṣil* (Polyarthritis)
- *Sailān al-Raḥim* (Leucorrhoea)
- *Waja' al-Qaṭn* (Lumbago)

(Khān, 2012; Anonymous, 2007a; Ghani, YNM; *Kabīruddīn*, 2000)

Important Formulations

Habb-i-Asgand, Safūf-i-Asgand, Maʻjūn Muqawwi Raḥim, Maʻjūn Suhāg Sonth, Maʻjūn-i-Salab, Zimād-i-Muḥallil, Kushta Gaodanti.

(Anonymous, 2007a; *Kabīruddīn*, 2000)

Pharmacological / Clinical studies (Evidence based studies)

Anti-aging activity

- Double-blind clinical trial carried out to study the effect of plant on prevention of ageing in 101 normal healthy males in 50-59 years age group. Root powder (0.5 g) of *Asgand* was given orally three times a day for 1 year. Results showed statistically significant increase in Hb, RBC, hair melanin, and seated stature in treated group in comparison to placebo group. Decrease in serum cholesterol was more in treated group than in placebo group. (Qamar Uddin *et al.,* 2012; Meher *et al.,* 2016)

Anti-oxidant activity

- The active chemical constituents found in *Withania somnifera* are powerful anti-oxidants. Many studies conducted on rat's brains showed the herb produced an increase in the levels of three natural anti-oxidants- superoxide dismutase, catalase and glutathione peroxidase. The anti-oxidant effect of active principles of *Withania somnifera* root may explain the reported anti-stress, cognition-facilitation, anti-inflammatory and anti-aging effects produced by them in experimental animals, and in clinical situations. (Meher *et al.,* 2016; Qamar Uddin *et al.,* 2012; Bhattacharaya *et al.,* 2001; Bhattacharaya *et al.,* 1997a; Mehrotra *et al.,* 2011)

Immunomodulatory activity

- *Withania somnifera* has shown a significant modulation of immune reactivity in animal models. Administration of *Withania somnifera* was found showing activity like immunosuppressive drugs, viz, cyclophosphamide, azathioprin and prednisolone. Treatment with *Withania somnifera* was found to significantly increase Hb concentration, RBC count, platelet count, and body weight in mice. Administration of *Withania somnifera* extract was found to significantly reduce leucopenia induced by cyclophosphamide (CTX) treatment. Administration of *Withania somnifera* extract increased the bone marrow cellularity and the number of α-esterase positive cells in the bone marrow of CTX treated animals, compared to the CTX alone treated group. Administration of *Withania somnifera* extract was found to significantly reduce leucopenia induced sub lethal dose of gamma radiation. (Meher *et al.,* 2016; Qamar Uddin *et al.,* 2012; Ziauddin *et al.,* 1996).

- In a study, administration of a powdered root extract from *Withania somnifera* to mouse was found to enhance total white blood cell count. In addition, this extract inhibited delayed-type hypersensitivity reactions and enhanced phagocytic activity of macrophages when compared to a control group. (Verma & Kumar, 2011)

- In another study, the efficacy of *Withania somnifera* on immunomodulation was tested in experimental azoxymethane induced colon cancer in mice. Azoxymethane (15 mg/kg) was injected intraperitoneally once a week for 28 days. The colon cancer was confirmed by the appearance of aberrant crypt foci (ACF) in the colons of the experimental mice. The progression in colon tumor development was correlated with the appearance of the histological biomarker and ACF. Animals were treated with 400 mg/kg body weight of *Withania somnifera* extract once a week for four weeks orally. After that the animals were sacrificed and analyzed for immunocompetent cells, immune complexes and immunoglobulins. *Withania somnifera* significantly altered the level of leucocytes, lymphocytes, neutrophils, immune complexes and immunoglobulins (Ig) A, G and M. The azoxymethane induced colon cancer and immune dysfunction was better controlled by *Withania somnifera*. These results suggested that the immunomodulatory effects of *Withania somnifera* could be useful in the treatment of colon cancer. (Meher *et al.,* 2016)

- *Withania somnifera* extract reduces the ovalbumin-induced paw edema in mice, almost similar to that of standard drug disodium chromoglycate. It also shows protective effect in cyclophosphamide-induced myelosuppression by significant increase in white blood cell counts and platelet counts in mice. Treatment with extracts counteracted the cyclophosphamide induced immunosuppression by significant increase in hemagglutinating antibody and hemolytic antibody responses towards sheep red blood cells. (John, 2014; Agarwal *et al.,* 1996)

- In a study, BALB/C mice treated with *Withania somnifera* extract showed significant inhibition of carcinogen ochratoxin A- induced suppression of chemotactic activity and productions of IL-1 and TNF-alpha by macrophages. In support to these findings, WS also reported to possess immunopotentiating and myeloprotective effect, which enhances the cytokine production, stem cell proliferation and its differentiation. (John, 2014; Senthilnathan *et al.,* 2006)

- Administration of *Withania somnifera* extract resulted in significant increase of bone marrow cellularity, total WBC count and α-esterase positive cell number. (John, 2014; Abhimanyu *et al.,* 2014)

- *Withania somnifera* extract inhibits delayed type hypersentivity reaction (Mantoux test) and enhances the phagocytic activity of peritoneal macrophages in mice. WS modulates cell mediated immune responses in mice by enhancing the proliferation of lymphocytes, bone marrow cells and thymocytes in responses to mitogens. Glycowithanolides and a mixture of sitoindosides IX and X isolated from WS demonstrated significant immunomodulatory potential in albino mice by showing positive effect on the mobilization and activation of peritoneal macrophages. (John, 2014; Davis *et al.,* 2002)

- *Withania somnifera* has the capacity to potentiate the cellular and humoral immune responses under immunesuppressed conditions, similar to that of levamisole. Oral administration of aqueous fraction of WS extract caused significant increase in the stress-induced depleted T-cell population and increased the expression of Th1 cytokines in chronically stressed mice. (John, 2014; Ghosal *et al.,* 1989)

- A study showed Withaferin A (WA) and Withanolide E (WE) exhibit specific immunosuppressive effect on human B and T lymphocytes and on mice thymocytes. WE shows specific effect on T lymphocytes whereas WA influences both B and T lymphocytes.(John, 2014)

- Oral feeding of standardized aqueous extract of *Withania somnifera* demonstrated immunopotentiation in laboratory animals immunized with DPT vaccine and immunoprotection against intra-cerebral challenge of live B. pertussis cells. It also shows immunoprotection in cancer chemotherapy.(John, 2014)

- Immu-21, a polyherbal formulation of WS is known for its immunomodulatory potential for modulating the proliferative response of splenic leukocytes to T cell and B cell mitogens. Pretreatment with Immu-21 selectively increased the proliferation of splenic leukocyte by B cell mitogen, LPS and cytotoxic activity against K 562 cells in mice. Immu-21 is also reported to show antigenotoxicity as well as inhibition of both classical and non-classical chromosomal aberrations in mice induced by cyclophosphamide. (John, 2014; Iuvone *et al.,* 2003; Khan *et al.,* 2006; Gautam *et al.,* 2004; Diwanay *et al.,* 2004; Jena *et al.,* 2003; Spelman, *et al.,* 2006)

Anti-carcinogenic activity

- *Withania somnifera* is reported to have anti-carcinogenic effect. Research on animal cell cultures has shown that the herb decreases the levels of the nuclear factor kappa B, suppresses the intercellular tumor necrosis factor, and potentiates apoptotic signaling in cancerous cell lines. One of the most exciting of the possible uses of *Asgand* is its capacity to fight cancers by reducing tumor size. To investigate its use in treating various forms of cancer, the anti-tumor effects of *Withania somnifera* have been studied by researchers. In one study, the herb was evaluated for its anti-tumor effect in urethane-induced lung tumors in adult male mice. Following administration of *Asgand* over a period of seven months, the histological appearance of lungs of animals which received the herb was similar to those observed in the lungs of control animals. (Meher *et al.,* 2016; Bhattacharaya *et al.,* 1997b).

- An *in-vitro* study showed withanolides from *Withania somnifera* inhibited growth in human breast, central nervous system, lung, and colon cancer cell lines comparable to doxorubicin. Withaferin A more effectively inhibited growth of breast and colon cancer cell lines than did doxorubicin. These results suggest *Withania somnifera* extracts may prevent or inhibit tumour growth in cancer patients, and suggest a potential for development of new chemotherapeutic agents (Verma & Kumar, 2011; Singh *et al.,* 2011; Sumathi *et al.,* 2007)

Additional activities

- The root of *Withania somnifera* has also been reported to possess anti-inflammatory, hepato-protective, anti-bacterial, psychotropic/anti-anxiety, anti-convulsant, skin care, healthy hair care, anti-peroxidative action, macrophage activating, haemopoitic, anti-biotic, anti-tumor, anti-hyperglycemic, morphine tolerance & dependence-inhibiting, cardio-protective, hypo-lipidemic and anti-atherogenic activities. (Qamar Uddin *et al.,* 2012; Meher *et al.,* 2016)

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Azārāqī
(Seed)
Strychnos nux-vomica L.

Introduction

The drug *Azārāqī* consists of dried seed of *Strychnos nux-vomica* L. (Family-Loganiaceae). The tree is found in tropical India upto 1200 m, commonly in Tamilnadu. The flowering and fruiting occurs from February to April. (Anonymous, 2007b)

Fig. *Azārāqī*

Vernacular Names

English: Nux vomica; Hindi: *Kuchla*; Urdu: *Kuchla, Azārāqī:* Arabic: *Khāniq al-Kalb, Azārāqī*; Persian: *Fulūs Māhī*, *Ḥabb al-ghurāb.* (Khān, 2012; Ibn Sīnā, 1987; Ghani, YNM; Anonymous, 2007b; *Kabīruddīn*, 2000)

Temperament

Ḥār (Hot)[3] *Yābis* (Dry)[3]

(Khān, 2012; Ibn Sīnā, 1987; Ghani, YNM; *Kabīruddīn*, 2000)

Chemical Constituents

Alkaloids, iridoid glycosides, flavonoids, glycosides, triterpinoids, steroids and organic acids; strychnine, brucine, pseudo strychnine, vomicine, icajine, isostrychnine, isobrucine, stryvomitine, novacine, 5 oxobrucine, strychnine-N-oxide, pseudobrucine, 15-hydroxystrychinine, 11-hydroxyl-Icajine, deoxy-isostrychnine chlorom ethochloride etc. (Kalam *et al.,* 2020; Victor *et al.,* 2016)

Pharmacological Actions

- *Muqawwī-i-Aʿṣāb* (Nervine tonic)

- *Muḥarrik-i-Aʿṣāb* (Nervine stimulant)
- *Dafiʿ-i-Amrāḍ ʿAṣbāniya* (Useful in nervine diseases)
- *Musakkin-i-Alam* (Analgesic)
- *Muḥallil* (Resolvent)
- *Munaffith-i-Balgham* (Expectorant)
- *Mukhrij-i-Balgham* (Expellant of phlegm)
- *Muqawwī-i Bāh* (Aphrodisiac)
- *Mushil* (Purgative)
- *Muṣaffī-i-Khūn* (Blood purifier)
- *Dafi'-i-Taʿaffun* (Antiseptic)

(Khān, 2012; Ibn Sīnā, 1987; Anonymous, 2007b; Ghani, YNM; *Kabīruddīn*, 2000; Kalam *et al.*, 2020)

Therapeutic Uses

- *Fālij* (Hemiplegia)
- *Laqwa* (Bell's palsy)
- *Riʿsha* (Tremor)
- *ʿIrq al-Nasā* (Sciatica)
- *Istirkhā-i-Mathana* (Flaccidity of urinary bladder)
- *Waja' al-Mafāṣil* (Polyarthritis)
- *Waja' al-Qaṭan* (Lumbago)
- *Ḍuʿf-i-Bāh* (Sexual debility)
- *Ḍuʿf-i-Ishtihā'* (Loss of appetite)
- *Surfa* (Dry cough)
- *Ḍīq al-Nafas* (Asthma)
- (Khān, 2012; Ibn Sīnā, 1987; Anonymous, 2007b; Ghani, YNM; *Kabīruddīn*, 2000; Kalam *et al.*, 2020)

Important Formulations

Habb-i-Azārāqī, Habb-i-Marwārīd, Maʿjūn Azārāqī, Maʿjūn Lanā, Raughan-i- Azārāqī (Anonymous, 2007b)

Pharmacological / Clinical studies (evidence based)

Anti-oxidant and anti-inflammatory activity

- Anti-oxidant and anti-inflammatory activity of *Strychnos nuxvomica* has been evaluated by Savita (2009) in albino rat model. Paw edema was induced in foster albino rats by alcohol extract of the *Strychnos nuxvomica*. Acute and chronic inflammation models were used to evaluate the anti-inflammatory activity (*in-vivo*). In acute model carrageenan was used to induce inflammation in rat hind paw and cotton-pellet induced granuloma method was used for chronic inflammation model. SGOT and SGPT were monitored. After proper studies and experiments, it was indicated that *Strychnos nuxvomica* possess potent anti-inflammatory activity with no detectable adverse effect. The results obtained confirmed the use of *Strychnos nuxvomica* traditionally for the treatment of Rheumatism and other inflammatory conditions. (Savita *et al.,* 2009)

Anti-amnesic activity

- In an experimental study, *Strychnos nuxvomica* extract inhibited acetylcholinesterase activity in the hippocampus and frontal cortex. These findings clearly suggest that, loganine possesses anti-amnesic activity that may hold significant therapeutic value in alleviating certain memory impairment observed in Alzheimer's disease. (Kalam *et al.,* 2020; Victor *et al.,* 2016)

Anti-convulsion effect

- In a research study, it was reported that ethanolic extract of *Strychnos nuxvomica* seeds reduced spontaneous motor activity and inhibited catalepsy. The seeds processed in milk exhibited marked inhibition of pentylenetetrazol (PTZ) induced convulsions and maximum potentiation of hypnosis, and were the safest LD50. (Victor *et al.,* 2016)

Anti-tumor activity

- A large number of studies have proved that brucine can significantly inhibit several tumor cells through different mechanisms.(Agrawal *et al.,* 2011; Guo *et al.,* 2018; Qin *et al.,* 2018; Ren *et al.,* 2019)

- **Breast Cancer:** Brucine could inhibit the bone metastasis of breast cancer by regulating the expression of bone metastasis-related factors such as matrix

metallopeptidase 2 (MMP-2), chemokine (C-X-C motif) receptor (CXCR4), receptor of NF-kB ligand (RANKL), and osteoclastogenesis inhibitory factor (OPG). (Serasanambati *et al.,* 2015)

- Xu et al. also found that in the co-culture system of triple negative breast cancer cells MDA-MB-231 and murine osteoblasts MC3T3-E1, brucine could indirectly regulate osteoclasts by regulating the expression and secretion of OPG and RANKL, thus inhibiting osteoclast differentiation and bone absorption (Xu *et al.,* 2019). Therefore, brucine can inhibit bone metastasis of MDA-MB-231 by regulating OPG/RANKL/RANK signal pathway. By observing the effect of brucine on MDA-MB-231 and Hs578-T cell lines, as well as the expression of epithelial-tomesenchymal transition (EMT) markers and matrix metalloproteinase (MMPs), studies found that the ability of migration, invasion or adhesion of MDA-MB-231, and Hs578- T cells decreased in a dose-dependent manner when treated with brucine (Li *et al.,* 2018). These results proved the inhibitory effects of brucine on the bone metastasis of breast cancer. Moreover, brucine also could induce MCF-7 death in G2 phase and inhibit the expression of NF-kB subunit (p65) when used alone or in combination with gemcitabine (Serasanambati *et al.,* 2015).

- **Liver Cancer:** At present, brucine has been extensively studied in the treatment of hepatocellular carcinoma. Brucine inhibited the proliferation of HepG2 cells *in-vitro* in a time- and dose-dependent manner. The mechanism might be that brucine first activated MAP kinase kinase-7 (MKK7) gene, and then the MKK7 kinase activated the pathway mediated by c-Jun N-terminal kinase (JNK) gene to induce apoptosis (Liang *et al.,* 2017). Brucine continuously down regulated the expression level of HIF-1 response gene *in-vivo* (Shu *et al.,* 2013).

- Brucine could also inhibit the proliferation of HepG2 cells by inducing cell contraction, vesicle formation, and apoptotic body formation. At the same time, brucine significantly reduced the expression of cyclooxygenase-2 (COX-2) in HepG2 cells, but increased the expression of Caspase-3 and the activity of Caspase-3-like protease (Deng *et al.,* 2006 a). Hematological Tumor Brucine also has certain inhibitory effect on hematological tumors. Xin et al. 2014 showed that brucine could inhibit the human monocytic leukemia cell line THP-1 cell growth in concentration- and time-dependent manners at the range of 50 to 400 ug/ml. Meanwhile, the expression of B cell lymphoma/

lewkmia-2 (Bcl-2) gene was decreased while the expression of Bcl-2 associated protein (Bax) gene increased (Xin *et al.,* 2014). Through regulating Bax/Bcl-2 balance and activating endogenous mitochondrial pathway, brucine couldalso induce the apoptosis of human chronic myeloid leukemia cell line KCL-22 in the concentration range of 50-400 ug/ml (Han *et al.,* 2016).

- **Colorectal Cancer:** It was showed that brucine was involved in the regulation of Wnt/b-catenin signaling pathway to inhibit the growth and migration of colorectal cancer cells LoVo *in-vitro* and *in-vivo* (Shi *et al.,* 2018). Moreover, the inhibition of brucine on colon cancer proliferation was related to Wnt/ b-catenin signaling pathway, in which the expression of dickkopf-related protein 1 (DKK1) increased significantly, while the expression of b-catenin decreased (Ren *et al.,* 2019).

- Brucine could also inhibited the secretion of VEGF and the expression of mammalian target of rapamycin (mTOR) of Lovo cells, down-regulated the mRNA and phosphorylation protein expression of kinase insert domain receptor (KDR), protein kinase C a (PKCa), phospholipase C-g (PLCg), and v-raf-1 murine leukemia viral oncogene homolog 1 (RAF1), suggesting that brucine has the effect of inhibiting the angiogenesis by mediating the KDR signal pathway (Luo *et al.,* 2013). Brucine might inhibit the activation of signal transducer and activator of transcription (STAT3) phosphorylation in IL-6/ STAT3 pathway to exert an antitumor effect on SW480 cells *in-vitro* . Meanwhile, brucine could induce apoptosis of Lovo cells in a dose-dependent manner by up-regulating Bax and Bcl-2, but down-regulating extracellular signal-regulated kinase 1/2 (ERK1/2), p38 and Akt protein phosphorylation (Zheng *et al.,* 2013).

- **Other Cancer:** In addition, brucine could significantly inhibit the proliferation of lung cancer cellA549 and induce apoptosis in a timedependent manner by inhibiting the expression of COX-2 and releasing prostaglandin E2(PGE2) (Zhu *et al.,* 2012). Brucine could also inhibit the proliferation of human lung cancer cell line PC-9 mainly by blocking the cell cycle at G0/G1 via downregulating the expression of Cyclin D1, Cyclin E (Li *et al.,* 2014).

- When concentration of brucine was no more than 0.4 mg/ml, it might induce apoptosis of myeloma cells U266, and the effect of brucine on apoptosis was dose-dependent and timedependent. RT-PCR was used to detect the changes of c-Jun expression after treatment with brucine or brucine combined with

JNK specific inhibitor SP600125. It was found that brucine induced apoptosis of U266 cells through c-Jun phosphorylation. Therefore, brucine can induce apoptosis of U266 through JNK signaling pathway and c-Jun phosphorylation (Ma *et al.,* 2013). Furthermore, experiments showed that brucine could reduce the expression of Bcl-2 and COX-2 in U251 glioma cells, up-regulate the expression of Bax, reduce the survival rate of glioma cells, and inhibit the growth of the xenografts *in-vivo* (Wang *et al.,* 2015).

- Brucine could inhibit the growth of transplanted human gastric cancer cell line SGC-7901 and improve the weight loss of transplanted tumor in nude mice (Zhao *et al.,* 2012).

- Agrawal et al. (2011) injected EAC cells into mice peritoneum to form ascites tumors, then treated with brucine at different doses. They found that brucine could induce anti-ascites tumor activity in a time-dose-dependent manner by reducing intraperitoneal angiogenesis and micro-vessel density *in-vivo*. (Lu Lu *et al.,* 2020; Qin *et al.,* 2011; Deng *et al.,* 2005; Deng *et al.,* 2006a; Deng *et al.,* 2006b)

Additional activities

- The seed of *Strychnos nux-vomica* has also been reported to possess anti-diabetic, anti-convulsant, analgesic, anti-inflammatory, anti-bacterial, anti-tumor and anti-ulcer activities. (Kalam et al., 2020)

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Bādām Shīrīn
(Seed)
Prunus amygdalus Batsch.

Introduction

The drug *Bādām Shīrīn* consists of seed of *Prunus amygdalus* Batsch. Syn. *Prunus dulcis* (Mill.) D.A.Webb (Family-Rosaceae). The middle sized tree distributed commonly in Europe and Central Asia. In India, it is cultivated in Kashmir and Himachal Pradesh. It occurs throughout the year, flowering takes place in the month of March whereas fruits set from April to August. (Anonymous, 2007b)

Fig. *Bādām Shīrīn*

Vernacular Names

English: Almond; Hindi: *Badām*; Urdu: *Bādām Shīrīn*; Arabic: *Al-Lawz al-Ḥulw*; Persian: *Bādām Shīrīn*. (Khān, 2012; Ibn Sīnā, 1987; *Ibn Baytār*, 2003; Ghani, YNM; Anonymous, 2007b)

Temperament

Ḥār (Hot)[1] *Raṭb* (Moist)[1] (Khān, 2012; Ibn Sīnā, 1987; Anonymous, 2007b)

Chemical Constituents

It contains protein, fat, carbohydrates, calcium, oxalic acid, phosphorous, iron, thiamine, nicotinic acid, riboflavin, folic acid, sodium, potassium, magnesium, copper, sulphur, chlorine, and iodine. Almond is good source of vitamin E, MUFA, PUFA, and arginine. The active constituents of almonds are globulins such as amandine and albumin; amino acids such as arginine, histidine, lysine, phenylalanine, leucine, valine, tryptophan, methionine and cystinen. The oil has been estimated to consist principally of diolein and triolein. Almond contains approximately 49% oil, of which 62% is monounsaturated oleic acid (omega 9 fatty

acid), 24% is linoleic acid (a poly unsaturated omega 6 essential fatty acid), and 6% is palmitic acid (saturated fatty acid). Various phenolic compounds have been extracted from almond byproducts which were identified as 3'Omethylquercetin, 3Oβ D-glucopyranoside, 3'Omethylquercetin 3Oβ Dgalactopyranoside, 3'Omethylquercetin, 3Oα Lrhamnopyranosyl (1→6) βDglucopyranoside, catechin, protocatechuic acid, vanillic acid, and phydroxybenzoic acid. Four different flavonol glycosides—isorhamnetin, rutinoside, isorhamnetin glucoside, kaempferol, rutinoside, and kaempferol glucoside have been reported in almond seed coats. (Masihuddin *et al.,* 2018; Anonymous, 2007b; Abdullah *et al.,* 2017)

Pharmacological Actions

- *Mu'mmir* (Longevity promoting agent)
- *Muqawwī-i-Ḥarārat Gharīziyya* (Tonic for innate heat)
- *Muqawwī-i-Dimāgh* (Brain tonic)
- *Musammin-i-Badan* (Body weight enhancer)
- *Muqawwī-i-Bāh* (Aphrodisiac)
- *Muwallid-i-Manī* (Spermatogenic)
- *Mulayyin* (Laxative)
- *Mulaṭṭif* (Demulscent)
- *Mufattiḥ-i-Sudad* (Deobstruent)
- *Musakkin* (Analgesic)
- *Kāsir-i-Riyāḥ* (Carminative)

  (Khān, 2012; Ibn Sīnā, 1987; *Ibn Baytār*, 2003; *Al-Harawi, 2002;* Ghani, YNM; Anonymous, 2007b; Abdullah *et al.,* 2017)

Therapeutic Uses

- *Ḍu'f-i-Ḥarārat Gharīziyya* (Innate heat insufficiency)
- *Ḍu'f-i-Dimāgh* (Cerebrasthenia)
- *Ḍu'f-i-'Ām* (General debility)
- *Ḍu'f-i-Bāh* (Sexual debility)
- *Qabḍ* (Constipation)
- *Su'āl* (Cough)
- *Sudad-i- Kabid* (Obstructions of liver)

(Khān, 2012; Ibn Sīnā, 1987; *Ibn Baytār*, 2003; *Al-Harawi, 2002;* Ghani, YNM; Anonymous, 2007b; Abdullah *et al.,* 2017)

Important Formulations

Rawghan Bādām Shirīn, Lubūb Kabīr, Lubūb Ṣaghīr, Banādiq al-Buzūr, Habb-i-Buḥḥa al-Ṣawt Muzmin, Habb-i- Mushil, Habb-i-Surfā Qawī, La'ūq Bādām, La'ūq Hulbā, La'ūq Zīq al-Nafas, Ma'jūn Mughalliz and Roghan Lubūb Sab'a Bārid. (*Kabīruddīn*, 2000; Anonymous, 2007b; Abdullah *et al.,* 2017)

Pharmacological / Clinical studies (evidence based)

Anti-aging activity

- In a scientific study, skin extract of *Prunus amygdalus* was used in herbal cosmetic formulation and evaluated for the protection of skin from solar ultraviolet induced photo-aging. The skin of treated mice groups showed stronger Anti-oxidant activity by significantly decreased and increased MDA and GSH level respectively as compared to irradiated control groups. (Abdullah *et al.,* 2017; Sachdeva *et al.,* 2011)

Anti-oxidant activity

- Many studies have been conducted on Anti-oxidant effect of fruit and various part of *Prunus amygdalus*. In a study concluded that methanolic extract of almond possesses anti-Anti-oxidant and anti-radical activities and their phenolic extract may be helpful in preventing or slowing the growth of various oxidative stress related diseases. (Esfahlan *et al.,* 2010)

- In another study conducted by Sang *et al.,* nine phenolic compounds were isolated from the ethyl acetate and nbutanol fractions of almond (*Prunus amygdalus*) skins. 2, 2D iphenyl1picrylhydrazyl (DPPH) free radical scavenging activities were determined. Some Compounds showed very strong DPPH radical scavenging activity. (Sang *et al.,* 2002)

Immunomodulatory activity

- Adriana Arena, *et al.,* evaluated in their study that with almonds, high levels of cytokine production were observed i.e. interferon-α (INF-α), interleukins (IL-12), INF-gamma and tumour necrosis factor (TNF-α). Their data suggested that almonds improved the immune surveillance of the peripheral blood

mono nuclear cells towards viral infections. Almonds also were found to induce a significant decrease in the Herpes simplex virus (HSV-2) replication. (Abdullah *et al.,* 2017)

Memory enhancing activity

- A study was carried out in scopolamine induced amnesia in rats. *Prunus amygdalus* which were administered in different doses in the respective groups significantly reversed scopolamine induced amnesia, as evidenced by a decrease in the transfer latency in the elevated plus maze (EPM) task and step down latency in the passive avoidance task. *Prunus amygdalus* also exhibited a remarkable cholesterol and triglyceride lowering property and slight increase in glucose levels in the present study. (Kulkarni *et al.,* 2010)

- In another study, Nootropic effects of almond were evaluated in rat models wherein almond paste was given orally with the help of feeding tube for 28 days. Memory function in rats was assessed by Elevated plus Maze (EPM) and Radial Arm Maze (RAM). Brain tryptophan, 5HT and 5HIAA were estimated at the end of the treatment by HPLCEC method. It was found that a significant improvement in learning and memory of almond treated rats was reported compared to control. (Haider *et al.,* 2012)

Additional activities

- The seed of *Prunus amygdalus* has also been reported to possess anti-hyperlipidimic, neuro-protective, anti-depressant, hypoglycemic, anti-stress, anti-cholinestrase, hepato-protective, anxiolytic, anti-fungal and anti-bacterial activities.(Masihuddin *et al.,* 2018; Abdullah *et al.,* 2017).

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Bādranjboya
(Leaf)
Nepeta hindostana (B. Heyne ex Roth) Haines

Introduction

The drug of *Bādranjboya* consists of dried leaves of *Nepeta hindostana* (B. Heyne ex Roth) Haines (Family- Lamiaceae). The plant is found in hilly parts of Punjab, Bengal, Bihar, Kumaon, Rajasthan, Deccan and Konkan. It occurs during winter season. (Anonymous, 2007b).

Fig. *Bādranjboya*

Vernacular Names

English: Catmint (Catnip, Catnep, Mountain Balm); Urdu: *Bādranjboya*; Hindi: *Billi Lawṯan*; Arabic: *Bādranjboya*, *Muffariḥ al-Qalb*, *Habaq al-Rayhānī*; Persian: *Bādranjboya*, *Bādrangboya*. (Khān, 2012; Ibn Sīnā, 1987; *Ibn Baytār*, 1985; Ghani, YNM; Anonymous, 2007b)

Temperament

Ḥār (Hot)[2] *Yābis* (Dry)[2] (Khān, 2012; Ibn Sīnā, 1987; Anonymous, 2007b)

Chemical Constituents

Pandey et al. (2015) revealed the GC-MS analysis of *Nepeta hindostana* oil and recognition of thirty three compounds, representing 91.0% (area percent) of the total oil composition. Oil was rich in sesquiterpene hydrocarbons, exhibited higher percentage of (E) *β*- farnesene (10.4%) followed by ageratochromene (9.7%), spiro [4.5] decan-1-one, 6-hydroxy (9.5%), *β*-caryophyllene (8.6%) and spiro [4.5] decan-6-ol, 6-methyl (8.2%). At 60 µL, oil showed 80.7% Anti-oxidant activity by *β*-carotene bioassay (IC50 = 8 µL) and 73.4% by DPPH free radical scavenging bioassay (IC50 = 8.5 µL). Additionally, presence of (E)-*β*- farnesene,

α-pinene, β-pinene, limonene, linalool and caryophyllene oxide in *N. hindostana* oil corroborate with essential oil composition of *N. camphorate* (Kalpoutzakis *et al.*, 2001).

The major compounds in essential oils of *Nepeta hindostana* were identified as β-sesquiphellandrene, cadina-1, 4-diene, α-cadinene, (*E*)-caryophyllene, α-humulene and β-bisabolene. At 100 µg/mL concentration, leaves essential oil showed strong 2, 2-diphenyl-1-picryl-hydrazyl-hydrate free radical scavenging activity with the IC_{50} 2.8 µg/mL and 34.0% by β-carotene bleaching assay (Siddique *et al.*, 2018).

Pharmacological Actions

- *Muqawwī-i-Ḥarārat Gharīziyya* (Tonic for innate heat)
- *Muqawwī-i-Qalb* (Cardiotonic)
- *Mufarriḥ* (Exhilarant)
- *Munḍij-i-Sawdā'* (Concoctive of black bile)
- *Muṣaffī-i-Dam* (Blood purifier)
- *Muḥallil-i-Waram* (Anti-inflammatory)
- *Musakkin* ((Soothing agent)

(Khān, 2012; Ibn Sīnā, 1987; *Ibn Baytār*, 1985; Al-Harawi, 2002; Ghani, YNM; Anonymous, 2007b; Kabīruddīn, 2000)

Therapeutic Uses

- *Ḍu'f-i-Ḥarārat Gharīziyya* (Innate heat insufficiency)
- *Ḍu'f-i-Qalb* (Cardiac insufficiency)
- *Khafaqān* (Palpitation)
- *Ṣar'* (Epilepsy)
- *Laqwa* (Bell's palsy)
- *Fālij* (Hemiplegia)
- *Waja' al-Mafāṣil* (Polyarthritis)

(Khān, 2012; Ibn Sīnā, 1987; *Ibn Baytār*, 1985; Al-Harawi, 2002; Ghani, YNM; Anonymous, 2007b; Kabīruddīn, 2000)

Important Formulation

Ma'jūn-i-Khadar (Anonymous, 2007b)

Pharmacological / Clinical studies (evidence based)

Anti-oxidant activity

- It is well-known that the anti-oxidant activity of plant essential oils containing terpenes is due to their capacity to be donors of hydrogen atoms or electrons and to capture the free radicals. DPPH analysis is one of the tests, used to prove the ability of the components of the *N. hindostana* oil to act as donors of hydrogen atoms. The oil of *N. hindostana* showed a significant effect in inhibiting free radicals produced by DPPH, reaching up to 73.4% at 60 µL and IC50 value was found as 8.5 µL. This capability was decreased with the decrease of oil concentration 40 (72.82), 20 (64.09), 10 (52.46) and 5 µL (32.79%). These findings suggested that oil was able to reduce the stable free radical 2, 2-diphenyl-1-picrylhydrazyl to the transparent diphenyl-picryl-hydrazine. In β-carotene bleaching bioassay, linoleic acid produces hydroperoxides as free radicals during incubation at 50 °C. The presence of Anti-oxidants in the essential oils minimizes the oxidation of β-carotene by hydroperoxides. Thus, the degradation rate of β-carotene depends upon the Anti-oxidant activity of the oils which can hinder the extent of β-carotene bleaching by acting on the lipid free radicals form in the system (Younes and Siegers, 1981; Pandey *et al.,* 2015).

- The essential oils of *Nepeta hindostana* were characterized by GC-FID and GC/MS and evaluated for their anti-oxidant and anti-microbial efficacy. The major components of the essential oil were sesquiterpene hydrocarbons (77.2, 80.5, 62.5, 77.8%), oxygenated sesquiterpenes (10.5, 9.2, 20.6, 9.2%) and oxygenated monoterpenes (5.3, 4.2, 2.5, 3.6%) in leaves, stem, flowers and aerial part, respectively. (Siddique et al. (2018)

Cardio-protective & dyslipidemic activity

- A study assessed the lipid lowering effect of *Nepeta hindostana* extracts in experimentally induced dyslipidemia in rats. The dyslipidaemia was induced by administration of intraperitoneal (i.p.) injection of triton WR 1339 (400 mg/kg) (acute study) and fed high cholesterol diet for 21 days (sub-acute study). The results showed that Methanolic extract (400 mg/kg) have lowest

atherogenic index and maximum % protection in triton and cholesterol diet induced dyslipidaemia. Lipid levels were significantly attenuated by different doses of extracts. The histology of blood vessels also proved the effectiveness of both extracts (at dose 400 mg/kg) in case of dyslipidaemia induced by cholesterol diet. Methanolic extract was found more effective than aqueous extract. The results also indicated to Anti-dyslipidemic effect of the plant extracts meditated through inhibition of biosynthesis, absorption and secretion of lipids. This may possibly and partly be due to the presence of Anti-oxidant constituents in this plant. Therefore, the study rationalizes the medicinal use of *Nepeta hindostana* in dyslipidemia and cardiovascular diseases. (Devi and Singh, 2017)

Additional activities

- The leaf of *Nepeta hindostana* has also been reported to possess anti-diabetic, anti-platelet aggregation, anti-inflammatory, cardio-protective, calcium channel antagonistic, anti-viral and anti-spasmodic activities. (Basar and Zaman, 2013).

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Balela
(Pericarp of Fruit)
Terminalia bellirica (Gaertn.) Roxb.

Introduction

The drug of *Balela* consists of pericarp of dried ripe fruit of *Terminalia bellirica* (Gaertn.) Roxb. (Family-*Combretaceae*). The drug yielding plant is a large deciduous tree, 10-12 m or more high, commonly found in plain and forests upto 900 m. Fruits ripen in November. (Anonymous, 2007a)

Fig. ***Balela***

Vernacular Names

English: Beleric, Bastard Myrobalan; Hindi: *Bahera, Bhaira*, *Bhera*, *Buhura*; Urdu: *Balela*; Arabic: *Balīlaj*; Persian: *Balayla*, *Balīlā.* (Khān, 2012; Ibn Sīnā, 1987; *Ibn Baytār*, 1985; Anonymous, 2007a)

Temperament

Bārid[2] (Cold) *Yābis*[2] (Dry) (Khān, 2012; Ibn Sīnā, 1987; *Kabīruddīn*, 2000)

Chemical Constituents

Its principle phytoconstituents are beta-sitosterol, gallic acid, ellagic acid, ethyl gallate, galloyl glucose, chebulagic acid, bellaricanin. Four lignans including termilignan, thannilignan, hydroxy-3', 4'-(methylenedioxy) flavan, and anolignan-B have been found.It also contains terpenoids (belleric acid and chebulagic acid), saponin (bellericoside and bellericanin) (Meena et al., 2010; Sharma, 2012) and tannins (23.60%-37.36%), which are composed of chebulinic acid, chebulagic acid, 1, 3, 6-trigalloylglucose and 1, 2, 3, 4, 6- pentagalloylglucose, corilagin, andglucogallin etc. (Saxena, et al., 2013; Gangadhar et al., 2011; Alam and Ansari, 2019; Anonymous, 2007a)

Pharmacological Actions

- *Muqawwī-i-Dimāgh* (Brain tonic)
- *Muqawwī-i-Miʻda* (Stomachic)
- *Muqawwī-i-Baṣar* (Eye tonic)
- *Mushtahī* (Appetizer)
- *Qābiḍ-i-Amʻā'* (Constipative)
- *Munaffith-i-Balgham* (Expectorant)
- *Mukhrij-i-Balgham* (Expellant of phlegm)

(Khān, 2012; Ibn Sīnā, 1987; *Ibn Baytār*, 1985; Anonymous, 2007a; *Kabīruddīn*, 2000)

Therapeutic Uses

- *Ḍuʻf-i-Dimāgh* (Cerebrasthenia)
- *Ḍuʻf-i-Miʻda* (Gastric debility)
- *Ḍuʻf-i-Baṣār* (Poor eyesight)
- *Ḍuʻf-i-Amʻā'* (Enteropathy)
- *Ishāl* (Diarrhoea)
- *Suʻāl* (Cough)
- *Ḍīq al-Nafas* (Bronchial asthma)

(Khān, 2012; Ibn Sīnā, 1987; *Ibn Baytār*, 1985; Anonymous, 2007a; *Kabīruddīn*, 2000)

Important Formulations

Maʻjūn-e-Jograj Gūgal, Itrīfal Muqil, Itrīfal Ṣaghīr, Itrīfal Ustūkhudūs, Maʻjūn Fanjnosh. (*Kabīruddīn*, 2000; Anonymous, 2007a)

Pharmacological / Clinical studies (evidence based)

Anti-oxidant activity

- Free radical scavenging activity and anti-oxidant potential of acetone extract of *T. bellerica* fruit was determined by in-vitro assays. Acetone extract was subjected to partitioning with ethyl acetate and water. Ethyl acetate fraction was found to be more effective as compared to crude acetone extracts in all

anti-oxidant assays i.e., DPPH, β-carotene bleaching inhibition and reducing power whereas for chelating ability on Fe^{++} ion, crude acetone extract showed higher activity. It was concluded that polyphenolic rich fractions were more effective than the crude extract. (Kumari *et al.,* 2017; Guleria *et al.,* 2010)

Immunomodulatory effect

- Methanolic extract of *T. bellerica* fruit showed stimulation of morphage phagocytosis through the production of superoxide and acid phosphatase. It also showed activation in lymphocyte proliferation assay with phytohemagglutinin, concanavalin A, lipopolysaccharide and pokeweed nitrogen. However, at lower concentrations, it showed suppressant activity with concanavalin A and pokeweed nitrogen. The results indicated that T-lymphocyte proliferation effect of extract occurred through the same mechanism exhibited by phyto-hemagglutinin, concanavalin A whereas Blymphocyte proliferation effect occurred through T-cell independent and T-cell dependent mechanisms, similar as lipopolysaccharide and pokeweed mitogen. Hence, the mouse immune system, specifically in-vitro cellular and humoral immune response was affected by methanol extract of *T. bellerica* making it useful for the treatment of human immune mediated diseases. (Manjunatha *et al.,* 2011; Kumari *et al.,* 2017)

Anti-Alzheimer's activity

- A comparative study was carried out using methanol extract of *Triphala* and its three major ingredients i.e., fruits of *Terminalia chebula*, *Terminalia bellerica* and *Emblica officinalis* for their acetylcholinestrase inhibitory properties. All extract showed inhibition of enzyme activity in a dose dependent manner. Phytoconstituents like gallic acid, ellagic acid and phenolic acids present in fruit of all three plants inhibited acetylcholinestrase. Being, acetylcholinestrase inhibitor, it could be used for symptomatic treatment of Alzheimer's diseases. (Kumari *et al.,* 2017; Nag, 2011)

Anti-depressant activity

- An investigation was carried out to study the anti-depressant activity of aqueous and ethanolic extracts of *Terminalia bellerica* fruits in Swiss young male albino mice using forced swim test (FST) and tail suspension test

(TST). Both the extracts were administered orally for 10 successive days. Ethanol extract and aqueous extract showed significant reduction in dose dependent manner in the mobility time of mice in FST as well as TST whereas there was no significant effect was observed on locomotor activity of mice. Activities of both the extract were found to be similar as imipramine and fluoxetine. Both the extracts showed reversed reserpine-induced extension of immobility period of mice in FST and TST. The aqueous and ethanolic extract induced Anti-depressant like effect in TST was significantly alternated by prazosin, sulpride and p-chlorophenylalanine. Hence, both the extracts exhibited significant anti-depressant-like effect in mice by interaction with adrenergic, dopaminergic and serotonergic systems. (Dhingra *et al.,* 2007; Kumari *et al,* 2017).

Anti-cancer activity

- A comparative study was performed to determine *in-vitro* anti-cancer and Anti-oxidant effects as well as total phenolic contents of five different extracts of *Terminalia bellerica* leaves i.e., methanol, aqueous methanol, ethyl acetate, chloroform and pet ether. A moderate correlation was observed between the total phenolic content of all the extracts whereas the anti-oxidant activity and the total phenol content increased with increase in polarity. Pet. ether extract showed most potent anti-cancer activities followed by chloroform against all cell lines namely ovarian carcinoma, liver carcinoma, breast carcinoma, HeLa contaminant, cervical carcinoma, breast carcinoma, cervical carcinoma, CNS-human glioblastoma, non-small lung cancer, colon adenocarcinoma, fibrosarcoma, leukemia and melanoma. Other extracts showed potent anti-cancer activity against leukemia and melanoma. According to results, petroleum ether extract exhibited the highest anti-cancer activity which would be used for further purification to isolate compound(s) responsible for the activities (Hanem *et al.,* 2015; Kumari *et al.,* 2017)

Additional activities

- The pericarp of *Terminalia bellerica* has also been reported to possess analgesic, anti-diabetic, anti-diarrhoeal, anti-fertility, anti-androgenic, anti-dyslipidaemic, anti-obesity, anti-fungal, anti-helminthic, anti-hypertensive, anti-microbial, anti-HIV, anti-spasmodic, bronchodialatory, anti-thrombotic

& thrombolytic, anti-ulcer, hepato-protective, wound healing and anti-atherogenic activities. (Alam and Ansari, 2019; Kumari *et al,* 2017; Tanaka *et al.,* 2016; Ahmad and Mishra, 2017; Pragya M *et al.,* 2016)

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Bazr-ul-Banj
(Seed)
Hyoscyamus niger L.

Introduction

The drug of *Bazr-ul-Banj* consists of the seed of *Hyoscyamus niger* L. (Solanaceae); an annual or biennial herb, native to the Mediterranean region and temperate Asia, occurring in Western Himalayas from Kashmir to Kumaon at an altitude of 1600 to 4000 m (Anonymous, 2008)

Fig. Bazr-ul-Banj

Vernacular Names

English: Henbane; Hindi: *Khurāsānī Ajvayan*; Urdu: *Ajwāyin Khurāsānī*; Arabic: *Bazr-ul-Banj* (Khān, 2012; Ghani, YNM; Anonymous, 2008)

Temperament

Bārid (Cold)[3] *Yābis* (Dry)[3] (Khān, 2012; Ghani, YNM; *Kabīruddīn*, 2000)

Chemical Constituents

Alkaloids - (hyoscyamine, hyoscine, scopolamine, atropine, volatile oil, glycoside, mucilage, albumin, steroidal glycosides (atroposide A, atroposide C and atroposide E), **phenolics** - (vanillic acid, vanillin, pinoresinol, and N trans-feruloyl tyramine), and phytosterols (daucosterol and betasitosterol) (Azhar and Mustehasan, 2020; Anonymous, 2008).

Pharmacological Actions

- *Dāfi'-i-Tashannuj* (Anti-spasmodic/ Anti-convulsant)
- *Mukhaddir* (Anesthetic)

- *Munashshi* (Narcotic)
- *Munawwim* (Hypnotic)
- *Musakkin* (Sedative)
- *Musakkin-i-Alam* (Analgesic)
- *Mushtahī* (Appetizer)
- *Hāḍim* (Digestive)
- *Kāsir-i-Riyāḥ* (Carminative)
- *Dāfi'-i-Ta'affun* (Anti-septic)
- *Qābiḍ* (Constipative)
- *Mudammil* (Cicatrizant)
- *Mujaffif* (Dryness producing drug)

(Khān, 2012; *Kabīruddīn*, 2000; Anonymous, 2008; Ghani, YNM)

Therapeutic Uses

- *Amrāḍ 'Aṣbāniya* (Nervine diseases)
- *Dard wa Alam* (Pain)
- *Sahar* (Insomnia)
- *Junūn* (Mania)
- *Ikhtilāj al-Qalb* (Palpitation)
- *Ḍīq al-Nafas* (Bronchial asthma)
- *Su'āl Yābis* (Dry cough)
- *Waja' al-Mafāṣil* (Polyarthritis)
- *Niqris* (Gout)
- *'Irq al-Nasā* (Sciatica)
- *Amrāḍ-i-Raḥim* (Uterine disorders)

(Khān, 2012; *Kabīruddīn*, 2000; Anonymous, 2008; Ghani, YNM)

Important Formulations

Barsha'shā', La'ūq Bazr-ul-Banj, Banādiqul Buzūr, Tiryāq-i-Nazlā, Qurṣ Mukhaddir, Qurṣ Muthallath, Habb-i-Ri'sha, Qurṣ Khashkhāsh, Habb-i-Aswad, Habb-i-Jiryān , Habb-i- Muqawwī, (Anonymous, 2008; Azhar and Mustehasan, 2020)

Pharmacological/ Clinical studies (evidence based)

Anti-oxidant activity

- Aqueous-methanolic extract of *Hyoscyamus niger*, significantly inhibited monoamine oxidase activity and attenuated 1-methyl-4-phenyl pyridinium (MPP+) - induced hydroxyl radical (OH) generation in isolated mitochondria. (Mohammad *et al.,* 2010; Alghazeer *et al.,* 2012; Sengupta *et al.,* 2011; Azhar and Mustehasan, 2020)

- Aerial parts of *Hyoscyamus niger* extract exhibit DPPH and ferric, reducing Anti-oxidant scavenging properties. (Azhar and Mustehasan, 2020)

- Hexane and water extracts of H. reticulates showed radical scavenging, anti-oxidant capacity, ferric, and cupric reducing powers. (Gunes *et al.,* 2016; Azhar and Mustehasan, 2020)

Anti-depressant activity

- *Hyoscyamus niger* ethanolic extract significantly reduced immobility duration of mice in forced swim test and tail suspension test in higher dose; it also showed anxiolytic activity.It's showed many pharmacological effects included anti-microbial, anti-cancer, analgesic, anti-inflammatory, anti-pyretic, anti-hypertensive, and anti-diarrhoeal activities in different clinical and experimental studies. (Patil *et al.,* 2013; Azhar and Mustehasan, 2020)

Anti-Parkinsonism activity

- Aqueous methanol extracts of *Hyoscyamus niger* seeds significantly attenuated motor disabilities (akinesia, catalepsy, and reduced swim score) and striatal dopamine loss in -methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine treated mice and also against the stereotaxically induced rotenone model of Parkinson's disease in rats due to Anti-oxidant activity. (Khatri *et al.,* 2015; Azhar and Mustehasan, 2020)

Anti-convulsant activity

- Methanolic extract of *Hyoscyamus niger* L. possesses Anti-convulsant activity against picrotoxin-induced seizures in mice by increasing latency and duration of seizure and also delayed the death as compared to control. Alcoholic

seed extract of *Hyoscyamus niger* has markedly alleviated pentylenetetrazol-induced seizure phases in male mice. (Reza *et al.,* 2009; Kiasalari *et al.,* 2010; Azhar and Mustehasan, 2020)

Additional activities

- The seed of Hyoscyamus *niger* has also been reported to possess anti-depressant, anti-diarhoeal, anti-hyperurecemic, anti-microbial, analgesic, anti-spasmodic, cardio-protective, anti-bacterial, anti-pyretic, bronchodilatory, insecticidal, anti-diabetic, anti-hypertensive and anti-inflammatory activities. (Azhar and Mustehasan, 2020).

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Bisbāsa
(Aril)
Myristica fragrans Houtt.

Introduction

The drug *Bisbāsa* consists of dried aril of *Myristica fragrans* Houtt. (Family-Myristicaceae). A medium sized evergreen tree 8-15 m high, native of the East Moluccas. It is cultivated in the Malaya Peninsula and the Malaya Islands. In India, it is found in a few localities, chiefly botanic gardens, Kerala where the climate is sufficiently hot and moist. (Anonymous, 2009)

Fig. *Bisbāsa*

Vernacular Names

English: Mace; Hindi: *Jāvitrī*; Urdu: *Jāvitrī*; Arabic: *Bisbāsa*; Persian: *Charkawn, Bazbāz*. (Khān, 2012; Ibn Sīnā, 1987; *Ibn Baytār*, 1985; Ghani, YNM; Anonymous, 2009)

Temperament

Ḥār (Hot)^2 *Yābis* (Dry)^2 (Khān, 2012; Ibn Sīnā, 1987; *Ibn Baytār*, 1985; *Kabīruddīn*, 2000)

Chemical Constituents

Fats, terpenoids, phenols, alcohol, saponins, resins, starch, carbohydrates, aluminium, strontium, calcium, magnesium, sodium, potassium, sulphate and phosphate. (Anonymous, 2009)

Pharmacological Actions

- *Muqawwī-i-Ḥarārat Gharīziyya* (Tonic for innate heat)

- *Muqawwī-i-Dimāgh* (Brain tonic)
- *Muqawwī-i-Miʻda* (Stomachic)
- *Muqawwī-i-Qalb* (Cardiotonic)
- *Hāḍim* (Digestive)
- *Kāsir-i-Riyāḥ* (Carminative)
- *Muḥallil-i-Waram* (Anti-inflammatory)
- *Mufarriḥ* (Exhilarant)
- *Mufattiḥ* (Deobstruent)
- *Muqawwī-i-Bāh* (Aphrodisiac)
- *Jādhib* (Absorbent)
- *Muqawwī-i-Raḥim* (Uterine tonic)

  (Khān, 2012; Ibn Sīnā, 1987; *Ibn Baytār*, 1985; Al-Harawi, 2002; *Kabīruddīn*, 2000; Ghani, YNM; Anonymous, 2009)

Therapeutic Uses

- *Ḍuʻf-i-Ḥarārat Gharīziyya* (Innate heat insufficiency)
- *Ḍuʻf-i-Dimāgh* (Cerebrasthenia)
- *Ḍuʻf-i-Miʻda* (Gastric debility)
- *Sū'-i-Haḍm* (Indigestion)
- *Nafkh-i-Shikam* (Flatulence)
- *Ḍuʻf-i-Bāh (Sexual debility)*

  (Khān, 2012; Ibn Sīnā, 1987; *Ibn Baytār*, 1985; Al-Harawi, 2002; *Kabīruddīn*, 2000; Ghani, YNM; Anonymous, 2009)

Important Formulations

Anoshdāru, Halwa-i-Baiḍa-i-Murgh, Itrīfal Kabīr, Jawārish Bisbāsa, Jawārish Kundur, Jawārish Narmushk, Jawārish-i-Utraj, Jawārish Zar'ūni Sāda, Lubūb Kabir, Maʻjūn Āarad Khurma, Maʻjūn Balādur, Maʻjūn Band Kushād, Maʻjūn Mulūkī, Maʻjūn Nānkhwāh, Maʻjūne Saʻlab, Mufarrih Sosambari, Raughan Bābūna Qawī, ʻArq Chobchīnī. (Anonymous, 2009)

Pharmacological / Clinical studies (evidence based)

Anti-oxidant activity

- Anti-oxidant properties have been determined by the ferric reducing Anti-oxidant power and trolox equivalent anti-oxidant capacity. Anti-oxidant property of nutmeg is contributed by various phytochemicals, mainly vitamins, carotenoids, terpenoids, alkaloids, flavonoids, lignans, simple phenols and phenolic acids, caffic acid and catechin (Shan 2005; (Tan *et al.,* 2013; Gowri *et al.,* 2008)

Memory enhancing activity

- Parle et al. (2004) have investigated the effect of *M. fragrans* seeds on learning capabilities and memory level in mice. Administration of the n-hexane extract of *M. fragrans* at the lowest dose of 5 mg/kg body weight for 3 successive days significantly improved the learning and memory level of young and aged mice. The extract said to have reversed scopolamine and diazepam induced impairment in learning and memory of young mice. The observed memory enhancing effect of *M. fragrans* may be attributed to a variety of properties (individually or in combination) such as anti-oxidant, anti-inflammatory, or procholinergic activity. (Neeraja and Margaret, 2016)

- The effect of *M. fragrans* extracts, on recovery capability of learning and memory, were studied on aged and young mice against their impairment induced by scopolamine (0.4 mg/kg intraperitoneal) and diazepam (1 mg/kg intraperitoneal). N-hexane extract of *M. fragrans* was given orally for 3 successive days in three doses (5, 10, & 20 mg/kg) and found that the dose of 5 mg/kg p. o. significantly improved the memory and learning of young and aged mice. The mechanism of action was not elicited in these studies, but the authors believed that it is a mechanism based on the proven pro-cholinergic activities, anti-inflammatory and anti-oxidant properties of this plant. (Neeraja and Margaret, 2016).

- Alzheimer's disease is treated on the basis of anticholinesterase inhibition by dropping the cognitive decline caused by reducing cholinergic deficits. In one study, it was found that a hydro-alcoholic extract of Nutmeg did show significant (50%) inhibition of acetylcholinesterase for the treatment of Alzheimer's disease. (Neeraja and Margaret, 2016).

Anti-convulsant activity

- *M. fragrans* hexane extract possesses anti-convulsant activity against the animal models of Grand mal, Petit mal and status epilepticus. Decreased dopaminergic transmission may be partly responsible for its anti-convulsant effect. (Sonavane *et al.*, 2002).

- *M. fragrans* essential oil was also found to possess significant anti-convulsant activity against electroshock induced hind limb tonic extension. It exhibited dose dependent anti-convulsant activity against pentylene tetrazole induced tonic seizures. It delayed the onset of hind limb tonic extensor jerks induced by strychnine. Also, it was anti-convulsant at lower doses, whereas weak proconvulsant at a higher dose against pentylene tetrazole and bicuculline induced clonic seizures. (Wahab *et al.*, 2009).

Anti-obesity activity

- In a study, it was found that tetrahydrofuran (THF) type lignans isolated from *Myristica fragrans* showed an anti-obesity effect in high fed diet (HFD) induced mice due to Adenosine Monophosphate (AMP)-activated protein kinase activation mechanism. The THF prevented the increase in adipose tissue mass, body weight, LDL levels and glucose in THF treated mice as compared to HFD group of mice (Nguyen , 2010)

Anti-cariogenic activity

- In one study, it was found that mace lignan, isolated from a methanolic extract of Nutmeg, had anti-bacterial property and strong inhibitory activity against Streptococcus mutans which is an oral pathogen causing dental caries. Mace lignan, at a concentration of 20µg/ml, completely inactivated *S. mutans* in 1 min. The minimum inhibitory concentration (MIC) of mace lignan was found to be very lower than that of other natural anti-cariogenic agents. Nutmeg can also be used for the treatment of periodontitis, which is an inflammation of supporting structures of teeth, due to its anti-inflammatory and anti-bacterial properties. (Neeraja and Margaret, 2016).

Additional activities

- The aril of *Myristica fragrans* has also been reported to possess anti-microbial, aphrodisiac, anti-inflammatory, anti-diabetic, anti-fungal, hepato-protective,

digestive, insecticidal and cardio-protective activities. (Neeraja and Margaret, 2016).

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Brahmi
(Whole plant)
Bacopa monnieri (L.) Pennell

Introduction

The drug of *Brhami* consists of dried whole plant of *Bacopa monnieri* (Linn.) Pennel. Syn. *Lysimache monnieri* Linn. (Fam. Scrophulariaceae); a glabrous, succulent, small, prostrate or creeping annual herb, found throughout in diameter in wet and damp places. (Anonymous, 2007 d)

Fig. *Brahmi*

Vernacular Names

English: Water hyssop, Indian pennywort, thyme-leafed gratiola, herb of grace, ; Hindi; *Brahmi*; Urdu: *Brahmi* (Ghani, YNM; Anonymous, 2007d; Kabīruddīn, 2000)

Temperament

Ḥār (Hot)^2 *Yābis* (Dry)^2 (Anonymous, 2007d; Ghani, YNM; Kabīruddīn, 2000)

Chemical Constituents

The extract of *B. monnieri* revealed the presence of tannins, flavonoids, glycosides, terpenoids, saponins, bacosides, bacopasides, bacopasaponins, and steroids. The major Chemical Constituents isolated and characterized from *B. monnieri* are dammaranes of triterpenoid saponins with pseudo-jujubogenin glycosides or jujubogenin glycosides.

- The pharmacological effects of *B. monnieri* are attributed to the presence of a number of biologically active compounds, including alkaloids, saponins and sterols. The compounds responsible for the memory enhancing effects of

Bacopa monnieri are triterpenoidsaponins called "bacosides". (Rastogi, 1990; Chandel et.al., 1977; Rastogi et.al, .1974; Garay et.al., 1996;)

- The major chemical entity shown to be responsible for neuropharmacological effect of *B. monnieri* is bacoside A, assigned as 3-(a-L-arabinopyranosyl)-O-b-D-glucopyranoside-10, 20--dihydroxy-16-keto-dammar-24-ene. Bacoside A usually co-occurs with bacoside B; the latter differing only in optical rotation. The isolation of D-mannitol and a saponin, hersaponin and potassium salts was also reported on acid hydrolysis. Bacosides yield a mixture of aglycones, bacogenin A1, A2, A3, which are artefacts, and two genuine sapogenins, jujubogenin and pseudo-jujubogenin and bacogenin A4, identified as ebelin lactone pseudo-jujubogenin, were iso-lated. (Singh, 2012; Kulshreshtha et.al., 1973)

- Successively, a minor saponinbacoside A1 and a new triperpenoidsaponin, bacoside A3, were isolated. [.Three new dammarane-type triterpenoidsaponins of biological interest, bacopasaponins A, B and C, isolated and identified as 3-O-α-L-arabinopyranosyl- 20-O-α-Larabinopyrasonyl-jujubogenin, 3-O-[α-Larabinofuranosyl-(1➔2)- α-L-arabinopyranosyl] pseudojujubogenin and 3-O-β- D- glucopyranosyl (1➔3)-{α-L-arabinofuranosyl-(1➔2)}-α-Larabinopyrasonyl] pseudojujubogenin and also a new dammarane-type pseudojujubogenin glycoside, bacopasaponin D, 3-O-[α-L-arabinofuranosyl-(1➔2)-β-D- glucopiranosyl] pseu-dojujubogenin were identified by spectroscopic and chemical transformation methods. In view of the increasing interest in this plant, yet two new pseudojujubogenin glycosides designated as bacopaside I and II were isolated from glycosidic fraction of the methanol. Subsequently, three new saponins from BM, designated as bacopasides III, IV and V with structures 3-O α-L- arabinofura-nosyl-(1➔2)-β-D-glucopyranosyljujubogenin, 3- O-β-D-glucopyranosyl- (1➔3)-α-L- arabinopyranosyljujuboge-nin, 3-O-β-D-glucopyranosyl-(1➔3)-α-Larabinofuranosyl pseudojujubogenin were isolated. In addition, the isolation of three new phenylethnoid glycosides, viz. monnierasides I-III along with the known analogue plantai-noside B was reported from the glycosidic fraction of BM.(Singh et.al., 2012; Sivaramakrishna et.al., 2005; Chatterji et.al., 1965)

- An isolation of a new saponin, a juju-bogenin, named bacopasaponin G, and a new glycoside, phenylethyl alcohol was also reported. The drug is

characteristically designated on the basis of its total bacosides content which is tetra cyclic triterpenoidsaponins. These steroidal saponins called Bacoside A & Bacoside B are considered Bacopa's most therapeutic constituents, bacoside A levorotatory, and, bacoside B dextrorotatory, triterpinoidsaponin and bacogenin. (Charoenphon et.al., 2016)

Pharmacological Actions

- *Muqawwī-i-Dimāgh* (Brain tonic)
- *Muqawwī-i-Aʿṣāb* (Nervine tonic)
- *Muqawwī-i-Baṣar* (Eye tonic)
- *Musakkin* (Analgesic)
- *Muṣaffī-i-Khūn* (Blood purifier)
- *Mudirr-i-Bawl* (Diuretic)

(Anonymous, 2007d; Ghani, YNM; Kabīruddīn, 2000)

Therapeutic Uses

- *Ḍuʿf-i-Dimāgh* (Cerebrasthenia)
- *Ḍuʿf-i-Aʿṣāb* (Nervine weakness)
- *Ṣudāʿ* (Headache)
- *Ḍuʿf-i-Baṣar* (Poor eyesight)
- *Wajaʿ al-Aʿṣāb* (Neuralgia)
- *Junūn* (Insanity)
- *Hurqat-i Bawl* (Burning micturition)

(Anonymous, 2007 d; Ghani, YNM; Kabīruddīn, 2000)

Important Formulation

- *Majūn Brahmi*

Pharmacological / Clinical studies (evidence based)

Anti-oxidant and adaptogenic activity

- As stress is linked to many diseases, research on an effective anti-stress agent (adaptogen) from plants has gained importance. In one of the study, the adaptogenic property of a standardized extract of *Bacopa monnieri* (BM)

against acute stress (AS) and chronic stress (CS) models in rats was studied (Rai et al., 2003)

- The Pre-treatment with *B. monnieri* at 40 mg/kg significantly reduced the AS-induced increase in the ulcer, adrenal gland weight, plasmaglucose, (aspartate aminotransferase) AST, and (creatine kinase) CK. A dose of 80 mg/kg significantly reversed the AS-induced changes in adrenal gland weight, spleen weight, plasma glucose, alanine aminotransferase (ALT), and AST. BM extract or bacosides have shown anti-oxidant and anti-stress activities. (Rai et.al., 2003; Singh et.al., 2006; Bafna and Balaraman, 2005; Sumathy et.al., 2006; Pawar et.al., 2001; Tripathi et.al., 1996; Kapoor et.al., 2008; v et.al., 1969; Singh et.al., 1996; Bhattacharya et.al., 2000)

- A previous study suggested an involvement of the GABA-ergic system in the mediation of these effects of BM. Based on animal study results, bacosides showed to have Anti-oxidant activity in the hippocampus, frontal cortex and striatum. Govindarajan et.al. 2005). One of the study has shown that BM extracts modulate the expression of certain enzymes involved in generation and scavenging of reactive oxygen species in the brain. (Chowdhuri et al., 2002; Rohini et al., 2004).

- In one of the study on rats, BM showed the potential to be effective in stress and could be beneficial in the management of stress related conditions. BM was found to induce the constitute expression of heat-shock protein (HSP 70), and also induced the (cytochrome P450) CYP 450 enzymes in all regions of brain. (Seiss et.al., 1993). The level of Hsp70 was found to be increased in brain as a response to stress. An increase in the activity of CYP 450-dependent enzymes 7-pentoxyresorufin-odealkkylase (PROD) and 7-ethoxyresorufin-o-deethylase (EROD) was observed in all the brain regions after exposure to stress alone and with both doses of BM although the magnitude of induction observed was less with a higher dose of the same. Thus, it was suggested that the BM primed the brain for stress by stockpiling these useful enzymes even before stressful conditions and that the susceptibility to stress could be lowered by using this medicinal herb. It was suggested that this induction may be an adaptive response to the stress which needs further investigation. The level of super oxide dismutase (SOD) was also increased when pre-treated with BM. The data indicated that BM has a potential to modulate the activities of HSP 70, CYP 450 and SOD and thereby possibly allowing the

brain to be prepared to act under adverse condition like stress. (Seiss et.al., 1993).

- One of the study concluded that BM helps in coping with combined hypoxic, hypothermic and immobilization stress that could lead to onslaught of 'free radicals'. The results also indicated that this extract exhibited interesting Anti-oxidant properties, expressed by its capacity to scavenge superoxide anion and hydroxyl radical, and to reduce H 2 O 2 -induced cytotoxicity and DNA damage in human fibroblast cells. BM extract has also showed neuro-protective effect against aluminium-induced oxidative stress in the hippocampus of rat brain.(Rai et.al., 2003; Jyoti et.al., 2006; Vijayan and Helen, 2007; Holcomb et al., 2006)

- In another study, aqueous extract of BM reduced nicotine-induced lipid peroxidation (LPO) and conferred geno protection in Swiss mice. One study showed the protective role of bacoside A against chronic cigarette smoking-induced oxidative damage in rat brain. This Anti-oxidant activity of BM is able to explain, at least in part, the reported anti-stress, cognition-facilitating and anti-aging effects of BM and may justify further investigation of its other beneficial biological properties and the potential anti-stress agent. (Pushkar et.al., 2014; Anbarasi et.al., 2006; Aloe et.al., 2002)

Memory enhancing activity

- Behavioural studies in animals have shown that BM improves motor learning, acquisition and retention, and delay extinction of newly acquired behaviour. The methanol extract and different fractions of *B. monnieri* were evaluated for Anti-depressant activity in the forced swimming test (FST) and tail suspension test (TST) in mice. The results showed that the methanol extract, ethanol and butanol fraction significantly reduced the immobility times both in FST and TST in mice after being administrated orally for 5 consecutive days. All tested samples, in the effective doses for FST and TST, showed no inhibitory effect against locomotor activity. (LA) in mice.(Shen et al., 2009; Kishore et al., 2005)

- In another study, it was found that bacosides facilitates anterograde memory and attenuate anterograde experimental amnesia induced by scopolamine and sodium nitrite possibly by improving the acetylcholine level and hypoxic conditions, respectively. In addition, bacosides also reversed BN52021 (a

platelet activating factor receptor antagonist) induced retrograde amnesia, probably due to increase in platelet activating factor synthesis by enhancing cerebral glutamate level. Memory deficits following cholinergic blockade by scopolamine were reversed by Bacopa treatment. Bacopa improved memory functioning in cognitively intact cohorts, with Pycnogenol improving working memory. (Kishore et.al., 2005; Ryan et al., 2008)

- Benzodiazepines are known to produce amnesia by the involvement of GABAergic system and by the interference of long term potentiation. The behavioral study showed that *Bacopa monniera* significantly reversed the diazepam induced amnesia. Bacopa administration with phenytoin significantly reversed phenytoin-induced cognitive impairment, as noted by improved acquisition and retention of memory. (Saraf et al., 2008; Vohora et.al., 2000)

- A clinical trial was carried out to assess the effects of 12 weeks administration of *Bacopa monnieri* (300mg/day) on memory performance in people over the age of 55 years. Bacopa significantly improved memory acquisition and retention in older persons. Significant cognitive enhancing benefits have been demonstrated with chronic administration of Bacopa extracts. (Reddy, *2019;* Morgan and Stevens, 2010)

- A double-blind, placebo-controlled, 12-week trial utilizing the same patient selection criteria and the same dose of Bacopa extract (300 mg daily) containing 55% combined bacosides, was carried out. Forty six healthy volunteers (ages 18-60) were randomly and evenly divided into treatment and placebo groups. The same series of tests administered in the acute dosage trial were administered at baseline, five, and 12 weeks after treatment began. At the end of the 12 week study, results indicated a significant improvement in verbal learning, memory consolidation, and speed of early information processing in the treatment group compared to placebo. These effects were not observed at baseline or at five weeks. (Reddy, *2019;* Stough et al., 2001)

- The Bacopa supplement was commercially available as Keen Mind (Flordis). This product is manufactured from the stems, leaves and roots of Bacopa and is extracted with 50% ethanol. It is standardized to contain active bacosides at levels of 55% ± 5%. Keen Min help develop novel preventative health practices and nutritional/pharmacological targets in the elderly for cognitive and brain health. Bacopa appeared to have multiple modes of action in the

brain, all of which may be useful in ameliorating cognitive decline in the elderly. These include: (i) direct pro-cholinergic action; (ii) Anti-oxidant (flavonoid) activity; (iii) metal chelation; (iv) Anti-inflammatoryeffects; (v) improved blood circulation; (vi) adaptogenic activity; and (vii) removal of b-amyloid deposits.(Reddy, *2019;* Stough et.al., *2012)*

- However , in a double blind randomized, placebo control study performed on 76 adults aged between 40 and 65 years, in which various memory functions were tested and levels of anxiety was measured, the rate of learning was unaffected by *Bacopa monnieri* suggesting that the drug decreases the rate of forgetting of newly acquired information. Tasks assessing attention, verbal and visual short term memory and the retrieval of pre-experimental knowledge were unaffected. Questionnaire measures of everyday memory function and anxiety levels were also unaffected.(Reddy, *2019;* Roodenrys *et al., 2002)*

Anti-depressant activity

- In a study using a rat model of clinical anxiety demonstrated that a BM extract containing 25% bacoside A exerted anxiolytic activity comparable to lorazepam, a common benzodiazepine anxiolytic drug, and it was attentively noted that the BM extract did not induce amnesia, side effects associated with lorazepam, but instead had a memory enhancing effect. (Reddy, *2019)*

- The anti-depressant potential of BM has been evaluated in an earlier study, wherein it showed a significant anti-depressant activity in the most commonly used behaviour paradigms in animal models of depression, namely, forced swim test and learned helplessness tests. In the study, the BM extract in the dose range of 20-40 mg/kg was given once daily for 5 days and it was found comparable to standard anti-depressant drug imipramine in anti-depressant activity in rodent animals. The same study has postulated the role of serotonin and GABA (gamma amino butyric acid) in the mechanism of action attributed for its anti-depressant action along with its anxiolytic potential, based on the compelling evidence that the symptoms of anxiety and depression overlap each other. (Reddy, *2019)*

Alzheimer's disease

- Goswami *et al.* (2011) evaluated the effect of 300 mg *B. monnieri* (orally) twice a day for 6 month in the newly diagnosed patients of Alzheimer's

disease in the Psychiatry Outdoor Patient Department in India. Mean age of 39 patients who completed the study was 65.23 years. Study patients showed statistically significant improvements in various components of Mini Mental State Examination Scale including orientation of time, place and person, attention and in their language component in terms of reading, writing and comprehension. The patients involved in this trial also reported improvement in their quality of life, and decrease in the irritability and insomnia.

- In 2013, Kunte and Kuna studied the neuro-protective properties of 100 mg *B. monnieri* per kg body weight for 180 days on memory deficits and biochemical changes in ATPase system of Alzheimer's disease induced mice. Their results revealed that *B. monnieri* showed positive effects on body weight, learning skills, memory and concentration, moreover, *B. monnieri* could revert all the constituents of ATPase system to normal levels in Alzheimer's disease induced mice. So, Kunte and Kuna concluded that *B. monnieri* had potential compounds which can prevent the learning and memory deficits effectively; and to maintain ion gradients across biological membranes, thus confer significant neuroprotection against Alzheimer's disease by stabilizing the structural and functional integrity of the membrane.

Parkinson's disease

- Jadiya *et al*. (2011) studied the effect of *B. monnieri* on two different strains of *Caenorhabditis elegans*, a transgenic model expressing "Human" Parkinson's disease. The results showed that *B. monnieri* reduced alpha synuclein aggregation, prevented dopaminergic neurodegeneration and restored the lipid content in nematodes, thereby proving its potential as a possible anti-Parkinsonian agent.

- Swathi *et al*. (2013) examined the neuro-protective effect of *B. monnieri* in rotenone induced Parkinson's disease with particular reference to glutamate metabolism in different regions of rat brain. Glutamine content and activity levels of glutamate dehydrogenase, glutamine synthetase were significantly depleted and elevated glutaminase activity was found in different brain regions of rat during rotenone induced Parkinson's disease when compared to control rats. Treatment with *B. monnieri* caused significant elevation in glutamine content and the activity levels of glutamate dehydrogenase, glutamine synthetase and depletion in glutaminase activity in different brain regions of rats when compared to induced Parkinson's disease rats. So the

results of Swathi *et al.* (2013) suggest the ability of *B. monnieri* extract to modulate glutamate metabolism in different brain regions of induced rodent model of Parkinson's disease.

Neuro-protective activity

- The active constituents responsible for *B. monnieri*'s cognitive effects are bacosides A and B, moreover, triterpenoid saponins are responsible to enhance nerve impulse transmission (Mahato *et al.*, 2000; Chakravarty *et al.*, 2003). The bacosides also aid in repair of damaged neurons by enhancing kinase activity, neuronal synthesis, restoration of synaptic activity, and nerve impulse transmission (Singh and Dhawan, 1997).

- Peth-Nui *et al.* (2012) demonstrated that *B. monnieri* suppresses acetylcholinesterase activity resulting in enhanced cholinergic function, which in turn enhances attention and memory processing and increases working memory in elderly people.

Additional activities

- *Bacopa monnieri* has also been reported to possess anti-cancer, anti-diabetic, anti-hypertensive, anti-hyper-lipidemic, anti-inflammatory, anti-microbial, hepato-protective and gastro-intestinal protective activities. (Reddy, *2019;* Pushkar et.al., 2014)

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Dār Chīnī
(Bark)
Cinnamomum verum J. Presl

Introduction

The drug of *Dār Chīnī* consists of dried inner bark devoid of cork and cortex of stem of *Cinnamomum verum* J. Presl. (Family-Lauraceae). Drug yielding plant is a moderate sized evergreen tree usually attaining a height of 6-7.5 m; cultivated on the Western Ghats and adjoining hills; bark collected during April-July and October-December. (Anonymous, 2007a)

Fig. *Dār Chīnī*

Vernacular Names

English: Cinnamon; Hindi: *Dāl chīnī*, *Qalmī Dār chīnī*; Urdu: *Dār Chīnī*; Arabic: *Dār Ṣīnī*, *Qirfā*; Persian: *Dār Chīnī*. (Khān, 2013; Ibn Sīnā, 1987; *Ibn Baytār*, 1986; Ghani, YNM; Anonymous, 2007a)

Temperament

Ḥār (Hot)[3] *Yābis* (Dry)[3] (Khān, 2013; Ibn Sīnā, 1987;; *Kabīruddīn*, 2000)

Chemical Constituents

Cinnamomum verum contains Cinnam aldehyde, cinnamate, cinnamic acid, essential oil; trans-cinnamaldehyde, cinnamyl acetate, eugenol, L-borneol, caryophyllene oxide, b-caryophyllene, L-bornyl acetate, E-nerolidol, α-cubebene, α-terpineol, terpinolene, and α-thujene. (Rao and Hua Gan, 2014; Anonymous 2007a)

Pharmacological Actions

- *Muqawwī-i-Ḥarārat Gharīziyya* (Tonic for innate heat)

- *Muqawwī-i-Qalb* (Cardio-tonic)
- *Muharrik-i- Qalb* (Cardiac stimulant)
- *Dāfi'-i-Ta'ffun* (Antiseptic)
- *Mulaṭṭif* (Demulscent)
- *Munaffith-i-Balgham* (Expectorant)
- *Muqawwī-i-Mi'da* (Stomachic)
- *Kāsir-i-Riyāḥ* (Carminative)
- *Qābiḍ* (Astringent)
- *Muqawwī-i-Kabid* (Hepato tonic)
- *Mudirr-i-Bawl* (Diuretic)
- *Mudirr-i-Ḥayḍ* (Emmenagogue)
- *Moḥarrik-i-Bāh* (libido stimulant)

(Khān, 2013; Ibn Sīnā, 1987; *Ibn Baytār*, 1986; Al-Harawi, 2002; Ghani, YNM; Anonymous, 2007a; *Kabīruddīn*, 2000)

Therapeutic uses

- *Ḍu'f-i-Ḥarārat Gharīziyya* (Innate heat insufficiency)
- *Ḍu'f-i-Qalb* (Cardiac insufficiency)
- *Ḍu'f-i-Mi'da* (Gastric debility)
- *Ḍu'f-i-Haḍm* (Delayed digestion)
- *Ḍu'f-i-Bāh* (Sexual debility)
- *Ḍīq al-Nafas* (Bronchial asthma)
- *Bakhr al-Fam* (Halitosis)
- *Bahaq* (Pityriasis)
- *Iḥtibās-i-Bawl* (Retention of urine)

(Khān, 2013; Ibn Sīnā, 1987; *Ibn Baytār*, 1986; Al-Harawi, 2002; Ghani, YNM; Anonymous, 2007a; *Kabīruddīn*, 2000)

Important Formulations

Jawārish Jālīnūs, Jawārish Bisbāsā, Raughan Dār Chīnī, Jawārish-i- 'Ūd Shīrīn, Jawārish-i- 'Ūd Tursh, Jawārish Pudīnā, Jawārish-i- Shahr Yārān Jawārish Utraj, Jawārish Zarooni Sādā, Ma'jūn Dabīdul Ward, Ma'jūn Falāsifā, Ma'jūn Fanjnosh,

Ma'jūn Jalāli, Ma'jūne Jālinūs-Lului, Ma'jūn Khadar, Ma'jūn Lana, Ma'jūn Mughalliz, Ma'jūn Mulūkī, Ma'jūn Rahul Mominīn, Ma'jūn Supārī Pāk, Ma'jūn 'Ushba, Tiryāq-i-Thamāniya, 'Arq Ambar, 'Arq Chob Chīnī, Iyārij Faiqrā, Safūf-i-Kishnīz, Safūf-i-Qaranful.(Anonymous, 2007a)

Pharmacological / Clinical studies (evidence based)

Anti-oxidant activity

- Anti-oxidant compounds present in food stuffs play a vital role in human life, acting as health-protecting agents. In addition to this role, Anti-oxidants are one of the key additives used in fats and oils. Even in the food processing industry, Mancini-Filho *et al.* 1998, reported that various extracts of cinnamon, such as ether, aqueous, and methanolic extracts have shown considerable Anti-oxidant activities. (Rao and Hua Gan, 2014)

- A study on rats reported that the administration of the bark powder of *Cinnamomum verum* (10%) for 90 days produced anti-oxidant activities as indicated by cardiac and hepatic anti-oxidant enzymes, lipid conjugate dienes, and glutathione (GSH). (Dhuley, 1999)

- A research group reported that cinnamon oil potentially exhibits superoxide-dismutase- (SOD-) like activity as indicated by the inhibition of the inhibiting capacity of pyrogallol anti-oxidation. (Kim *et.al.,* 1995)

- The aqueous and alcoholic extract (1:1) of cinnamon potentially significantly inhibits fatty acid oxidation and lipid peroxidation *in-vitro*. Different flavonoids isolated from cinnamon have free-radical-scavenging activities and anti-oxidant properties. (Rao and Hua Gan, 2014)

- A study of the inhibitory effects of cinnamaldehyde and other compounds of cinnamon on nitric oxide production revealed that cinnamaldehyde possesses potential activity against the production of nitric oxide as well as the expression of inducible nitric oxide. The highest inhibitory activities were reported as 81.5%, 71.7%, and 41.2% at 1.0, 0.5, and 0.1 μg/μL, respectively. (Lee *et al.,* 2002)

- Overall, cinnamon exhibited higher anti-oxidant activities compared to that of other dessert spices. The essential oils and some of the major compounds present in cinnamon, including (E)-cinnamaldehyde, eugenol, and linalool, were investigated in reference to peroxynitrite induced nitration and lipid

peroxidation. Eugenol and the essential oils were more effective than the other two compounds. (Chericoni, *et al.,* 2005)

- In a comparative study among 26 spices, cinnamon showed the highest anti-oxidant activity, indicating that it can be applied as an anti-oxidant used in foods. Another study investigated the effectiveness of a mixture of spices on oxidative stress markers as well as the anti-oxidant activity in high fructose-fed insulin-resistant rats. The mixture, which consisted of 1 g/100 g cinnamon bark, showed a significant anti-oxidant activity compared to the fructose alone group. (Rao and and Hua Gan, 2014)

Neurological disorders

- Parkinson's disease (PD) is the second major widespread neurodegenerative disorder after Alzheimer's disease, with a prevalence of 2% in people of 65 years and older. PD protein 7 (PARK7) is an autosomal recessive form of early-onset Parkinsonism caused by alterations in the DJ1 gene. Khasnavis and Pahan reported that sodium benzoate, a cinnamon metabolite, upregulates DJ-1 by modulating mevalonate metabolites. Cinnamon and its metabolite sodium benzoate also upregulate the neurotropic factors BDNF (brain-derived neurotropic factors) as well as neurotrophin-3 (NT-3) in the mouse central nervous system. PARK7 is one of the main neuro-protective proteins that protects cells from damage and from the further detrimental effects of oxidative stress; therefore, this protein may be an effective molecule that can be incorporated into the therapeutic intervention of Parkinson's disease (Brahmachari *et al.,* 2009; Khasnavis *et al.,* 2012)

- A natural compound isolated from cinnamon extract (CEppt) significantly reduces the formation of toxic β- amyloid polypeptide (Aβ) oligomers and prevents its toxicity on neuronal pheochromocytoma (PC12) cells. The study indicated that CEppt resolved the reduced permanence, fully improved deficiencies in locomotion, and totally eradicated the tetrameric species of Aβ in the brain of the fly model of Alzheimer's disease, leading to a noticeable reduction in the 56 kDa Aβ oligomers, reducing plaques and improving the cognitive performance of transgenic mice models. (Khasnavis *et al.,* 2012)

- Another study reported that the aqueous extract of C. zeylanicum can reduce tau aggregation and filament formation, two of the main features of Alzheimer's disease. The extract can also encourage the complete fragmentation of

recombinant tau filaments and cause the considerable modification of the morphology of paired helical filaments from Alzheimer's disease brain, indicating the potential of cinnamon in the treatment of Alzheimer's disease. (Marom *et al.,* 2011; Peterson *et al.,* 2009; Rao and and Hua Gan, 2014)

Anti-cancer activity

- The use of *Cinnamomum verum* is increasing in the treatment of various types of ulcers and cancers (Bhagavathy & Latha, 2015). Ezzat *et al.,* 2017 evaluated the Anti-cancer effect of cinnamon bark aqueous extract on 7, 12 dimethylbenz[*a*]anthracene (DMBA) induced oral cancer in sixty male Syrian hamster's cheek pouch (HCP) mucosa via different cytotoxicity assays such as 3-(4, 5-dimethylthiazol- 2-yl)-2, 5-diphenyl tetrazolium bromide (MTT) assay, DNA fragmentation assay, etc. Cancer-induced hamsters supplemented with cinnamon aqueous extract were noticed with significantly suppressed oral cancer progression. Goyal et al. (2018) compared the immunomodulatory effects of water-soluble polysaccharides and other expression phase II Anti-oxidant enzyme and reduced the oxidative stress. Thus, the cinnamon reduces the generation of free radicals and minimizes oxidative stress. The signaling pathway involved by cinnamon to reduce oxidative stress is depicted. (Singh *et al.,* 2020)

Additional activities

- The Bark of *Cinnamomum verum* has also been reported to possess anti-inflammatory, anti-anxiety, anti-depressant, anti-HIV, cardio- protective, gastro-protective, wound healing and anti-diabetic activities. (Singh *et al.,* 2020)

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Filfil Darāz
(Fruit)
Piper longum L.

Introduction

The drug of *Filfil Darāz* consists of the fruit of *Piper longum* L. (Family-Piperaceae), an annual or biennial shrub. occurring in warmer parts of India, from Central Himalayas to Assam, lower hills of West Bengal; Uttar Pradesh, Andhra Pradesh, Western Ghats from Konkan southwards to Trivandrum. (Osman gani et al., 2019)

Fig. *Filfil Darāz*

Vernacular Names

English: Long pepper; Hindi: *Pīpal, Pīplī*, *Gajpīpal;* Urdu: *Filfil Darāz*, *Pīplī*; Arabic: *Dār Filfil*; Persian: *Filfil Darāz*. (Khān, 2013; Ibn Sīnā, 1987; Ghani, YNM; *Kabīruddīn*, 2000)

Temperament

Ḥār (Hot)^3 *Yābis* (Dry)^2 (Khān, 2013; Ibn Sīnā, 1987; *Kabīruddīn*, 2000)

Chemical Constituents

Alkaloids and related compounds: piperine, methyl piperine, pipernonaline, piperettine, asarinine, pellitorine, piperundecalidine, piperlongumine, piperlonguminine, retrofractamide A, pergumidiene, brachystamide-B, a dimer of desmethoxypiplartine, N-isobutyl decadienamide, brachyamide-A, brachystine, pipercide, piperderidine, longamide, dehydropipernonaline piperidine, and tetrahydro piperine. Newly identified chemical constituents are 1-(3_, 4_-methylenedioxyphenyl)- 1E-tetradecene, 3-(3_, 4_- methylenedioxophenyl)-propenal, piperoic acid, 3_, 4_-di-hydroxy-biabola-1, 10-diene, eudesm-4(15)-ene1beta, 6-alpha-diol, 7-epi-eudesm-4(15)-ene-1beta, 6beta-diol, guineesine,

and 2E, 4E dienamide, (2E, 4E, 8E) - Nisobutylhenicosa- 2, 4, 8-trienamide. The main lignans present in the fruits are sesamin, pulviatilol, and fargesin. The fruits contain tridecyl-dihydro-p-coumarate, eicosanyl-(E)-p-coumarate, and Z-12- octadecenoicglycerol- monoester. The essential oils of the fruit are a complex mixture. Excluding the volatile piperine, the three major components are caryophyllene, pentadecane (both about 17.8%), and bisaboline (11%). Others include thujone, terpinolene, zingiberene, p-cymene, pmethoxyacetophenone, dihydrocarveol, and vitamins A and E. The major organic acids present are palmitic acid and tetrahydropiperic acid. (Osman gani *et al.,* 2019)

Pharmacological Actions

- *Muqawwī-i-Ḥarārat Gharīziyya* (Tonic for innate heat)
- *Muqawwī-i-Miʿda* (Stomachic)
- *Mushtahī* (Appetizer)
- *Hāḍim* (Digestive)
- *Kāsir-i-Riyāḥ* (Carminative)
- *Munaffith-i-Balgham* (Expectorant)
- *Moḥarrik-i-Bāh* (Libido stimulant)
- *Muqawwī-i Bāh* (Aphrodisiac)
- *Muḥallil* (Resolvent)

(Khān, 2013; Ibn Sīnā, 1987; Al-Harawi, 2002; *Kabīruddīn*, 2000; Ghani, YNM)

Therapeutic Uses

- *Ḍuʿf-i-Ḥarārat Gharīziyya* (Innate heat insufficiency)
- *Ḍuʿf-i-Miʿda* (Gastric debility)
- *Sū'-i-Haḍm* (Indigestion)
- *Nafkh-i-Shikam* (Flatulence)
- *Suʿāl* (Cough)
- *Damā* (Bronchial asthma)
- *Shahīqā* (Whooping cough)
- *Laqwā* (Bell's palsy)
- *Waja' al-Mafāṣil* (Polyarthritis)

- *'Irq al-Nasā* (Sciatica)
- *Niqris* (Gout)
- *Ṣar'* (Epilepsy)

(Khān, 2013; Ibn Sīnā, 1987; Al-Harawi, 2002; *Kabīruddīn*, 2000; Ghani, YNM)

Important Formulations

Jawārish Bisbāsa, *Jawārish Utraj*, *Jawārish Jālīnūs, Ma'jūn Falāsifā, Ma'jūn Lanā, Ma'jūn Suhāg Sonth.*

Pharmacological / Clinical studies (evidence based)

Anti-oxidant activity

- *Piper longum* exhibits promising anti-oxidant potential against free radical-induced oxidative damage. Petroleum ether extract of the root and piperine from roots of *Piper longum* Linn. decreases lipid peroxide levels and maintains glutathione content, demonstrating anti-oxidant activity. (Osman gani *et al.,* 2019; Yadav *et al.,* 2014; Seon *et al.,* 2005)

Immunomodulatory activity

- The immunomodulatory potential of *Piper longum* and piperinic acid, one of its active constituent, in Balb/C mice (in vivo) and human PBMCs (*in-vitro*) models showed a dose dependent decrease of lymphocytes (CD4+ and CD8+ T cells) and cytokine levels in sensitized Balb/C mice with a marked inhibition. (Devan *et al.,* 2007; Zaveri *et al.,* 2010)

- Alcoholic extract of the fruits of *Piper longum* and its component piperine was studied for their immunomodulatory and anti-tumor activity. Alcoholic extract of the fruits and piperine were found to be cytotoxic. (Sunila *et al.,* 2006; Zaveri *et al.,* 2010)

- An aqueous extract of *Piper longum* fruit powder showed 100% giardicidal activity found to offer protection against externally induced stress. A famous Ayurvedic preparation containing long pepper in pippli rasyana was tested in mice infected with Giardia lamblia and found to produce significant activation of macrophages, as shown by an increased MMI and phagocytic activity. (Agarwal *et al.,* 1994; Zaveri *et al.,* 2010)

- The specific and non-specific immune-stimulatory actions of *Piper longum* fruits have been evaluated by hemagglutination titer, macrophage migration index and phagocytic index in mice. Long pepper was tested in mice infected with Giardia lamblia and found to activate macrophages, as shown by an increased macrophage migration index and phagocytic index, indicating immune-stimulatory activity. (Tripathi *et al.,* 1999; Osman gani *et al.,* 2019)

Anti-apoptosis activity

- Yadav et al. illustrated the anti-apoptosis and Anti-oxidant activity of *Piper longum* through TUNEL ASSAY and Radical scavenger activity (DPPH ASSAY). They evaluated the effect of hexane: ethanol (2:8) *Piper longum* extract on GM-induced hair cell loss in basal, middle and apical regions in a neonatal cochlea cultures. An anti-apoptosis effect and potent radical scavenger activity of subfraction PL extract protects from GM induced hair cell loss at basal, middle and apical regions in neonatal cochlea cultures (Yadav *et al.,* 2014).

Anti-depressant activity

- Treatment with piperine (6.25–25 μM) for 72 h reversed the (corticosterone) CORT-induced reduction of BDNFmRNA expression in cultured hippocampal neurons. A bioassay-guided isolation of the ethanol extract from the fruits of *Piper longum* yielded a known piperidine alkaloid, piperine having potent anti-depressant-like properties which are mediated in part through the inhibition of MAO activity, and therefore represent a promising pharmacotherapeutic candidate as an anti-depressant agent. (Song *et al.,* 2007; Song *et al.,* 2005; Zaveri *et al.,* 2010)

- Ethanol extraction of *Piper longum* fruits yields a known piperidine and piperine alkaloid, as a monoamine oxidase inhibitor. Thus the *Piper longum* fruits represent a promising pharmacotherapeutic candidate against depression. (Osman gani *et al.,* 2019; Lee *et al.,* 2008)

Anti-cancer activity

- *Piper longum* is reported to exhibit significant anti-tubercular activity. The effect of piperine on the inhibition of lung metastasis induced by B16F-10 melanoma cells was studied in C57BL/6 mice. Simultaneous administration of the compound with tumor induction produced a significant reduction (95.2%)

in tumor nodule formation along with reduced lung collagen hydroxyproline, uronic acid and hexosamine content in the piperine-treated animals. (Pradee *et al.,* 2007)

- *Piper longum* showed an inhibitory effect on α-MSH-induced tyrosinase synthesis. It was found that oral administration of ethanolic extract protected the cell surface and maintained the structural integrity of the cell membranes during DMBA induced hamster buccal pouch carcinogenesis. Selvendiran *et al.,* 2004; Min *et al.,* 2004; Senthil *et al.,* 2007; Zaveri *et al.,* 2010)

- The two active principles, ethyl 3', 4', 5'- trimethoxycinnamate and piperine were isolated and characterized from the combined hexane and chloroform extracts of Piper longum. The extracts significantly blocked the adhesion of neutrophils to endothelium in a time- and concentration-dependent manner. Piplartine and piperine alkaloidal amides were isolated from Piper. It showed cytotoxic activity towards several tumor cell lines. The study clearly demonstrated that piperine has the anti-oxidative, anti-apoptotic, and restorative ability against cell proliferative mutagenic response and phenotypic alterations by piperine, suggesting its therapeutic usefulness in immunocompromised conditions. (Pathak *et al.,* 2006; Zaveri *et al.,* 2010)

Anti-tumor activity

- A study showed the effect of piperine and piplartine on Sarcoma 180 tumors transplanted in mice where they observed significant reduction of tumor weight in piplartine- and piperine-treated animals (Bezerra *et al.,* 2006; Osman gani *et al.,* 2019).

- Another study proved the antitumor activity of piperine is related to its immunomodulatory properties, which involves the activation of cellular and humoral immune responses. The anti-tumor properties of piperine marks it as a potential candidate for future cancer therapy. (Sunila and Kuttan, 2004).

Additional activities

- The fruit of *Piper longum* has also been reported to possess anti-stress, anti-diabetic, anti-microbial, anti-fungal, anti-tubercular, anti-inflammatory, anti-arthritic, anti-fertility, hepato- protective and cardio-protective activities. (Zaveri *et al.,* 2010; Osman gani *et al.,* 2019)

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Filfil Siyāh
(Fruit)
Piper nigrum L.

Introduction

The drug of *Filfil Siyāh* consists of fully mature dried fruit of *Piper nigrum* L. (Family-Piperaceae), a climber, cultivated from Konkan Southwards, especially in North Konkan, Kerala and also in Assam; fruits ripen from December to March, depending upon climatic conditions, fruits harvested from December to April. (Anonymous, 2007d)

Fig. *Filfil Siyāh*

Vernacular Names

English: Pepper (Black & white); Hindi: *Kālīmirch*; Urdu: *Filfil Siyāh*, *Kālī Mirch*; Arabic: *Filfil*, *Filfil Aswad*; Persian: *Filfil Siyāh*. (Khān, 2013; Ibn Sīnā, 1987; *Ibn Baytār*, 1999; Ghani, YNM; Anonymous, 2007d)

Temperament

Ḥār (Hot)[3] *Yābis* (Dry)[3] (Khān, 2013; Ibn Sīnā, 1987; *Kabīruddīn*, 2000)

Chemical Constituents

- **Essential oil**-Globulol, alphapinene, betacaryophyllene and alpha-terpinene and nerolidol.
- **Alkaloids-** (Piperine, Chavicine; Piperidine. Piperetine), Essential oil. Steroids, Saponin, glycoside, Polysaccharides and Sugar. Potassium, Magnesium, Iron, Mangnese, Phosphorus, Chlorine and Iodine are also present.
- Phenolics, various derivatives of Lignans, Terpenes, Chalcones, Flavonoid
- **Alkaloid and Steroid**- Brachyamide B, Dihydropipericide, benzamide group

as well as Isobutyl-eicosaterienamide, isobutyl decadienamide, piperamide, piperamine, piperettine, pipericide, piperine, piperolein B, Trichostachine, sarmentine, sarmentosine. (Anonymous, 2007d; Sohel *et al.,* 2020)

Pharmacological Actions

- *Muḥarrik* (Stimulant)
- *Muqawwī-i-Miʿda* (Stomachic)
- *Kāsir-i-Riyāḥ* (Carminative)
- *Muqawwī-i-Kabid* (Hepato tonic)
- *Muqawwī-i-Aʿṣāb* (Nervine tonic)
- *Muddir-i-Bawl* (Diuretic)
- *Mudirr-i-Ḥayḍ* (Emmenagogue)
- *Muqawwī-i Bāh* (Aphrodisiac)
- *Munaffith-i-Balgham* (Expectorant)
- *Tiryāq-i-Miʿda* (Gastric antidote)

(Khān, 2013; Ibn Sīnā, 1987; *Ibn Baytār*, 1999; Ghani, YNM; Anonymous, 2007d; Khan, *et al.,* 2016)

Therapeutic Uses

- *Ḍuʿf-i-Miʿda* (Gastric debility)
- *Nafkh-i-Shikam* (Flatulence)
- *Fasād-i-Haḍm* (Indigestion)
- *Ḍuʿf-i-Haḍm* (Delayed digestion)
- *Kathrat-i-Riyāḥ* (Excessive flatulence)
- *Ḍuʿf-i-Aʿṣāb* (Nervine weakness)
- *Baraṣ wa Bahaq* (Vitilig & Pityriasis)

Khān, 2013; Ibn Sīnā, 1987; *Ibn Baytār*, 1999; Ghani, YNM; Anonymous, 2007d; Khan *et al.,* 2016)

Important Formulations

Dawā-ul-Shifā, Jawārish Kamūni, Jawārish Kamūni Kabīr, Jawārish Falāfilī, Habb-i-Kabid Naushādrī, Jawārish Jālīnūs. (Anonymous, 2007d; Sohel *et al.,* 2020)

Pharmacological / Clinical studies (evidence based)

Anti-oxidant activity

- Some *in-vitro* studies revealed that piperine inhibited free radicals and reactive oxygen species, therefore known to possess protective effects against oxidative damage. *Piper nigrum* or piperine also found to decrease lipid peroxidation *in-vivo*. *Piper nigrum* reported to possess Anti-oxidant activity that might be due to the presence of flavonoids and phenolic contents. *Piper nigrum* was found to prevent the oxidative stress by inhibiting lipid peroxidation, human lipoxygenase and arresting hydroxyl and superoxide free radicals, decrease lung carcinogenesis in animal studies. The memory enhancing and Anti-oxidant proprieties of the methanolic extract of *Piper nigrum* L. fruits at a doses of 50 and 100 mg/kg, orally, for 21 days in amyloid beta (1-42) were investigated in Alzheimer's disease model in rats (Selvendiran and Sakthisekaran, 2004; Ahmad *et al.,* 2010).

- The memory-enhancing effects of the extract were studied by means of *in-vivo* (Y-maze and radial arm-maze tasks) approaches. While, the anti-oxidant activity was evaluated by measuring activities of glutathione peroxidase, catalase, superoxide dismutase, and by measuring the total content of reduced glutathione, malondi aldehyde, and protein carbonyl levels in the hippocampus. The amyloid beta (1-42)-treated rats showed the diminishing of spontaneous starvariation percentage within Y- maze task and enhancement of work memory and reference memory errors within radial arm-maze task. Administration of the methanolic extract of *Piper nigrum* significantly improved memory performance and exhibited anti-oxidant potential. These studies suggest that methanolic extract of *Piper nigrum* ameliorates amyloid beta (1-42)-induced spatial memory deterioration by depletion of the oxidative stress in the hippocampus of rats (Hritcu *et al.,* 2014)

- The anti-oxidant effect of three Piper species viz P. nigrum, P. guineense and P. umbellatum was evaluated for the protection of renal, cardiac, and hepatic anti-oxidant status in atherogenic diet fed hamsters. Animals were fed atherogenic diet addition with different doses of Piper species viz P. nigrum, P. guineense and P. umbellatum at a dose of 1 g/kg and 0.25 g/kg for 12 weeks. Piper species significantly inhibited the atherogenic diet induced increased lipid profile and alteration in anti-oxidant enzymes activities. This study showed an anti-oxidant protective role of the extracts of Piper species

against atherogenic diet induced oxidative stress in renal, cardiac and hepatic tissues (Agbor *et al.,* 2012).

Immunomodulatory & anti-allergic activity

- The immunomodulatory potential of piperine has demonstrated promising potential. Bezerra et al. reported that the incubation of tumor cell lines with 5-fluorouracil (5-FU) in the presence of piperine produced an increase in growth inhibition, observed by lower IC50 values for 5-FU. At the same time, leucopoenia induced by treatment with 5-FU was reduced by the combined use with piperine, showing improved immunocompetence hampered by 5-FU. (Bezerra *et al.,* 2008).
- In the study of Bernardo et al. which evaluated the effect of piperine to B cell functioning and on the humoral immune response to T-un/dependent antigens, it was found that, *in-vitro* , it inhibits proliferative response induced by lipopolysaccharide (LPS) and immunoglobulin α-IgM antibody. Also, piperine resulted in inhibition of IgM antibody secretion and reduced expression of cluster of differentiation CD86. (Bernardo *et al.,* 2015)
- A recent study of Lee et al. demonstrated that piperine in combination with gamma-aminobutyric acid (GABA) mediated p38 and JNK MAPK activation, which increased EPO and EPO-R expression, resulting in up-regulation of IL-10 and NF-κB . In addition to immunomodulation, piperine exhibits significant anti-allergic activity in ovalbumin-induced allergic rhinitis in mice. Piperine significantly ameliorated sneezing, rubbing, and redness induced by sensitization of nerve endings resulted from histamine released in response to antigen-antibody reaction, but also decreased nitric oxide (NO) levels due to lower migration of eosinophils into nasal epithelial tissue. As in the histo pathological section of the nasal mucosa, it was found that piperine treatment attenuated inflammation, redness, and disruption of alveoli and bronchiole. (Lee *et al.,* 2018; Aswar *et al.,* 2015)
- In an ovalbumin-induced asthma model, the administration of piperine decreased the infiltration of eosinophils and reduced airway hyper responsiveness by suppressing T cell activity and Th2 cytokine production. (Kim *et al.,* 2009)

Neuro-protective and other neurological activity

- Piperine increases the cell viability and restored mitochondrial functioning and primary neurons in rotenone-induced neurotoxicity in SK-N-SH cells.

It also inhibits mTORC1 and activates protein phosphatase 2A, leading to neuro-protective effects in Parkinson's disease model. (Liu *et al.,* 2016; Fu *et al.,* 2010)

- This compound exerts protective effects against neurotoxicity induced by corticosterone (PC12 Cells) and 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine. Also, piperine exhibits the neuro-protective effect on primarily cultured hippocampal neurons and suppresses the neurite extension in developing neurons. (Mao *et al.,* 2012; Singh *et al.,* 2010; Unchern *et al.,* 1994)

- In rats with streptozotocin (STZ)-induced experimental dementia of the Alzheimer's type, intra peritoneal administration of piperine (2.5, 5, and 10 mg/kg), vehicle, and memantine (10 mg/kg) for two weeks after the first STZ administration resulted with cognitive-enhancing effect. The results of cognitive function were consistent with a reduced level of malondialdehyde in cerebrospinal fluid (CSF) and hippocampus (HC) of the treated rats. Based on the described results, the cognitive-enhancing effect of piperine was attributed to its positive effects on the redox balance of CSF and HC neurons. (Khalili-Fomeshi *et al.,* 2018)

- In a pilocarpine-induced rat model of epilepsy, administration of piperine reduced oxidative stress and inflammation and ameliorated memory impairment. (Stojanovic-Radi *et al.,* 2019)

- Piperine alone was found to produce a weak anti-depressant-like effect in the tail suspension and forced swimming tests, while in combination with trans-resveratrol (tR), it enhanced its anti-depressive action. Further testing indicated that the effect of tR and piperine on depressive-like behaviors might be partly due to the potentiated activation of mono-aminergic system in the brain (Huang *et al.,* 2013). Similar results were found in several other studies on piperine alone, in combination with ferulic acid, and its various derivatives. Piperine relieves the depression in chronic unpredictable mild stress rats by modulating the function of the hypothalamic-pituitary-adrenal axis. (Stojanovic-Radi *et al.,* 2019)

- Piperine was found to possess analgesic and Anti-convulsant effects, where intraperitoneal (i.p.) administration of piperine (30, 50 and 70 mg/kg) significantly inhibited the acetic acid-induced writhing in mice, while tail-

flick assay resulted in prolonged reaction time of mice at doses of 30 and 50 mg/kg. The Anti-convulsant effect of piperine has been demonstrated through delayed onset of pentylenetetrazole- and picrotoxin-induced seizures in mice. (Bukhari *et al.,* 2013)

- These anti-seizure effects of piperine were found to be related to transient receptor potential cation channel subfamily V member 1 (TRPV1) receptors. (Stojanovic-Radi *et al.,* 2019)
- Another study reported analgesic activity of piperine, where hot plate reaction test and acetic acid test were used and confirmed analgesic efficacy of intraperitoneally administered piperine. (Stojanovic-Radi *et al.,* 2019)

Additional activities

- The fruit of *Piper nigrum* has also been reported to possess anti-hypertensive, anti-platelet, anti-tumor, anti-asthmatics, analgesic, anti-inflammatory, anti-diarrheal, anti-spasmodic, anti-depressant, anti-convulsant, anti-thyroid, anti-bacterial, anti-fungal, hepato-protective, insecticidal & larvicidal, anti-obesity, anti-pyretic, anti-diabetic, anti-epileptic, anti-fertility, anti-cancer, CNS stimulant, diuretic, aphrodisiac, blood purifier and antiplatelet activities. (Sohel *et al.,* 2020)

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Gilo
(Stem)
Tinospora cordifolia (Thunb.) Miers

Introduction

The drug of *Gilo* consists of dried, matured pieces of stem of *Tinospora cordifolia* (Thunb.) Miers (Family-Menispermaceae). Drug yielding plant is a perennial climber found throughout Tropical India; drug collected during summer preferably in the month of May, drug is used in fresh form also. (Anonymous, 2007a)

Fig. *Gilo*

Vernacular Names

English: Heart-leaved Moonseed; Hindi: *Giloy, Gurcha*; Urdu: *Gilo*; Persian: Gulbel. (Khān, 2018; Ghani, YNM; Anonymous, 2007a)

Chemical Constituents

- **Alkaloid** (berberine, palmatine, giloin, crude giloinin)
- **Glucoside** (18-norclerodane glucoside, glycosides Furanoid, diterpene glucoside, Tinocordiside, Tinocordifolioside, cordioside, Cordifolioside A, Cordifolioside B, Syringin, Syringin-apiosylglycoside, Palmatosides C, Palmatosides F, Cordifoliside A, Cordiofoliside B, Cordifoliside C, Cordifoliside D, Cordifoliside E, arabinogalactan polysaccharide (TSP)
- **Steroids** (ecdysterone, makisterone a, giloinsterol), sesquiterpenoid (tinocordifolin)
- **Diterpenoid** (Furanolactone, Lactones, Clerodane, tinosporon, Tinosporides, Jateorine, Columbin, tinosporic acid, cordifolisides A to E, syringe). (Mittal *et al.,* 2014; Tiwari *et al.,* 2018)

Temperament

Muraqab al-Quwa (Khān, 2018)

Pharmacological Actions

- *Muqawwī-i-Badan* (General tonic)
- *Dāfi'-i- Ḥummā* (Antipyretic)
- *Muṣaffī-i-Dam* (Blood purifier)
- *Muḥallil-i-Awrām* (Resolvent)
- *Muddir-i-Bawl* (Diuretic)
- (Khān, 2018; Ghani, YNM; *Kabīruddīn*, 2000; Anonymous, 2007a)

Therapeutic Uses

- *Ḍu'f-i-'Ām* (General debility)
- *Ḥummā* (Fever)
- *Tap-i-Diq* (Tuberculosis)
- *Waja' al-Mafāṣil* (Polyarthritis)
- *Ishāl* (Diarrhea)
- *Zaḥīr* (Dysentery)
- *Jarayān* (Semenorrhoea)
- (Khān, 2018; Ghani, YNM; *Kabīruddīn*, 2000; Anonymous, 2007a)

Important Formulations

Safūf Satt-i-Gilo, Safūf Satt-i-Gilo Sartāni. (Anonymous, 2007a)

Pharmacological / Clinical studies (evidence based)

Anti-oxidant activity

- Various extracts of *T. cordifolia* exhibit an anti-oxidant potential by scavenging the free radicals and other reactive species respectively. *T. cordifolia* significantly reduces the regulation of lipid peroxidation process thereby decreasing the level of reactive free radical species in a diabetic rat

model (alloxan induced diabetes) and up regulates anti-oxidant enzymes like catalase and glutathione indicating its anti-oxidant effects. (Bhawya *et al.,* 2010; Sivakumar *et al.,* 2010)

- A clinical research has reported that the extract shows anti-oxidant effect by raising the level of GSH and reducing the expression of inducible nitric oxide synthase gene, while it is also useful in treatment of cataract by inhibiting the enzyme aldol reductase. (Tiwari *et al.,* 2018)
- A study also suggests that *T. cordifolia* bark extract (ethanol) shows the higher free radical scavenging activity as well as the highest phenolic content compared to the methanol extracts. The plant derived polysaccharide compound named as 'arabinogalactan' shows a protection against free radicals in rat model indicating its anti-oxidant action. *T. cordifolia* is reported to modify the levels of different enzymatic system which then controls the production of these reactive species and thereby maintains the oxidative load by regulating the lipid peroxidation process and glutathione level. This plant also protects the mice from γ-radiation due to its anti-oxidant property by inhibiting the ferrous sulphate generated lipid peroxidation. (Subramanian *et al.,* 2002; *Tiwari et al.,* 2018)
- Aqueous extract of this plant has already been reported to show scavenge activity due to the presence of anti-oxidant against free radicals generated during aflatoxicosis. Further alkaloids such as choline, tinosporine, isocolumbin, palmetine, tetrahydropalmatine and magnoflorine from *T. cordifolia* showed protection against aflatoxin induced nephrotoxicity. (Mittal *et al.,* 2014)
- Furthermore, *T. cordifolia* shows protective effect by lowering the concentration of thiobarbituric acid reactive substance (TBARS) and enhancing the glutathione (GSH), ascorbic acid, protein and the activities of anti-oxidant enzymes viz., superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase, glutathione S-transferase (GST) and glutathione reductase (GR) in kidney. However, leaf and stem extract of *T. cordifolia* has been reported to show Hepato-protective effect in male albino mice against lead nitrate induced toxicity. Similarly, oral dose of plant extract prohibited the lead nitrate induced liver damage. (Mittal *et al.,* 2014)
- *Gilo* has a potential ability to scavenge free radical and shows a protective effect by altering different hormone and mineral levels. *T. cordifolia* has

been reported to reverse the toxicity caused by aflatoxin in kidney (Swiss albino mice) where, it substantially elevates the hormone level (such as Glutathione) and enzyme activities (such as catalase, glutathione reductase); and decreases the reactive oxygen species (ROS). This anti-toxin activity is primarily brought by the alkaloids of this plant. Lead nitrate toxicity in swiss albino mice shows a decreased value in erythrocyte and leucocyte count in blood serum. However, the leaf and stem extract of *Gilo* works against these changes by overcoming the lead induced toxicity over haematological value. (Tiwari *et al.,* 2018)

- Extract of *Gilo* when given orally, has also reported to counter the toxic effects caused by lead nitrate in mice (swiss albino) liver. The study shows a decrease in level of the enzymes like glutamic pyruvic transaminase (GPT) or alanine aminotransferase (ALT) and aspartate aminotransferase (AST) and a rise in the enzyme responsible for scavenging free radical such as catalase. (Jayaprakash *et al.,* 2015; Tiwari *et al.,* 2018)

- *T. cordifolia* has found its importance in overcoming cyclophosphamide induced toxicity by substantially elevating the level of lowered GSH content, cytokines and gradually declining inflammatory cytokines (Tumor necrosis factor) level in urinary-bladder and hepatic cell preventing the damage which confirms its anti-toxin activity. (Tiwari *et al.,* 2018)

Immunomodulatory activity

- *T. cordifolia* is well known for its immunomodulatory response. This property has been well documented by scientists. A large variety of compounds which are responsible for immunomodulatory and cytotoxic effects are 11- hydroxymuskatone, N-methyle-2-pyrrolidone, Nformylannonain, cordifolioside A, magnoflorine, tinocordioside and syringin. These natural compounds have been reported to improve the phagocytic activity of macrophages, enhancement in nitric acid production by stimulation of splenocyte, and production of reactive oxygen species (ROS) in human neutrophil cells. (Mittal *et al.,* 2014; Upadhyay *et al.,* 2011; More *et al.,* 2010)

- Isolated chemical compounds such as cordifolioside A and syringin of guduchi are reported as immunomodulating agent in the clinical study. *T. cordifolia* stem alters the level of enzymes such as catalase and stimulates lymphocyte

cells maintaining the immune strength, thus highlighting the immuno-protective role of this shrub. (Sharma *et al.,* 2012; Tiwari *et al.,* 2018)

- Macrophage cell when exposed to *T. cordifolia* extract, increases the production of different enzymes including 'myeloperoxidase' that enhances the anti-microbial action so as to protect the immunity. On the other hand, it also increases the phagocytic activity of macrophages. Additionally, it stimulates splenocytes and macrophages. Because of enhanced nitric oxide production signifying anti-tumor as well as immuno-protective activity. (Aher *et al.,* 2012; Tiwari *et al.,* 2018)

- A clinical study showed that *T. cordifolia* lotion causes a decline in the level of interleukin i.e. IL-1 and IL-6 in scabies animal model. It inhibits hyperkeratosis and infiltration of inflammatory cells into scabietic gash, showing its anti-scabies activity. (Upadhyay *et al.,* 2011; Castillo *et al.,* 2014)

- Aqueous extract of *T. cordifolia* induces cellular mitosis, stimulates the production and activation of cytokine and immune effector cells. *T. cordifolia* is also able to increase the response of immune cell and neutrophil activity highlighting it as a potent agent for the prophylaxis of immune susceptible diseases. (Sudhakaran *et al.,* 2006; Upadhyay *et al.,* 2011; Tiwari *et al.,* 2018)

- Compounds of *Gilo* including alkaloids, steroids, aliphatic compounds etc. when tested preclinically in rat models, have shown a potent immuno-protective activity. A polysaccharide compound obtained from *T. cordifolia* recognised as G1-4A, enhances the proliferation and differentiation of immune cells i.e. T-cell and B-cell associated with the expression of the anti-apoptotic gene. (Raghu *et al.,* 2009; Tiwari *et al.,* 2018)

- The compound α-D-glucan obtained from *T. cordifolia,* has shown to maintain the body physiology by activating the cells of lymphocytes. Polymorphonuclear leucocyte (PMN) cells are important components of the host defense system. Extracts of T. cordifolia stimulated the PMN cells for phagocytosis. (Tiwari *et al.,* 2018; Koppada *et al.,* 2009; Salkar *et al.,* 2014)

- Oral administration of *T. cordifolia* alcoholic extract (100mg/kg) initiates an increase in foot pad thickness as well as in white blood cell (WBC) count and bone marrow cells indicating a stimulatory effect on haemopoetic system which shows a potent immunomodulatory action. (Umretia *et al.,* 2013; Aher *et al.,* 2010)

Anti-cancer/anti-tumor activity

- Various experimental models of animal have been taken to show the anti-cancer activity of plant *Gilo*. The radio protective property is well characterized by this plant as it considerably increases the weight of various tissues as well as body weight. In addition to this, it also protects from the gamma radiation (sub-lethal range) radiated on the testes of mice (Swiss Albino). The cultured HeLa cells when exposed to different concentration of methylene chloride extracts of *T. cordifolia* such as 0, 5, 10, 25, 50, and 100 µg/ml; it showed an increase in cell death or cell killing as compared to untreated cultured cell (control) in a dose dependent manner. (Tiwari *et al.,* 2018; Jagetia *et al.,* 1998; Singh *et al.,* 2006)

- A study has also reported that, the hydro-alcoholic extract of roots (aerial) of *T. cordifolia* on exposure to the liver as well as extra hepatic organs of mice (Swiss Albino) at 50 and 100mg/kg body weight shows an increase in Glutathione (GSH) level and other metabolizing enzymes. In addition to this, there is a significant decrease in production of malonaldehyde (MLD) level representing a decrease in free radical formation providing an antioxidative state of cell. (Tiwari *et al.,* 2018; Chaudhary *et al.,* 2008)

- An exposure of hexane extract of *Gilo* on mice having Ehrlich ascites tumor shows an inhibition of the proliferation of these tumor cell (G1 phase) and simultaneously it enhances the expression of 'Bax' gene (pro-apoptic) leading to apoptosis principally brought by caspases. (Tiwari *et al.,* 2018; Rao *et al.,* 2008)

- *Gilo* has been reported to possess a potent anti-tumor activity through a two stage skin carcinogenesis model conducted in mouse. It shows a decrease in papillary tumors, its weight and its occurrence while it also brings up the level of phase-II enzymes in the treatment group correspondingly. (Tiwari *et al.,* 2018; Thippeswamy *et al.,* 2007)

- *T. cordifolia* exhibited an add-on effect when combined with γ-radiation on mice introduced with cultured Ehlrich cells by decrease in Glutathione (GSH) level causing oxidative damage to these cancerous cells. (Verma *et al.,* 2011)

- *Gilo* extract in researcher's skin cancer model has shown to prevent the degree of micronucleus production in bone marrow cell and hence increases

the survival time in mice. However, *T. cordifolia* in combination with cyclophosphamide drug exhibits a cumulative effect in tumor inhibitory rate and survival percentage respectively. (*Tiwari et al.,* 2018; Ali *et al.,* 2013)

- An extract of the isolated active constituent palmatine of plant *T. cordifolia* clearly indicates the anti-cancer potential in a Dimethyl benzanthracene induced (DMBA) skin cancer model conducted in mice (Swiss Albino). (Mishra *et al.,* 2013)
- *T. cordifolia* also possesses anti-neoplastic property as it has significant ability in treating the brain tumor in C-6 glioma cell by decreasing the proliferation and differentiation rate as reported. The anti-cancer activity of secondary metabolite (such as magnoflorine, palmatine, jatrorrhizine, yangambin etc.) isolated from *Gilo* were tested in different types of tumor cells and among them 'palmatine' and 'yangambin' reported to treat KB cells while tinocordiside for colon cancer cell and oral cancerous cell (KB) respectively. On the contrary, most of the chemotherapeutic agents are synthetic by nature and have a number of adverse as well as severe toxic effects which is very minimal in case of herb *T. cordifolia*. So, it can be considered as a 'safe drug' for treating cancer disease as far as patient health is concerned. (Bala *et al.,* 2015; Tiwari *et al.,* 2018)

Additional activities

- The stem of *Tinospora cordifolia* has also been reported to possess anti-toxin, anti-diabetic, anti-cancer, anti-HIV, anti-microbial and hepato-protective activities.(Tiwari *et al.,* 2018; Mittal *et al.,* 2014)

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Gurmār
(Leaf and Root)
Gymnema sylvestre R. Br.

Introduction

The drug of *Gurmār* consists of leaf and root of *Gymnema sylvestre* R. Br. (Family-Apocynaceae), a large woody, climber, much branched, with pubescent young parts, found throughout India in dry forests up to 600 m. (Anonymous 2007b; Anonymous, 2008)

Fig. *Gurmār*

Vernacular Names

English: Gymnema, Periploca of the woods, small indian ipecac; Hindi: *Gurmār, Meshāsringī*; Urdu: *Gurmār Būtī*.(Anonymous 2007b; Anonymous, 2008; *Kabīruddīn*, 2000; Ghani, YNM; Nadkarni, 1976)

Temperament

Ḥār (Hot)^2 *Yabis* (Dry)^2 (Anonymous 2007b; Anonymous, 2008; *Kabīruddīn*, 2000; Ghani, YNM)

Chemical Constituents

Leaves of *G. sylvestre* contain triterpene saponins belonging to oleanane and dammarene classes. Oleanane saponins are gymnemic acids and gymnema saponins, while dammarene saponins are gymnemasides. The leaves also contain resins, albumin, chlorophyll, carbohydrates, tartaric acid, formic acid, butyric acid, anthraquinone derivatives, inositole alkaloids, organic acid (5.5%), parabin, calcium oxalate (7.3%), lignin (4.8%), cellulose (22%). The gymnemic acids contain several acylated (tiglolyl, methylbutyroyl etc.) derivatives of deacylgymnemic acid (DAGA) which is a 3-O-β-glucouronide of gymnemagenin (3β, 16β, 21β, 22α, 23, 28-hexahydroxy-olean-12-ene). The individual gymnemic acids (saponins)

include gymnemic acids I-VII, gymnemosides A-F, gymnema saponins. The presence of gymnemic acids, (+) quercitol, lupeol, (-) amyrin, stigma sterol etc. have been reported from *G. sylvestre*. A new flavonol glycoside namely kaempferol 3-O-beta-D-glucopyranosyl-(1-->4)- alpha-Lrhamnopyranosyl-(1-->6)-beta-D-galactopyranoside has also been found in aerial parts of *G. sylvestre*.

Three new oleanane type triterpene glycosides i.e. beta-O-benzoylsitakisogenin 3-O-beta-D-glucopyranosyl (1-->3)-beta-D-glucuronopyranoside, the potassium salt of longiospinogenin 3-O-beta-D-glucopyranosyl (1-->3)-beta-D-glucopyranoside and the potassium salt of 29- hydroxylongispinogenin 3-O-beta-D-glucopyranosyl (1-->3)-beta-D-glucopyranoside along with sodium salt of alternoside II were isolated from an ethanol extract of the leaves of *G. sylvestre*. Four new triterpenoid saponins, gymnemasins A, B, C and D isolated from the leaves of *G. sylvestre* were identified as 3-O-[beta-D-glucopyranosyl(1-->3)-beta-Dglucopyranosyl]-22-O-tiglyol-gymnemanol, 3-O-[beta-D glucopyranosyl (1-->3)-beta-D-glucuro - nopyranosyl]- gymnemanol, 3-O-beta-D-glucuronopyranosyl-22-O-tigloyl-gymnemanol and 3- O-beta-D-glucopyranosyl-gymnemanol respectively. The aglycone, gymnemanol, which is a new compound, was characterized as 3 beta-16 beta-22 alpha-23-28-pentahydroxyolean-12-ene. Gymnestrogenin, a new pentahydroxytriterpene from the leaves of *G. sylvestre* has been reported. (Anonymous 2007b; Saneja *et al.,* 2010; Khan *et al.,* 2019)

Pharmacological Actions

Leaf

- *Musakkin-i-'Aṣab* (Nervine sedative)
- *Muqawwi-i-A'ṣāb* (Nervine tonic)
- *Mulayyin* (Laxative)
- *Mulaṭṭif* (Demulscent)

Root

- *Musakkin-i-'Aṣab* (Nervine sedative)
- *Muqawwī-i-'Aṣab* (Nervine tonic)
- *Dāfi'-i- Sumūm* (Antidote)
- *Dāfi'-i-Dhayābīṭus* (Anti-diabetic)
- *Muqī* (Emetic)

- *Mukhrij-i-Balgham* (Expectorant)

(Anonymous 2007 b; Anonymous, 2008; *Kabīruddīn*, 2000; Ghani, YNM)

Therapeutic Uses

Leaf

- *Dhayābīṭus Sukkari* (Diabetes mellitus)
- *Amrāḍ-i-Qalb* (Cardiovascular diseases)
- *Salas al-Bawl* (incontinence of urine)

Root

- *Amrāḍ-i-Qalb* (Cardiovascular diseases)
- *Sammiyat-i-Afyūn* (Opium poisoning)
- *Dhayābīṭus* (Diabetes mellitus)

(Anonymous 2007 b; Anonymous, 2008; *Kabīruddīn*, 2000; Ghani, YNM)

Important Formulations

Qurṣ Dhayābīṭus Khāṣ (Anonymous 2007b)

Pharmacological / Clinical studies (evidence based)

Anti-oxidant activity

- Ethanol extract of this plant revealed significant ($p < 0.05$) 1, 1-diphenyl-2-picrylhydrazyl (DPPH) radical scavenging activity and showed better Anti-oxidant potential than *A. bilimbi* and *C. Frutescens*. (Rahman *et al.,* 2014)
- Anti-oxidant activity of *G. sylvestre* against DPPH was also observed in an investigation by Rupanar et al. (2012). This plant was found to have better DPPH radical scavenging than butylated hydroxyl toluene (BHT) and in another study it was also found to reduce LDL oxidation. (Ohmori *et al.,* 2005; Rupanar *et al.,* 2012)
- Recently, in another study, hydroxyl free radical scavenging activity and significant antioxidative potential of this plant against DPPH was reported where DPPH inhibition was at the level of 87.3% and hydroxyl free radical inhibition was 59.8%. (Gunasekaran *et al.,* 2019) It was also found to have

significant radical scavenging activity against ferric ($p < 0.05$), super oxide ($p < 0.05$) and also against hydrogen peroxide ($p < 0.05$). (Rachh *et al.,* 2009)

- *G. sylvestre* showed anti-oxidant activity in several conditions such as against high fat diets, hydrogen peroxide, nitric oxide, and superoxide radically induced oxidative stress in rats. (Arun *et al.,* 2014; Kishore and Singh, 2015)
- Anti-oxidant compounds like flavonoids, tannins, alkaloids, phenols, cinnamic acid, folic acid, ascorbic acid, butyric acid, tartaric acid etc. type of Anti-oxidants are present in *G. sylvestre*.

Immunomodulatory activity

- Methanolic leaf extract of *G. sylvestre* (MLEGS) showed immune-suppressive activity in Swiss Albino mice when it was tested by performing hemagglutination antibody (HA) titer, delayed-type hypersensitivity (DTH) tests and flow cytometric techniques for the estimation of B lymphocytes (CD3 and CD19) and Th2 cytokines (IL-2, IFN-γ and IL-4). This plant significantly reduced primary and secondary antibody response and DTH response in a dose-related manner. At 200 mg/kg body weight, the maximal reductions occurred in the production of CD3, CD19, IL-2, IFN-γ and IL-4 at the level of 31.59, 32.12, 29.51, 32.45 and 33.53%, respectively. (Ahirwal *et al.,* 2015) However, it was also perceived that *G. sylvestre* enhances the level of myeloid and lymphoid components of the immune system. Methanolic extract of this plant significantly increased ($p < 0.05$) the stimulation of Nitric oxide (NO) and Reactive Oxygen Species (ROS) by stimulation of macrophage activity and, also, significantly ($p < 0.05$) reduced nitroblue tetrazolium. (Singh *et al.,* 2015)
- Aqueous extract of *G. sylvestre* also stimulated the phagocytic function of human neutrophils suggesting an immunostimulatory activity. (Jitender *et al.,* 2009)
- Ethanol extract of this plant was observed to improve immunosuppressed condition induced by cyclophosphamide in Albino Rats. In this study, the plant extract significantly improved haemagglutination titer, phagocytic activity and decreased paw edema ($p < 0.01$, $p < 0.05$ and $p < 0.05$ respectively), when compared with cyclophosphamide treated control. (Kar *et al.,* 2019)
- In another study, potent immunostimulatory potential of the aqueous extract of this plant was observed. (Gupta *et al.,* 2009)

Anti-diabetic activity

- The most widely known effect of *G. sylvestre* is anti-diabetic activity. Ethanol extract of this plant is reported to reduce glucose level by 46% where the water extract reduced glucose level by 26% and methanol extract by 12%. (Mcburney and Gent, 1978; Luo *et al.,* 2006; Shah *et al.,* 2011; Shah *et al.,* 2012)

- In dexamethasone-induced insulin resistance rats, aqueous extract of this plant was found to be improving the altered glucose, insulin and lipid profile. (Kumar S, *et al.,* 2015) Administration of this plant in a diabetic animal model resulted in reductions in the blood levels of insulin, protein, triglycerides, cholesterol, and glucose, as well as a reduction in body weight and was found to improve liver histopathology. (Sujin, 2008)

- In another study where alloxan-induced diabetic rats were used, this plant extract significantly ($p < 0.05$) reduced fasting blood glucose level, total cholesterol, serum triglycerides and increase HDL-cholesterol level and is also described to significantly alter ($p < 0.05$) the elevated level of urea, uric acid and creatinine levels in diabetic rats to nearly normal levels. (Sathya *et al.,* 2008) *G. sylvestre* reduced the level of blood glucose levels after both acute and chronic administration of methanolic extract of this plant on Wister rats. (Dholi and Raparla, 2014)

- In the case of Streptozotocin-induced diabetic rats, it has been shown that treatment using this plant significantly ($p < 0.05$) decreased the elevated blood glucose, ALT, AST, triglycerides, total cholesterol, LDL-cholesterol, and malondialdehyde, and significantly ($p < 0.05$) increased insulin, HDL-cholesterol, and erythrocyte superoxide dismutase levels in diabetic rats and also is capable of regenerating insulin producing β-cells. (Aralelimath and Bhise, 2012; Kumar *et al.,* 2017)

- Gymnemic acids (a type of triterpene saponin compounds) are the class of active constituents isolated form *G. sylvestre*. It was found that gymnemic acid IV given at a dose of 3.4/13.4 mg/kg administered for 6 hours decreased blood glucose levels by 14.0–60.0% as compared to glibenclamide. Also, gymnemic acid IV increased plasma insulin levels in STZ-diabetic mice when administered at a concentration of 13.4 mg/ kg. (Sugihara *et al.,* 2000)

- In a study, oral administration of small concentrations (0.2 g/kg) of this plant produced a reduction in the elevated levels of blood sugar induced by sucrose. (Kang *et al.,* 1990) However, Galletto et al. (2004) also informed an absence of anti-diabetic activity of *G. sylvestre* in an alloxan treated animal model. (Khan *et al.,* 2019; Galletto *et al.,* 2004)

Anti-obesity activity

- *G. sylvestre* helps to promote weight loss possibly through its ability to reduce cravings for sweets and control blood sugar levels. It has been reported that the gurmarin peptide block the ability to taste sweet or bitter flavors and thus reduces sweet cravings. A standardized *G. sylvestre* extract in combination with niacin-bound chromium and hydroxycitric acid has been evaluated for antiobesity activity by monitoring changes in body weight, body mass index (BMI), appetite, lipid profiles, serum leptin and excretion of urinary fat metabolites. This study showed that the combination of *G. sylvestre* extract and hydroxycitric acid, niacin bound chromium can serve as an effective and safe weight loss formula that can facilitate a reduction in excess body weight and BMI while promoting healthy blood lipid levels. (Preuss *et al.,* 2004; *Saneja et al.,* 2010)

Anti-cancer activity

- *G. sylvestre* was found to have anti-cancer activity in various investigations. Its constituent gymnemagenol (C30H50O4) showed positive Anti-cancer activity against HeLa cells. (Khanna, 2010)

- The ethanolic, ethyl and chloroform extract were tested for anti-cancer activity against A549 (human lung adenocarcinoma) and MCF7 (human breast carcinsoma) cell lines. Theses extract revealed anti-cancer activity with a similar IC50 value against MCF cell lines where in the case of A549, ethyl and chloroform extract were more active than the ethanol extract. (Srikanth *et al.,* 2010)

- Ethanolic extract of *G. sylvestre* showed Anti-cancer activity in A375 cells (human skin melanoma). It showed cytotoxic activity against A375 cell and antitumor activity in skin Papilloma model where, in the case of normal liver cells WRL-68, it showed no cytotoxic activity. (Chakraborty *et al.,* 2013) It was revealed to have significant ($p < 0.0001$) inhibitory effect against intestinal breast cancer resistance protein (BCRP). (Tamaki *et al.,* 2010)

- In a study, the administration of flavonoids was found to be inhibiting BCRP and subsequently, improving multi-drug resistance of BCRP substrates that was induced by it. (Imai *et al.,* 2004) Thus, it can be suggested that inhibition of this protein by *G. sylvestre* may improve the activity of BCRP substrates methotrexate, daunorubicin, topotecan, epirubicin, flavopiridol, and so on by increasing systemic availability and absorption. (Mao, 2005)
- Ethanolic extract of this plant exhibited anti-proliferative effects in mice with two-stage carcinogenesis with a 50% inhibitory dose of 50–555 nmol/ear. (Yasukawa *et al.,* 2014) Polysaccharides (GSP11, GSP22, GSP33, GSP44 and GSP55) isolated from *G. sylvestre* was reported to have anti-cancer activity by improving immunological function through increasing phagocytic function, enhanced serum hemolysin levels, thymus, and spleen indexes. GSP11 and GSP33 showed inhibitory rates of 78.6% and 83.8%, respectively, against U937 cells and GSP22 showed activity against SGC cells with an inhibitory rate of 78.2%. (Wu *et al.,* 2012)
- In another study, anti-tumor potential of this plant was observed when methanolic extract of *G. sylvestre* was administered on Swiss albino mice where papillomagenesis was induced using carcinogen 7, 12 - dimethylbenz (a) anthracene (DMBA). Decreased tumor incidence, tumor burden and the cumulative number of papillomas were observed after the treatment with the plant extract. (Khan *et al.,* 2019)

Additional activities

- The drug *Gymnema sylvestre* has also been reported to possess anti-arthritic, hypo-lipidaemic, anti-microbial, free radical scavenging and anti-inflammatory activities. (Khan *et al.,* 2019; Saneja *et al.,* 2010)

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Halayla Zard
(Fruit)
Terminalia chebula Retz.

Introduction

The drug of *Halayla Zard* consists of the pericarp of mature fruit of *Terminalia chebula* Retz. (Family-Combretaceae), drug yielding plant is a moderate sized or large tree found throughout India, chiefly in deciduous forests and areas of light rainfall, but occasionally also in slightly moist forests, up to about 1500m elevation, throughout India; flowers appear from April-August and fruits ripen from October-January. (Anonymous, 2007a)

Fig. Halayla Zard

Vernacular Names

English: Chebulic Myrobalan; Hindi: *Harra, Harad, Har, Pīlī Har*; Urdu: *Halayla, Halayla Zard*; Arabic: *Halaylaj, Ihlīlaj Aṣfar*; Persian: *Halayla Kābulī* (Khān, 2018; Ibn Sīnā, 1987; *Ibn Baytār*, 2003; Ghani, YNM; Anonymous, 2007a)

Temperament

*Bā*rid (Cold)[1] *Yābis* (Dry)[2] (Khān, 2018; Ibn Sīnā, 1987; *Kabīruddīn*, 2000)

Chemical constituents

Tannins (about 32-34%): The tannins of *T. chebula* are of pyrogallol (hydrolysable) type. A group of researchers found 14 components of hydrolysable tannins (gallic acid, chebulagic acid, punicalagin, chebulanin, corilagin, neochebulinic acid, ellagic acid, chebulinic acid, 1, 2, 3, 4, 6-penta-O-galloyl*β*-D-glucose, 1, 6-di-o-galloyl-D-glucose, casuarinin, 3, 4, 6-tri-o-glloyl-D-glucose, terchebulin) from *T. chebula* fruits. Other constituents include **phenolics** such as chebulinic acid, ellagic acid and anthraquinones. Some of the other minor constituents were **polyphenols**

such as corilagin, galloyl glucose, punicalagin, terflavin A, maslinic acid. Besides, fructose, amino acids, succinic acid, betasitosterol, resin and purgative principle of anthraquinone are also present. **Flavonol, glycosides, triterpenoid**s, coumarin conjugated with gallic acids called chebulin as well as other phenolic compounds were also isolated. Twelve fatty acids were isolated from *T. chebula* of which palmitic acid, linoleic acid and oleic acid were main constituents. Triterpenoid glycosides such as chebulosides I and II, arjunin, arjunglucoside, 2αhydroxyursolic acid and 2α-hydroxymicromiric acid also have been reported. Oil extracted from kernels yielded palmitic, stearic, oleic, linoleic, behenic and arachidic acids. (Bae *et al.,* 2004; Bag *et al.,* 2013; Anonymous, 2007a)

Pharmacological Actions

- *Mu'mmir* (Longevity promoting agent)
- *Muqawwī-i-Dimāgh* (Brain tonic)
- *Muqawwī-i- Ḥāfiza* (Memory enhancer)
- *Muqawwī-i-Baṣar* (Eye tonic)
- *Muqawwī-i-Mi'da* (Stomachic)
- *Hāḍim* (Digestive)
- *Muqawwī-i- Am'ā'* (Intestinal tonic)
- *Musakkin* (Analgesic)
- *Muqawwī-i-Qalb* (Cardiotonic)
- *Mufarriḥ* (Exhilarant)
- *Muṣaffī-i-Dam* (Blood purifier)
- *Mushil-i-Sawdā'* (Melanagogue)
- *Musawwid-i-Sha'r* (Hair blackener)

(Khān, 2018; Ibn Sīnā, 1987; *Ibn Baytār*, 2003; Al-Harawi, 2002; Ghani, YNM; Anonymous, 2007a; *Kabīruddīn*, 2000)

Therapeutic Uses

- *Ḍu'f-i-Dimāgh* (Cerebrasthenia)
- *Ḍu'f-i-Mi'da* (Gastric debility)
- *Ḍu'f-i-Am'ā'* (Enteropathy)

- *Ḍu'f-i- Baṣar* (Poor eyesight)
- *Mālankhūliyā* (Melancholia)
- *Laqwa* (Bell's palsy)
- *Bawāsīr* (Haemorrhoids)
- *Khafaqān* (Palpitation)

(Khān, 2018; Ibn Sīnā, 1987; *Ibn Baytār*, 2003; Ghani, YNM; Anonymous, 2007a; *Kabīruddīn*, 2000)

Important Formulations

Iṭrīfal Kishnīzī, Iṭrīfal Zamānī, Iṭrīfal Ustūkhūdūs, Iṭrīfal Shāhtrā, Iṭrīfal Ṣaghīr, Iṭrīfal Mulayyin, Iṭrīfal Kabīr, Ma'jūn Kundur, Ma'jūn Khabath al-Ḥadīd, Kuḥl al-Jawāhir (Anonymous, 2007a)

Pharmacological / Clinical studies (evidence based)

Antio-xidant and free radical scavenging activity

- The leaves, bark and fruit of *T. chebula* possessed high anti-oxidant activity and phenolics were found to be responsible for this activity. (Bag *et al.,* 2013; Chang *et al.,* 2010)
- Aqueous extract of *T. chebula* inhibited xanthine/xanthine oxidase activity and was also an excellent scavenger of DPPH radicals. (Bag *et al.,* 2013; Naik *et al.,* 2004)
- *T. chebula* in a polyherbal formulation (Aller-7/ NR-A2) inhibited free radical induced hemolysis and also significantly inhibited nitric oxide release from lipopolysaccharide stimulated murine macrophages. (*Mahesh et al.,* 2009; Bag *et al.,* 2013)
- Six extracts and four compounds of *T. chebula* fruit exhibited Anti-oxidant activity at different magnitudes of potency. Strong anti-oxidant activity of aqueous extract of *T. chebula* was observed by studying the inhibition of radiation induced lipid peroxidation in rat liver microsomes at different doses, and methanolic extract was also found to inhibit lipid peroxide formation and to scavenge hydroxyl and superoxide radicals *in-vitro*. (Hazra *et al.,* 2010; Lee *et al.,* 2005; Lee *et al.,* 2007; Bag *et al.,* 2013)

- Acetone extract has stronger Anti-oxidant activity than alphatocopherol and HPLC analysis with diode array detection indicated the presence of hydroxybenzoic acid derivatives, hydroxycinnamic acid derivatives, flavonol aglycones and their glycosides, as main phenolic compounds. (Chen *et al.*, 2011; Bag *et al.*, 2013)

Immunomodulatory activity

- Crude extract of *T. chebula* stimulated cell-mediated immune response in experimental amoebic liver abscess in golden hamsters, aqueous extract of *T. chebula* produced an increase in humoral antibody titer and delayed type hypersensitivity in mice. Crude extract of *T. chebula* stimulated cell mediated immune response in experimental amoebic liver abscess in golden hamsters. (Bag *et al.*, 2013; Aher *et al.*, 2010)

- Immunomodulatory activity: Aqueous extract of *T. chebula* produced an increase in humoral antibody titer and delayed type hypersensitivity in mice. (Gambari *et al.*, 2006; Bag *et al.*, 2013)

Cyto-protective activity

- Gallic acid (GA) and CA were isolated from the extract of the herbal medicine *Kashi* (myrobalan, the fruit of *T. chebula*) as active principal that blocked the cytotoxic Tlyphocyte-mediated cytotoxicity. Granule exocytosis in response to anti-CD3 stimulation was also blocked by GA and CA at the equivalent concentrations. (Bag *et al.*, 2013; Chang *et al.*, 2010 a)

- The ethanolic extract of *T. chebula* fruit exhibited a notable cyto-protective effect on the HEK-N/F cells. In addition, its extract exhibited significant cyto-protective effect against UV-induced oxidative damage. These observations were attributed to the inhibitory effect of the *T. chebula* extract on the age dependent shortening of the telomere length as shown by the Southern Blots of the terminal restriction fragments of DNA extracted from sub-culture passages. (Minkyun *et al.*, 2004; Lee *et al.*, 2010; Bag *et al.*, 2013)

- It exhibited the development of duodenal ulcers and appeared to exert a cyto-protective effect on the gastric mucosa in vitvo. Cyto-protective effect on oxidative stress and inhibitory effect on cellular aging of its fruits have also been documented (Bag *et al.*, 2013)

Anti-carcinogenic activity

- A group of researchers have reported the inhibitory action on cancer cell growth by the phenolics of *T. chebula* fruit and found that chebulinic acid, tannic acid and ellagic acid were the most growth inhibitory phenolics of *T. chebula*. (Saleem *et al.,* 2002; Reddy *et al.,* 2009)
- Ethanol extract of *T. chebula* fruit inhibited cell proliferation and induced cell death in a dose dependent manner in several malignant cell lines including human (MCF-7) and mouse (S115) breast cancer cell line, human osteosarcoma cell line (HOS-1), human prostate cancer cell (PC-3) and a non-tumorigenic immortalized human prostate cell line (PNT1A). Besides, acetone extract of bark and fruit powder of *T. chebula* harbors constituents with promising anti-carcinogenic activity. (Bag *et al.,* 2013)
- Some pharmacological activities of *T. chebula:* Antimutagenic, radio-protective and chemopreventive and anti-mutagenic activity of aqueous extract and hydrolyzable tannins from *T. chebula* in Salmonella typhimurium has been documented. (Saleem *et al.,* 2002; Reddy *et al.,* 2009)
- Gamma radiationinduced strand breaks formation in plasmid PBR322 DNA was inhibited by aquesous extract of *T. chebula*. The administration of aqueous extract of *T. chebula* prior to whole body irradiation of mice resulted in a reduction of peroxidation of membrane lipids in the mice liver as well as a decrease in radiation induced damage to DNA. It also protected the human lymphocytes from undergoing the gamma radiation-induced damage to DNA exposed *in-vitro* . (Saleem *et al.,* 2002; Reddy *et al.,* 2009)
- *T. chebula* showed chemopreventive effect on nickel chloride -induced renal oxidative stress, toxicity and cell proliferation response in male Wistar rats (Bag *et al.,* 2013)

Additional activities

- The fruit of *Terminalia chebula* has also been reported to possess anti-mutagenic, radio-protective & chemopreventive, hepato-protective, cardio-protective, anti-bacterial, anti-fungal, anti-viral, anti-protozoal, anti-inflammatory, anti-arthritic, adaptogenic, anti-anaphylactic, hypo-lipidemic, hypo-cholesterolemic, gastro-intestinal motility improving & anti-ulcerogenic, anti-spasmodic, wound healing, purgative and anti-allergic activities. (Bag *et al.,* 2013)

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Jadwār
(Root)
Delphinium denudatum Wall.

Introduction

The drug of *Jadwār* consists of dried tuberous roots of *Delphinium denudatum* Wall. (Family-Ranunculaceae), an annual glabrous or slightly downy herb found in Western Himalayas from Kumaon to Kashmir at altitudes of 3, 000 to 4, 500 m specially on grassy slopes. (Anonymous, 2009)

Fig. *Jadwār*

Vernacular Names

English: Blood veined sage; Hindi: *Judwar*, *Nirbishi*; Urdu: *Jadwār*; Arabic: *Jadwār, Balūṭ al-Arḍ*; Persian: *Māh Parvīn.* (Khān, 2013; Ibn Sīnā, 1987; *Ibn Baytār*, 1985; Ghani, YNM; *Kabīruddīn*, 2000; Anonymous, 2009)

Temperament

Ḥār (Hot)[2] *Yābis* (Dry)[2] (Khān, 2013; Ibn Sīnā, 1987; Anonymous, 2009)

Chemical Constituents

- *Delphinium denudatum* (DD) have many bioactive constituents, some of which are flavonoids, triterpenoids, alkaloids, including delphocurarine, staphisagrine, delphine, condelphine, talatizidine, isotalatizidine, panicutine, hetisinone, 3-hydroxy-2-methyle-4H-pyran-4-one, denudatin, delnudine, delnuline, vilmorri anonymouse, vilmorrianone, diterpinoid alkaloid; 8-acetylhetero-phyllisine, and a diterpenoid alkaloid C25H39NO6 identical to condelphine. Diterpenoid alkaloids are generally of the veatchine or atisine type. Several pharmacologically active diterpenoid alkaloids of C19 and C20 were reported from different Delphinium species. (Aleem *et al.,* 2020; Asif *et al.,* 1981; Nayab *et al.,* 2017; Nizami *et al.,* 2006)

- Ahmad et al. isolated three new DD norditerpenoid alkaloids, 1β-hydroxy, 14β-acetyl condelphine, jadwarine-A, jadwarine-B, together with two known isotalatizidine hydrate and dihydropentagynine alkaloids. Denudatine (C21H33N02) contains two hydroxyls, an N-methyl, a C-methyl, and an exocyclic methylene group. Selenium dehydrogenation of denudatine gave 1-methyl-6-ethylphenanthreneandl-methyl-6-ethyl-3-azaphenanthrene characteristic products of the dehydrogenation of atisine. (Aleem *et al.,* 2020; Ahmad *et al.,* 2018; Abid *et al.,* 2017; Atta-ur-Rahman *et al.,* 1997)

- Sterol and fatty acids were detected at the roots of *Jadwār*. Campesterol, stigmasterol, and sitosterol were almost exclusively produced from sterols. Cholesterol and delta 5-avenasterol have also been identified in trace quantities. The gas-liquid chromatography analysis showed that there was a 1:3 ratio of saturated and unsaturated fatty acids. Characteristic higher plant fatty acids were also present. Fatty acids of DD are Capric, Lauric, Myristic, Palmitic, Palmitoleic, Stearic, Oleic, Linoleic, Linolenic. *Jadwār* root also contains sugar, protein, phenol, carbohydrate, iron, zinc, calcium, magnesium, and potassium. (Aleem *et al.,* 2020; Pelletier *et al.,* 1970)

Pharmacological Actions

- *Muqawwī-i-Ḥarārat Gharīziyya* (Tonic for innate heat)
- *Muqawwī-i-Aʿṣāb* (Nervine tonic)
- *Muqawwī-i-Aʿḍā' Raʾīsa* (Tonic for vital organs)
- *Muqawwī-i-Qalb* (Cardiotonic)
- *Mufarriḥ* (Exhilarant)
- *Musakkin* (Soothing agent)
- *Tiryāq-i- Sumūm* (Antidote)
- *Dāfiʿ-i- Ḥummā* (Anti-pyretic)
- *Mufattiḥ* (Deobstruent)
- *Muḥallil* (Resolvent)

(Khān, 2013; Ibn Sīnā, 1987; *Ibn Baytār*, 1985; Al-Harawi, 2002; Ghani, YNM; *Kabīruddīn*, 2000; Anonymous, 2009)

Therapeutic uses

- *Ḍuʿf-i-Ḥarārat Gharīziyya* (Innate heat insufficiency)

- *Ḍu'f-i-A'ṣāb* (Nervine weakness)
- *Ḍu'f-i-Qalb* (Cardiac insufficiency)
- *Ḍu'f-i-Mi'da* (Gastric debility)
- *Ḍu'f-i-Kabid* (Hepatic insufficiency)
- *Nazla Muzmin* (Chronic catarrh)
- *Iltihāb-i-Tajāwīf-i-Anf* (Sinusitis)
- *Ṣar'* (Epilepsy)
- *Istirkhā'* (Atony/flaccidity)
- *Hayḍa* (Cholera)
- *Yarqān* (Jaundice)
- *Qūlanj* (Colic)

(Khān, 2013; Ibn Sīnā, 1987; *Ibn Baytār*, 1985; Al-Harawi, 2002; Ghani, YNM; *Kabīruddīn*, 2000; Anonymous, 2009)

Important Formulations

Habb-i-Jadwār, Khamīra Gāozabān Ambarī Jadwār 'Ūd Salīb Wālā, Jawāhar Mohra, Marham-i-Jadwār. (Anonymous, 2009)

Pharmacological / Clinical studies (evidence based)

Anti-oxidant activity

- Siddique et al. evaluated the *In-vitro* and *In-vivo* anti-oxidant activity of aqueous root extract of DD. DPPH-HPLC method was used to carry out the free radical-scavenging activity of aqueous root extract. The *in-vivo* anti-oxidant potential of aqueous extract was screened in the animal model, and oxidative stress was induced by cisplatin. The result showed that aqueous root extract showed 83.38 per cent inhibition, where ascorbic acid (standard drug) was produced as a 92.67 per cent inhibition. It is concluded that the DD aqueous root extract has anti-oxidant activity and could offer a promising role in the treatment of nephrotoxin-induced renal injury such as cisplatin. (Siddique *et al.*, 2014; Aleem *et al.*, 2020)

Anti-anxiety activity

- Abid et al. investigated the anti-anxiety properties of DD root and *Amaranthus spinosus* leaves. The hydroalcoholic extract of both drugs was given to Wistar albino rats, and Elevated Plus Maze, Staircase, Actophotometer, and Light and Dark tests were used to evaluate antianxiety properties. Both the hydroalcoholic extracts have produced good anxiolytic activity in a dose-dependent manner. The best result was obtained by a combination of them in a higher dose. (Abid *et al.,* 2017; Aleem *et al.,* 2020)

Anti-depressant activity

- Zafar et al. evaluated the central depressant activity of the aqueous extract of *Jadwār* in mice, using pentobarbitone sodium-induced hypnosis (PSH), spontaneous motor activity (SMA), and open-field behaviour (OFB) tests. The results show that *Jadwār* induced a significant increase in pentobarbitone sodium-induced hypnosis in sleeping time. A significant decrease in activity counts on photo actometer readings was observed in the SMA test. In all the tests, the *Jadwār* extract showed consistent and significant depressant activity. (Zafar *et al.,* 2002; Aleem *et al.,* 2020)

Anti-convulsant activity

- Haidary et al. examined the impact of the jadwār-isolated aqueous fraction on Sustained Repetitive Firing (SRF) in neonatal cultured rat hippocampal pyramidal neurons. SRF blockade is one of the main cellular-level mechanisms of antiepileptic drugs. The aqueous fraction (0.2-0.6 mg/mg) results were compared to phenytoin, the standard antiepileptic drug. The findings indicate that Repeated Repetitive Firing in hippocampal neurons is inhibited by the aqueous fraction like phenytoin, in a use-dependent and voltage-dependent. The result concludes that aqueous fraction contains potent Anti-convulsant compounds. (Haidary *et al.,* 2004)

- Another research describes the FS-1 subfraction's anti-convulsant activities, which were obtained by purifying an aqueous fraction extracted from the *Jadwār* roots. In CF 1 mice, FS-1 showed very potent anti-convulsant activity, which was analogous to the effects of the well-known antiepileptic drug phenytoin in the Maximum Electroshock Test. Like the antiepileptic drug valproic acid (350 mg/kg), FS-1 also suppressed PTZ-induced trigger seizure and weakening of the righting reflex with tonic fore and hind limb

extension by 100 per cent. In 80 per cent of animals, BIC-induced seizures were suppressed. Nevertheless, FS-1 exhibited a weak anti-convulsant effect on PIC-induced seizures, significantly decreasing mortality and delaying seizures. FS-1 did not affect the extensor seizures caused by strychnine (STN). The results show the compounds' strong and potent Anti-convulsant activity in *Jadwār* FS-1. (Raza *et al.,* 2001a; Aleem *et al.,* 2020)

- In another study, Raza et al. performed anti-convulsant activity of *Jadwār's* ethanolic extract (EE) and aqueous fraction (AF) using maximum electroshock test (MEST) and pentylenetetrazol (PTZ), bicuculline (BIC), picrotoxin (PTX), and strychnine (STN) induced subcutaneous for anti-convulsant activity. In PTZ and BIC induced seizures, EE showed weak dose-dependent Anti-convulsant properties. AF comparatively more potent anti-convulsant activity against seizures induced by PTZ and BIC and exhibited dose-dependent activity against MEST's hind limb tonic extension phase. (Raza *et al.,* 2001b)

Morphine de-addiction activity

- A study assesses the role of ethanolic and methanolic extracts of the roots of DD in morphine dependence. Both extracts were administered p.o. in a different regimen. The result showed that the administration of EE and MF orally in both morphine-dependent groups caused a significant reduction in scores of "counted" and "checked" signs of morphine abstinence syndrome compared to the morphine control group. The EE and MF significantly reduced the mean scores of different 'counted signs' and 'checked signs' of morphine withdrawal syndrome and could prove to be an alternative remedy for morphine de-addiction. (Zaheer *et al.,* 2016)

- The de-addiction properties of DD in morphine-dependent rats are explored in another study. Rats have been made morphine-dependent by intra-peritoneal morphine sulphate injection. The alcoholic extract of DD was administered per oral in different regimens. The result showed that the DD extract caused a significant reduction in the frequency of "counted signs, " as well as "checked signs, " and can be an alternative remedy for morphine de-addiction. (Rahman *et al.,* 2002; Aleem *et al.,* 2020)

- In another study, the aqueous extract showed a substantial effect against morphine-induced tolerance and addiction in mice. Oral extract administration showed a significant dose-dependent withdrawal inhibition of

naloxone (Zafar *et al.,* 2002). Chronic treatment with DD suppressed dose-dependent morphine withdrawal. Repeated administration of DD attenuated the development of tolerance to the morphine analgesic effect, also produces a significant dose-dependent change in tail-flick latency from the pre-treated saline group. (Zafar *et al.,* 2001)

CNS activity

- In the 6-hydroxydopamine (6-OHDA) rat model of Parkinsonism, Ahmad et al. (2006) investigated the impact of *Jadwār* extract on the neuronal injury. Rats were treated for three weeks with *Jadwār* extract (200, 400, and 600 mg/kg BW). On day 22, 2 uL of 6-OHDA or a vehicle is injected into the animals' right striatum. The result showed that the dose-dependent *Delphinium* extract attenuated SOD and CAT activities in the striatum, which was substantially decreased by the lesion. After 6-OHDA injection, a substantial decrease in the dopamine level and its metabolites and an increase in dopaminergic D2 receptors in the striatum were observed. Both parameters were significantly recovered with extract treatment. Another research indicates that isotalatazidine hydrate isolated from the *Jadwar* aerial portion has a potent dual cholinesterase inhibitor and can *be used in Alzheimer's disease as a targeted drug. (Ahmad et al.,* 2017; Aleem *et al.,* 2020)

Additional activities

- The root of *Delphinium denudatum* has also been reported to possess anti-microbial, anti-nociceptive, hepato-protective, nephro-protective, cardio-protective and anti-asthmatic activities.(Aleem *et al.,* 2020).

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Jawz
(Kernel of fruit)
Juglans regia L.

Introduction

The drug of *Jawz* consists of kernel of fruit of *Juglans regia* L. (Family-Juglandaceae), a large deciduous, monoecious tree with tomentose shoots, found throughout the Himalayas upto an altitude of 900-3300 m. wild as well as cultivated and in Khasi Hills. (Anonymous, 2007d)

Fig. *Jawz*

Vernacular Names

English: Walnut; Hindi: *Akharot*; Urdu; *Maghz Akhrot*; Arabic: Jawz; Persian: *Girdgān, Gawz.* (Khān, 2013; Ibn Sīnā, 1987)

Temperament

Ḥār (Hot)[2] *Yābis* (Dry)[2] (Khān, 2013; Ibn Sīnā, 1987)

Chemical Constituents

Walnuts are nutrient-rich food due to high contents of fats, Juglandic acid, juglonone, proteins, vitamins and minerals. They are also good source of flavonoids, sterols, pecticsubstances, phenolic acids and related polyphenols. Triacylglycerols-monounsaturated fatty acids (FAs) (mainly oleic acid) and polyunsaturated FAs (PUFAs; linoleic and α-linolenic acids) are present in high amounts. Walnuts have high amount of omega-6 and omega-3 PUFA, which are essential dietary fatty acids. **Vitamis**- Folates, Niacin, Pantothenic acid, Pyridoxine, Riboflavin, Thiamin, Vitamin A, Vitamin E-y, Vitamin K. **Minerals**-Potassium, Phosphorus, Calcium, Magnesium, sodium, Iron, Copper, Manganese, Zinc and Aluminum. **Fatty acids**-Unsaturated fatty acids-Palmitoleic acid, Oleic acid, Gadoleic acid C20, Total MUFA, Linoliec acid C18, Lineliec acid C18, Total PUFA, Saturated fatty acid-

Myristic acid C14, Palmitic acid C16, Stearci acid C18, Archidic acid C20, Total SFAPUFA/SFA. (Abu Taha and Al-wadaan, 2011; Muradoglu *et al.*, 2010)

Pharmacological Actions

- *Muqawwī-i-Aʿḍā' Raʾīsa* (Tonic for vital organs)
- *Muqawwī-i-Aʿṣāb* (Nervine tonic)
- *Muqawwī-i Bāh* (Aphrodisiac)
- *Muwallid-i-Mani* (Spermatogogue)
- *Mulayyin* (Laxative)
- *Mulaṭṭif* (Demulcent)

(Khān, 2013; Ibn Sīnā, 1987; *Ibn Baytār*, 1985; Anonymous, 2007d; Ghani, YNM; *Kabīruddīn*, 2000)

Therapeutic Uses

- *Ḍuʿf-i-Dimāgh* (Cerebrasthenia)
- *Ḍuʿf-i-Aʿṣāb* (Nervine weakness)
- *Ḍuʿf-i- Ḥāfizā* (Poor memory)
- *Ṣudāʿ-i-ʿAṣabī* (Headache with neurological involvement)
- *Ḍuʿf-i-Bāh* (Sexual debility)

(Khān, 2013; Ibn Sīnā, 1987; *Ibn Baytār*, 1985; Anonymous, 2007d; Ghani, YNM; *Kabīruddīn*, 2000)

Important Formulations

Lubūb-ī-Kabīr, Lubūb-ī-Ṣaghīr (Anonymous, 2007d)

Pharmacological / Clinical studies (evidence based)

Anti-oxidant activity

- The anti-oxidant potential of ethyl acetate, butanol, meta-nol, ether and aqueous methanol extract of walnut kernels, husks and leaves were measured by different methods such as reducing power, scavenging activity on 2, 2-diphenyl-1-picrylhydrazyl (DPPH) radicals and lipid oxidation inhibition by β-carotene linoleate system. All the extracts showed strong anti-oxidant

activity (Qamar and Sultana, 2011; Carvalho *et al.,* 2010; Rahimipanah *et al.,* 2010; Zhang *et al.,* 2009b; Pereira *et al.,* 2008; Fukuda *et al.,* 2003).

- Bullo et al. (2010) reported a decrease in the Anti-oxidant burden observed in enzymatic and non-enzymatic Anti-oxidant systems after the consumption of a whole-walnut or a walnut-skin diet in C57BL/6 mice. The same author also reported that consumption of walnuts and walnut skins have no deleterious effect on low-density lipoprotein (LDL) oxidizing capability, despite their higher contents of omega-6 PUFAs.

- Several phenolic compounds isolated from *J. regia* such as pyrogallol, p-hydroxybenzoic acid, vanillic acid, ethyl gallate, protocatechuic acid, gallic acid, 3, 4, 8, 9, 10-pentahydroxydibenzo pyran-6-one, tannins, glansrins, adenosine, adenine etc., could provide a chemical basis for some of the health benefits claimed for *J. regia* in foods and folk medicine. (Zhang *et al.,* 2009a; Fukuda *et al.,* 2003).

Learning and memory activity

- The brain requires a sufficient amount of water, vitamins (such as folate, thiamine, vitamins B6, and B12), α-lipoic acid, lutein, and n-3 fatty acids. Walnuts contain a number of potential neuro-protective compounds such as gamma tocopherol (vitamin E), folate, melatonin, flavonoids, and phenolic acid (ellagic acid) and a significant amount of n-3 α-linolenic acid (ALA) (a plant-based omega-3 fatty acid). When 1, 113 different food items were analyzed for anti-oxidant content, walnuts ranked second. Memory is the process by which a learning experience is maintained over time. A single memory can be recalled by presenting a proper stimulus. Polyphenols have been shown to modulate critical neuronal signaling pathways involved in processes of learning and memory. The performance of C57BL/6J mice for learning and memory was done by Morris water maze test. Polyphenolic extracts from Walnut testa (42%) improved learning and memory functions in hypercholesterolemic mice based on obesity, hypercholesterolemia and oxidative stress. (Shi et al., 2014).

- Another researcher describes the neuro-protective activity of a 6% walnut diet against neurotoxicity in male rats induced by the anti-cancer drug cisplatin. The results showed that administration of walnut improved the cognitive and motor functions, demonstrating the potential benefits of including walnut in

the diet for combating chemotherapy induced disruptions of the motor and cognitive function. Previously it is studied that walnut extract can inhibit amyloid-β fibrillization, can solubilize its fibrils and has a protective effect against Aβ induced oxidative stress and cellular death. Recently researcher proved that dietary supplementation with walnuts 6% or 9% improved learning skills, memory, anxiety, locomotor activity, and motor coordination in the Tg2576 transgenic mouse model of Alzheimer's diseas. (Shabani et al., 2012; Muthaiyah et al., 2014)

Anti-depressant activity

- The macerated hexane extract of *J. regia* fruit produced significant anti-depressant activity at both doses of 100 and 150 mg/kg body weight when compared with standard drug fluoxetine on male Wistar rats. The anti-depressant activity was evaluated by forced swimming and tail suspension test. (Rath and Pradhan, 2009).

Hypotriglyceridemic activity

- Oral administration of a polyphenol-rich extract (WP) from walnuts (100 and 200 mg/kg) in high fat diet fed mice significantly reduced liver weight and serum triglycerides (TG) whereas hepatic β-oxidation in cytosol, including peroxisome, was enhanced by WP (50-200 mg/kg). A polyphenol-rich extract was found to possess hypotriglyceridemic activity via enhancement of peroxisomal fatty acid β-oxidation in the liver. These results suggest that tellimagrandin I is involved in the hypotriglyceridemic mechanism. (Shimoda *et al.,* 2009).
- Many Clinical studies suggest that omega-3 PUFA present in *Akhrot* have significant role in prevention of coronary heart disease (Davis *et al.,* 2007)

Anti-cancer activity

- Juglone has been reported to inhibit intestinal carcinogenesis induced by azoxymethane in rats and might be a promising chemopreventive agent in human intestinal neoplasia. (Sugie *et al.,* 1998)
- Juglone was also proven to be a potent cytotoxic agent *in-vitro* in human tumor cell lines, including human colon carcinoma (HCT15) cells, human leukemia (HL-60) cells and doxorubicinresistant human leukemia (HL-60R) cells. (Kamei *et al.,* 1998; Segura-Aguilaretal, 1992)

- In a recent study, Juglone inhibited the growth and induce apoptosis of sarcoma and 180 SGC-7901 cells *in-vivo*. The mechanism is mediated by the activation of the mitochondrial death pathway, which requires the generation of reactive oxygen species (ROS), downregulation of Bcl-2 protein expression and up-regulation of Bax protein expression. (Ji *et al.,* 2011)

- Walnut methanolic extracts obtained from J. regia seed, green husk and leaf showed concentration dependent growth inhibition against human renal cancer cell lines A-498, 769-P and the colon cancer cell line Caco-2. Concerning A-498 renal cancer cells, all extracts exhibited similar growth inhibition activity (IC50 values between 0.226 and 0.291 mg/mL), while in 769-P renal and Caco-2 colon cancer cells, walnut leaf extract showed a higher antiproliferative efficiency (IC50 values of 0.352 and 0.229 mg/mL, respectively) than green husk or seed extracts. (Carvalho *et al.,* 2010)

- The tested dried fine powder of *J. regia* light petroleum seed extract in cancer induced in Swiss albino mice with the help of 7, 12- Dimethylbenz(a) anthracene (DMBA) and croton oil showed the petroleum extract was significant in reducing the cancer cells. (Kumudhavalli *et al.,* 2010)

Additions activities

- The kernels of *Juglans regia* has also been reported to possess anti-bacterial, anti-fungal, anti-viral, anti-diabetic, analgesic, anti-inflammatory, anthelmintic, anti-tyrosinase, hepato-protective, cardio-protective and aphrodisiac activities. (Abu Taha and Al-wadaan, 2011).

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Jawzbuwa
(Fruit)
Myristica fragrans Houtt.

Introduction

The drug of *Jawzbuwa* is a fruit of *Myristica fragrans* Houtt. (Family-Myristicaceae). Nutmeg tree is an evergreen tree about 10–20 m in height, indigenous to India, Indonesia, and Sri Lanka. The nutmeg is ovoid, 2.0–3.5 cm long × 1.5–2.8 cm diameter, grayish brown in color with minute reddish brown spots and lines and is reticulately furrowed. In India, it is found in a few localities, chiefly botanic gardens, Kerala where the climate is sufficiently hot and moist. (Anonymous, 2007a)

Fig. *Jawzbuwa*

Vernacular Names

English: : Nutmeg; Hindi *Jāiphal*; Urdu: *Jawzbuwa*, *Jāiphal*; Arabic: *Jawz buwwa*, *Jawz al-Ṭīb*; Persian: *Jawzbuwa.* (Khān, 2013; Ibn Sīnā, 1987; *Ibn Baytār*, 1985; Ghani, YNM; Anonymous, 2007a; Ali *et al.,* 2018)

Temperament

Ḥār (Hot)[2] *Yābis* (Dry)[3] (Khān, 2013; Ibn Sīnā, 1987; *Ibn Baytār*, 1985; *Kabīruddīn*, 2000)

Chemical Constituents

Principal constituents of nutmeg are fixed oil, volatile oil, and starch. It also contains proteins cellulose, pentosans, resin, and mineral elements. Volatile oil is responsible for flavor and therapeutic action. Nutmeg is a good source of potassium, phosphorus, and magnesium. Nutmeg is reported to contain moisture,

14.3%; protein, 7.5%; carbohydrates, 28.5%; fiber, 11.6%; ether extract, 36.4%; and mineral matter, 1.7%; phosphorus, 0.24%; calcium, 0.12%; and iron, 4.6 mg/100 g. It contains volatile oil (6–16%), starch (14.6–24.2%), pentosans (2.25%), furfural (1.5%), and pectin (0.5–0.6%). It is a fair source of vitamins. The constituents of nutmeg can be broadly classified into terpenoids, fatty acids, phenolic acids, lignans, neolignans, and miscellaneous compounds. (Ali *et al.,* 2018)

Pharmacological Actions

- *Muqawwī-i-Ḥarārat Gharīziyya* (Tonic for innate heat)
- *Muqawwi-i-Aʿṣāb* (Nervine tonic)
- *Muqawwī-i-Qalb* (Cardio tonic)
- *Mufarriḥ (Exhilarant)*
- *Muqawwī-i-Baṣar* (Eye tonic)
- *Muqawwī-i-Miʿda* (Stomachic)
- *Hāḍim* (Digestive)
- *Kāsir-i-Riyāḥ* (Carminative)
- *Muqawwī-i-Kabid* (Hepato tonic)
- *Muqawwi-i-Bāh* (Aphrodisiac)
- *Moḥarrik-i-Bāh* (Libido stimulant)
- *Muqawwī-i-Raḥim* (Uterine tonic)
- *Dāfiʿ-i- Suʿāl* (Anti-tussive)
- *Dāfiʿ-i-Taʿaffun (antiseptic)*
- *Mudirr-i-Bawl* (Diuretic)
- *Mufattiḥ (Deobstruent)*
- *Musakkin-i-Alam* (Analgesic)

  (Khān, 2013; Ibn Sīnā, 1987; *Ibn Baytār*, 1985; Al-Harawi, 2002; Ghani, YNM; Anonymous, 2007a; *Kabīruddīn*, 2000; Ali *et al.,* 2018)

Therapeutic Uses

- *Ḍuʿf-i-Ḥarārat Gharīziyya* (Innate heat insufficiency)
- *Amrāḍ-i-Bārida* (Diseases of cold temperament)

- *Ḍu'f-i-Qalb* (Cardiac insufficiency)
- *Amrāḍ-i-Qalb* (Cardiac diseases)
- *Ḍu'f-i-Mi'da* (Gastric debility)
- *Sū'-i-Haḍm* (Indigestion)
- *Ḍu'f-i-Jigar* (Hepatic insufficiency)
- *Ḍu'f-i-Bāh* (Sexual debility)
- *Fālij* (Hemiplegia)
- *Istirkhā'* (Atony/flaccidity)
- *Khadar* (Numbness)
- *Laqwa* (Bell's palsy)
- *Ri'sha* (Tremor)
- *Waja' al-Mafāṣil* (Polyarthritis)

(Khān, 2013; Ibn Sīnā, 1987; *Ibn Baytār*, 1985; Al-Harawi, 2002; Ghani, YNM; Anonymous, 2007a; *Kabīruddīn*, 2000; Ali *et al.*, 2018)

Important Formulations

Anoshdārū, *Arq-i-Maullaham Khāṣ, Habb-i Mumsik Wa Mubahhi, Habb-iMuqawwi, Habb-i Zafaran, Jawarish Ood Shirin, Kushta-i Faulad, Kushta-i Shangarf, Luboob-i Kabeer, Majun-i Chob Chini, Majun-i Aarad Khurma, Majun-i Supari Pak, Safoof-i Mughalliz Jadid, Safoof-i Namak Sulaimani Khāṣ* (*Kabīruddīn*, 2000; Ali *et al.*, 2018)

Pharmacological / Clinical studies (evidence based)

Anti-oxidant activity

- The aglycone fraction from glycosidically bound volatiles of nutmeg had a stronger Anti-oxidant activity compared with free volatiles from its essential oil. Higher Anti-oxidant activity of nutmeg oil was reported at 180°C. This might be due to the volatilization of the hydrocarbons at higher temperature, resulting in the accumulation of phenolic constituents in the remaining oil. Administration of eugenol (10.7 mg/kg of body weight/day) removes the oxidative stress from rats imposed by CCl4. Eugenol, an allylbenzene and ingredient of nutmeg, that inhibits the accumulation of lipid peroxidation products in red blood cells and maintains the Anti-oxidant enzymatic activities such as superoxide dismutase, glutathione peroxidase, catalase,

glutathioneS-transferase(s), glutathione reductase, and glucose-6- phosphate dehydrogenase at normal levels. (Jukić *et al.,* 2006)

- Anti-cholinesterase activity tested of the ethyl acetate fraction of the methanol extract of *M. fragrans* Houtt. seeds isolated by various chromatographic techniques demonstrate it could be used beneficially in the treatment of Alzheimer's disease. (Kumaravelu *et al.,* 1996; Ali *et al.,* 2018)

Anti-depressant activity

- N-hexane extract of *M. fragrans* Houtt. seeds studied on depression in mice using the forced swim test (FST) and the tail suspension test (TST), extract elicited significant anti-depressant-like effect in both the TST and the FST. (Dhingra *et al.,* 2006; Ali *et al.,* 2018)

Anti-convulsant activity

- Volatile oil of nutmeg tested for its effects in maximal electroshock, subcutaneous pentylenetetrazole, strychnine, and bicuculline seizure tests. The results indicate its effect against grand mal and partial seizures, it prevents seizure. Slight potentiation of clonic seizure activity limits its use for the treatment of myoclonic and absence seizures. (Wahab *et al.,* 2009)

Anti-cancer activity

- The lignan constituents in the nutmeg are Anti-carcinogenic. The essential oil of nutmeg possesses admirable anti-carcinogenic activity, which have been well documented involving animals. The essential oil interferes with the activities of the host enzymes associated with activity and detoxicity of xenobiotic compounds including chemical carcinogens and mutagens. (Banerjee *et al.,* 1994)

- *In-vitro* and *in-vivo* mutagenic and anti-mutagenic effects of aqueous fraction of *M. fragrans* Houtt. (AFMF) leaves on TA100 strain of *Salmonella typhimurium* and *Mus musculus* (male Swiss albino mice), respectively, reveal that phytochemical is responsible for the observed anti-mutagenic activity. AFMF seems to contain a promising chemo-therapeutic agent for the prevention of genetic damage that is crucial for cancer development. (Akinboro *et al.,* 2014)

- The water extracts from the seeds of *M. fragrans* Houtt. Inhibit the *in-vitro* enzymatic activity of lactate dehydrogenase. The results showed as a potential

candidate for the development into a novel drug against cancer through inhibition of lactate dehydrogenase activity. (Kim *et al.,* 2016)

- A study of myrislignan on A549 cells *in-vitro* and *in-vivo* reveal a potential mechanism for the anti-cancer effect of myrislignan on human lung cancer, while suggesting that myrislignan may be a capable compound for the management of lung cancer. (Lu *et al.,* 2017; Ali *et al.,* 2018)
- Extract of *M. fragrans* Houtt. Fruit possessed strong inhibitory activity against *S. mutans*. The anti-cariogenic compound macelignan isolated from the methanol extract of *M. fragrans*, MIC of macelignan against *S. mutans* was 3.9 µg/mL, which was much lower than those of other natural anti-cariogenic agents such as 15.6 µg/ mL of sanguinarine, 250 µg/mL of eucalyptol, 500 µg/ mL of menthol and thymol, and 1000 µg/mL of methyl salicylate. Macelignan also possessed preferential activity against other oral microorganisms such as *Streptococcus sobrinus, Streptococcus salivarius, Streptococcus sanguis, Lactobacillus acidophilus*, and *Lactobacillus casei* in the MIC range of 2–31.3 µg/mµ. (Chung *et al.,* 2006; Ali *et al.,* 2018)

Additional activities

- The fruit of *Myristica fragrans* has also been reported to possess anti-bacterial, anti-amebic, anti-fungal, hypo-lipidemic, aphrodisiac, anxiogenic, analgesic, sedative, anti-inflammatory, hepato-protective, anti-diarrheal, digestive and anti-platelet activities. (Grover *et al.,* 2002; Wahab *et al.,* 2009; Sohn *et al.,* 2008; Zhang *et al.,* 2016; Morita *et al.,* 2003; Ali *et al.,* 2018)

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Kabāba
(Fruit)
Piper cubeba L.f.

Introduction

The drug of *Kabāba* consists of mature, dried fruit of *Piper cubeba L.f.* (Family-Piperaceae). Drug yielding plant is woody, climbing, perennial with dioecious flowers in spike, cultivated to a small extent in India, especially in the Karnataka state; fruits are collected when mature but still unripe and carefully dried. (Anonymous, 2007 a)

Fig. *Kabāba*

Vernacular Names

English: Cubebs, Tailed pepper; Hindi: Seetal Chini; Urdu: *Kabāb Chīnī* Arabic: *Ḥabb al-A'rūs, Kabāba*; Persian: *Kabābah*.(Khān, 2018; Ibn Sīnā, 1987; Ibn Baytār, 2003; Ghani, YNM; Anonymous, 2007a)

Temperament

Ḥār (Hot)[2] *Yābis* (Dry)[2] (Khān, 2018; Ibn Sīnā, 1987)

Chemical Constituents

The dried P. *cubeba* fruits contain essential oil consisting of monoterpenes: sabinene, β-elemene, α-thujene, carene, 1, 4-cineol and 1, 8-cineol; sesquiterpenes: b-caryophyllene, copaene, α- and β-cubebene, dcadinene, cubebol and germacene; and some lignans including the dibenzylbutyrolactone lignin i.e. (-) cubebin. Other Chemical Constituentsinclude allo aromadendrene, α-muurolene, α-pinene, α-terpinene, α-terpineol, asarone, β-bisabolene, β-pinene bicyclosesquiphellandrene, calamene, cesarone, cubebic acid, cubebinolide, cubenol, epicubenol, g-humulene,

g-terpinene, gum, ledol, limonene, linalol, myrcene, nerolidol, ocimene, resinoids, sabinol, and safrole. A lignan profile of P. cubeba from Indonesia has revealed 13 lignans found in the fruits, 15 in the leaves and only five lignans in the stalk. The structures of the lignans are very bio-diversified comprising of furanofuran lignans commonly found in the genus Piper such as cubebin, hinokinin, yatein, isoyatein, and neolignans with a curious structure such as kadsurin A and piperenone (Alam et al., 2013; Bharathi et al., 1985)

Pharmacological Actions

- *Muqawwī-i-Ḥarārat Gharīziyya* (Tonic for innate heat)
- *Muqawwī-i-Miʿda* (Stomachic)
- *Kāsir-i-Riyāḥ* (Carminative)
- *Muqawwī-i-Kabid* (Hepatotonic)
- *Muḥarrik* (Stimulant)
- *Muḥallil-i-Waram* (Anti-inflammatory)
- *Mufattit-i-Hasāt* (Lithotriptic)
- *Mufattiḥ-i- Sudad* (Deobstruent)
- *Mulaṭṭif* (Demulscent)
- *Qābiḍ* (Astringent)
- *Dāfiʿ-i-Taʿaffun (Antiseptic)*
- *Muddir-i-Bawl* (Diuretic)
- *Musakkin* (Soothing agent)

  (Khān, 2018; Ibn Sīnā, 1987; Ibn Baytār, 2003; Al-Harawi, 2002; Anonymous, 2007a; *Ghani, YNM;* Kabīruddīn, *2000;* Ahmad *et al., 2017)*

Therapeutic Uses

- *Ḍuʿf-i-Ḥarārat Gharīziyya* (Innate heat insufficiency)
- *Ḍuʿf-i- Miʿda* (Gastric debility)
- *Ḍuʿf-i-Kabid* (Hepatic insufficiency)
- *Khafaqān* (Palpitation)
- *Qulāʿ* (Stomatitis)
- *Qurūḥ-i-Lissa* (Gingival ulcers)

- *Bū-i Dahn* (Halitosis)
- *Waja' al-Mafāṣil* (Polyarthritis)
- *Yarqān* (Jaundice)
- *Su'āl Balghami* (Phlegmatic cough)
- *Iḥtibās-i-Bawl* (Retention of urine)

(Khān, 2018; Ibn Sīnā, 1987; Ibn Baytār, 2003; Al-Harawi, 2002; Anonymous, 2007a; *Ghani, YNM;* Kabīruddīn, *2000;* Ahmad *et al., 2017)*

Important formulations

Majūn-i-Anṭakī, Labūb-i-Saghīr, Sanūn-i-Mujalli, Dharūr-i- Qulā'Abyaz, Dharūr-i-Kath. (Kabīruddīn, *2000; Anonymous, 2007 a)*

Pharmacological / Clinical studies (evidence based)

Anti-oxidant activity

- Gayatri, studied and examined the pyridine class alkaloid i.e. piperine available in rich amount in Piper *nigrum* and *Piper cubeba having* family of Piperaceae. It is commonly used in preparation of various herbal cough syrups and used as anti-malarial, anti-inflammatory and anti-leukemia. Ethanol extract of *Piper cubeba is* also found to have high Anti-oxidant activity. (Gayatri and Sahu, 2011; Ahmad *et al., 2017*)
- Aboul-Enein, studied and examined *Piper cubeba* isolates for anti-oxidant action viz. magnitude of *Piper cubeba* capabilities to search free radicals, DPPH, hydroxyl radical (HO) and superoxide anion radical in different systems.(Aboul-Enein, 2010; Ahmad *et al., 2017)*

Anti-oxidant & hepato-protective activity

- Methanol and water extract of P. *cubeba* berries have shown to display an inhibitory effect against the hepatitis C virus. (Hussein et al., 2000)
- *Piper cubeba* ethanolic extract has been found effective in prevention of CCl4-induced hepatic damage in rats. Findings demonstrated that the treatment with PCEE significantly and dose dependently prevented drug induced increase in serum levels of hepatic enzymes. Furthermore *Piper cubeba* ethanolic extract significantly reduced the lipid peroxidation in the liver

tissue and restored activities of defense anti-oxidant enzymes NP-SH and CAT towards normal levels. The hepato-protective effect of PCEE is attributed to down regulation of pro-inflammatory cytokines, for example, TNF-□ and IL-6 mRNA expression as well as mRNA expression of iNOS and HO-1 gene, and up-regulation of the IL-10. Histopathological studies have also shown that the PCEE and silymarin could prevent CCl4-induced hepatic damage in the liver. (Mansour et al., 2015; Ahmad *et al., 2017)*

- The fruits of the *Piper cubeba* plant were studied for anti-oxidant and Hepato-protective activity. The anti-oxidant potential of the ethanol extract was examined using a 1, 1-diphenyl-2-picrylhydrazyl (DPPH) free radical scavenging activity, reducing power, hydroxyl radical scavenging activity, nitric oxide radical scavenging activity and hydrogen peroxide radical scavenging activity. The extract had significant dose-dependent anti-oxidant activity in all *in-vitro* experiments. Hepato-protective activity of the extract was evaluated in rat model of carbon tetrachloride (CCl4) induced liver damage. CCl4 significantly altered serum marker enzymes and total protein. The ethanol extract of *Piper cubeba* attenuated CCl4 induced serum marker enzymes and total protein. Histology of liver sections of the animals treated with the extracts showed the presence of normal hepatic cords, absence of necrosis and fatty infiltration which further evidence the Hepato-protective activity. (Amol et al., 2013; Ahmad *et al., 2017*

- In a study, extracts of *Piper cubeba* fruit were prepared using mechanical method. These extracts include alcoholic, acetonic, chloroformic and water extract. The chemical composition of each extract was analysed also. After that the anti-bacterial activity of these extracts were tested against gram negative (G-) Escherichia coli, Pseudomonas aeruginosa and gram positive (G+) Staphylococcus aureus. All extracts showed anti-bacterial activity on these bacteria, but ethanol and acetone extracts showed the best anti-bacterial activity aginst S. aureus, followed by chloroform extract and then water extract. On the other hand water extract showed inhibition activity against E. coli and P. aeruginosae followed by ethanol, acetone and chloroform extract. (Tamadher et al., 2013; Ahmad *et al., 2017)*

Anti-cancer activity

- Yatein is also an interesting lignan due to its biological activity and its function as a biosynthetic precursor of deoxypodophyllotoxin and podophyllotoxin

that are well known for their anti-cancer properties. It was found that P9605 significantly inhibited growth induced by beta-estradiol in MCF-7, a human breast cancer cell line. It inhibited aromatase activity, which is responsible for transforming androgens into oestrogens. Competitive binding assays also indicated P9605 binding to both human apoptosis. This anti-growth effect was less pronounced in androgen-independent PC-3 prostate cancer cell lines. P9605 potently inhibited 5 alpha-reductase II activity, which is responsible for converting testosterone to its active form, dihydrotestosterone (DHT), in the prostate. It also acted as an antagonist at recombinant wild-type androgen receptors (AR). P9605 suppressed cell growth and prostate-specific antigen (PSA) secretion stimulated by physiological concentrations of DHT in LNCaP cells. Interestingly, it down-regulated AR levels. In conclusion, the findings suggest that P9605 may potentially retard the growth of androgen-dependent PC via several mechanisms. (Miyakado and Nakayama 1989; Tepy et al., 2005; Ahmad et al., 2017)

Additional activities

- The fruit of *Piper cubeba* has also been reported to possess diuretic, nephro-protective, anti-microbial, anti-inflammatory, analgesic, anti-arthritic, anti-leishmanial and anthelmintic activities. (Muraleedharan et al., 1990; Karthikeyan et al., 2003; Ahmad *et al., 2017)*

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Khūlanjān
(Rhizome)
Alpinia galanga (L.) Willd.

Introduction

The drug of *Khūlanjān* consists of dried rhizomes of *Alpinia galanga* (L.) Willd. (Family-Zingiberaceae). The plant is found in the eastern Himalayas and South west India. It is also cultivated throughout India especially in East Bengal and South India. The plant occurs during late summer or early. Flowering takes place during April-May. (Anonymous, 2007b)

Fig. *Khūlanjān*

Vernacular Names

English: Galangal, Greater galangal, Siamese ginger; Hindi: *Kulanjan*; Urdu: *Khūlanjān*; Arabic: *Khūlanjān*; Persian: *Khusrūdārū* (Khān, 2013; Ibn Sīnā, 1987; Ibn Baytār, 1986; Anonymous, 2007b)

Temperament

Ḥār (Hot)^2 *Yābis* (Dry)^2 (Khān, 2013; Ibn Sīnā, 1987)

Chemical Constituents

A. galanga has been thoroughly studied by various researchers and a number of major as well as minor chemical constituents belonging to different classes of natural products have been isolated. In a study, 1'S'- 1'-acetoxychavicol acetate, 1'S'-1'-acetoxyeugenol acetate, 1'S'-1'-hydroxychavicol acetate, trans-*p*-hydroxycinnamaldehyde, trans-*p*-coumaryl alcohol, trans-*p*-hydroxycinnamyl acetate, and trans-*p*- coumaryl diacetate have been isolated from rhizomes. (Daubresse et al., 1994; Lee and Ando, 2001; Loubinoux et al., 1989).

The pungent principal compound, 1'S'- 1'-acetoxychavicol acetate has been reported to possess various biological activities such as anti-tumor, anti-inflammatory, anti-fungal, antioxidative and xanthineoxidase inhibitory activity (Zheng et al., 2002).

The GC–MS analysis showed that the main compounds of galangal extract are 1, 8-cineole, β- bisaboline and β-selinene. Whereas β-selinene, farnesene, 1, 2-benzenedicarboxylic acid, germacrene B and pentadecane are the minor components (Sookkongwaree et al., 2006). 1, 8- Cineole is an oxygenated monoterpenes, while β- caryophyllene is a sesquiterpene. In addition, β-bisabolene and β-selinene are terpenes. Mallavarapu *et al*, also reported similar main compounds in galangal, i.e., 1, 8-cineole, β-fenchyl acetate and camphor (Mallavarapu et al., 2002).

The rhizome also contains flavonoids, some of which have been identified as kaemperol, kaempferide, galangin and alpinin. Kaempferide, galangin and alpinin have also been isolated from galangal roots. The pale yellow oil with a pleasant odour is obtained from green rhizomes on distillation. The oil contains 48% methyl cinnamate, 20-30% cineole, α-pinene, β-pinene and camphor. Galangin (3, 5, 7-trihydroxyflavone) is a flavonoid with multiple biological activities. Several studies with this flavonoid suggest that it may have a potent anti- cancer effect, specifically through inhibition of the detoxification enzyme CYP1A1 and modulation of the aryl hydrocarbon receptor (Someya et al., 2001). Unique aroma components i.e., Hydroxy-1, 8-cineole glucopyranosides, (1R, 2R, 4S) and (1S, 2S, 4R)-trans- 2-hydroxy-1, 8-cineole β-D-glucopyranosides and (1R, 3S, 4S)-trans-3-hydroxy-1, 8-cineoleβ-D- glucopyranoside which are precursors of acetoxy-1, 8-cineoles have been isolated from the rhizomes of greater galangal (Someya et al., 2001).

Three new 8-9' linked neolignans, galanganal, galanganols A and B and a sesquineolignan, galanganol C, have also been isolated. The structures of new neolignans have been determined on the basis of physicochemical and chemical evidences (Morikawa et al., 2005; Chudiwal *et al.,* 2010).

Glycosides, proteins, carbohydrates, resins, steroids, triterpens, sodium, potassium, calcium, magnesium, iron, chloride, phosphate and sulphate, essential oil from rhizomes contained seven components-methyl cinnamate, cineole, 1-camphene, 1-borneol, methyl chavicol, cargene and α-pinene etc. are the common constituents present in the rhizome of Alpinia galangal. (Husain et al.1992; Anonymous, 2007b)

Pharmacological Actions

- *Muqawwī-i-Qalb* (Cardiotonic)
- *Mufarriḥ* (Exhilarant)
- *Muqawwī-i-Aʻṣāb* (Nervine tonic)
- *Muqawwī-i-Bāh* (Aphrodisiac)
- *Munaffith-i-Balgham* (Expectorant)
- *Mudirr-i-luāb-i-Dahan* (Sialagogue)
- *Musakkin* (Sedative)
- *Kāsir-i-Riyāḥ* (Carminative)
- *Jālī* (Detergent)

(Khān, 2013; Ibn Sīnā, 1987; Ibn Baytār, 1986; Anonymous, 2007b)

Therapeutic Uses

- *Ḍuʻf-i-Qalb* (Cardiac insufficiency)
- *Amrāḍ-i- Aʻṣāb* (Nervine diseases)
- *Ḍuʻf-i-Miʻda* (Gastric debility)
- *Ḍuʻf-i-Bāh* (Sexual debility)
- *Suʻāl* (Cough)
- *Buhūha al-Sawt* (Hoarseness)
- *Khushuna al-Halaq* (Irritation of throat)
- *Ḍīq al-Nafas* (Bronchial asthma)
- *ʻIrq al-Nasā* (Sciatica)
- *Qūlanj Rīhī* (Colic)
- *Amrāḍ-i- Jild* (Skin diseases)

(Khān, 2013; Ibn Sīnā, 1987; Ibn Baytār, 1986; Anonymous, 2007b)

Important Formulations

Habb-i-ʻĀmbar, Habb-i- Mumsik, Ḥalwa-i-Gazar, Jawārish Jālinūs, Jawārish Kundur, Jawārish Nārmushk, Jawārish Ūd shīrīn, Labūb Kabīr, Labūb Saghīr, Majūn Khadar Majūn Sīr ʻĀ lvī Khān (Anonymous, 2007 b)

Pharmacological / Clinical studies (evidence based)

Anti-aging activity

- Ahlina et al. (2020) studied the influence of the ethanolic extract of *A. galanga*l on normal fibroblast cells (NIH 3T3 cells) in order to investigate the anti-aging potential of *A. galanga*l ethanolic extract via a senescence inhibitory effect on NIH 3T3 fibroblast cells detected by a SA-Gal senescence-based assay. They found that the extract showed promising anti-aging potential to decrease cell senescence. (Ahlina et al. 2020)

Anti-oxidant activity

- Mahae & Chaiseri (2009) studied the anti-oxidant activity of aqueous extract containing 50% ethanol, and its composition compared with two other samples, namely essential oils and water extracts. Anti-oxidant activity was measured using the oxygen radical absorption capacity (ORAC) and 2, 2-diphenyl-1-picrillhidrazil (DPPH). It is reported that an ethanol extract had the highest free radical DPPH neutralizing ability and it is also reported that galangal rhizome has anti-oxidant activity when extracted with 1-acetoxychavicol acetate and its compounds. (Rao et al., 2010).

- A study was carried out with a methanolic extract from *Alpinia galanga* to evaluate anti-oxidant activity (AOA) and total phenolic content using the DPPH test, chelating iron ions, reducing power (RP) and the AOA β-carotene bleaching tests, the result showed that methanolic extract from *Alpinia galanga* has potent anti-oxidant activity. (Wong et al., 2009).

Immunostimulatory activity

- Ganesan et al. (2020) reported Immunomodulatory activities of flavonoid and phenolic content of methanolic extracts of *Alpinia galanga* (L.) Willd. Similarly, study reported Immunostimulating activity of the hot water-soluble polysaccharide extracts of *Alpinia galanga* and found potent immunostimulating activity in mice (Ganesan et al. 2020)

- Hot water polysaccharide extracts of *Alpinia galanga* (L.) Willd. Showed marked stimulating effect on the reticulo-endothelial system (RES) and increased the number of peritoneal exudate cells (PEC), and spleen cells of mice. Hence, hot water polysaccharide extracts of *Alpinia galanga* has immuno-stimulating activity. (Chouni and Paul, 2018)

- Immunomodulatory activity was carried out by examining T cell proliferation, splenocyte proliferation and by delayed type hypersensitivity reaction measurement. The flavonoid fraction of *Alpinia galanga* L. extract significantly stimulated (P <0.001) T cell proliferation and splenocyte proliferation in mice spleen at a dose of 100 mg/kg body weight of mice. The aqueous fraction had a lower stimulatory effect than the flavonoid fraction. The presence of quercetin in the flavonoid fraction was confirmed by chromatographic studies. The flavonoid fraction of *A. galanga* L. rhizomes has greater immunostimulating effects as well as Anti-oxidant effects in mice and the result showed that the extract has immunomodulatory effect. (Pal et al., 2012).

Anti-cancer activity

- An aqueous acetone extract from the fruit of *Alpinia galanga* demonstrated inhibitory effects on melanogenesis in theophylline-stimulated murine B16 melanoma 4A5 cells (IC50 = 7.3 µg/ml). In the investigation of the potential of *Alpinia galanga* rhizomes to induce cytotoxic and apoptotic effects in the cultured human breast carcinoma cell line, (MCF-7) in comparison with the non-malignant (MRC-5) cells cultured in DMEM medium, the percentage of apoptotic cells was determined by flow cytometry using Annexin-V fluorescein isothiocyanate. It was found that *Alpinia galanga* induced apoptosis in MCF-7 cells, as determined by flow cytometry. (Samarghandian et.al., 2014)

- The active compound, 1'S'-1'- acetoxychavicol acetate were found to provide inhibition of the growth of oral squamous cell carcinoma in *in-vitro* or *in-vivo* by inhibition of the constitutive activation of NF-κB through suppression of IKK*α/β* activation. The effect of the compound is also correlated with a down-regulation of NF-B regulated gene (FasL and Bim), including proinflammatory (NF-B and COX-2) and proliferative (cyclin D1) biomarkers in tumor tissue. (Arshad et.al., 2012; Itokawa et.al., 1987)

- *Alpinia galanga* was found to cause anti-tumor activity. Active compounds from *A. galanga* such as 1'-acetoxychavicol acetate and 1'-acetoxyeugenol acetate were isolated as anti-tumour principles against Sarcoma 180 ascites. The high dose of methanolic extract of *A. galanga* treated albino mice showed no estrogenic activity rather showed decrease uterine wet weight as well as morphologically constricted uterine horns which clearly suggests anti-estrogenic activity.1'-acetoxychavicol acetate (ACA) obtained from the rhizomes of *Alpinia galanga* induces apoptosis in myeloid leukemic cells

via independent dual pathways. ACA has potential as a novel therapeutic agent for the treatment of myeloid leukaemia. It is evident that low-dose ACA dramatically inhibited cellular growth of leukemic cells by inducing apoptosis. NB4 promyelocytic leukemic cells are sensitive to ACA. Reactive oxygen species production triggers ACA-induced apoptosis. In NB4 cells, ACA-induced apoptosis is in association with the loss of mitochondrial transmembrane potential and activation of caspase-9, suggesting that ACA-induced death signaling is mediated through a mitochondrial oxygen stress pathway. (Ito et.al., 2004; Phuah et.al., 2017; Sing et.al., 2012).

Additional activities

- The Rhizome of *Alpinia galanga* has also been reported to possess anti-microbial, anti-fungal, anti-inflammatory, hepato-protective, anti- HIV, anti-diabetic, anti-ulcer and anti-allergic activities. (Chouni and Paul, 2018)

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Kundur
(Exudate/Gum)
Boswellia serrata Triana & Planch.

Introduction

The drug of *Kundur* consists of exudate of *Boswellia serrata* Triana & Planch. (Family-Burseraceae), a moderate sized, deciduous tree, up to 18 m in height and up to 2.4 m in girth, commonly found in the dry forests from Punjab to West Bengal and in peninsular India. (Upaganlawar & Ghule, 2009)

Fig. *Kundur*

Vernacular Names

English: Olibanum; Hindi: *Shallaki;* Urdu: *Kundur*; Arabic: *Lubān*; Persian: *Kundur*. (Khān, 2018; Ibn Sīnā, 1987; Ibn Baytār, 2003; Kabīruddin, 2000; Ghani, YNM)

Temperament

Ḥār (Hot)^2 *Yābis* (Dry)^2 (Khān, 2018; Ibn Sīnā, 1987)

Chemical Constituents

The different species of Boswellia have more than 200 phytochemicals in oleo-gum-resin mixture. These compounds include essential oil, pure resin and mucus. The content and composition of oleo gum resin may vary from species to species depending upon age, quality of resin, geographical conditions. The resins of Boswellia species chiefly contain higher terpenoids i.e. pentacyclic triterpenes and tetracyclic triterpenes but the former are mainly considered to be responsible for its pharmacological effects. Chemically BA is 3-hydroxyurs-12-ene-23-oic acid. The BAs are common chemical characteristic features of all species of genus Boswellia.

The six major BAs are; a and b Boswellic Acids (BA, 10–21%), Acetylated a and b-Boswellic Acids (ABA, 0.05–6%), 11-keto-b-Boswellic acid (KBA, 2.5–7.5%) and 3-O-acetyl-11-keto-b-Boswellic acid (AKBA, 0.1–3%) are present in all Boswellia species. (Gupta et al., 2011; Gerbeth et.al., 2011; Al-Harrasi et.al., 2013; Husain *et al*., 1992)

Pharmacological Actions

- *Muqawwī-i-Ḥarārat Gharīziyya* (Tonic for innate heat)
- *Muqawwī-i-Qalb* (Cardiotonic)
- *Muqawwī-i-Dimāgh* (Brain tonic)
- *Muḥallil-i-Waram* (Anti-inflammatory)
- *Muqawwī-i-Bāh* (Aphrodisiac)
- *Hābis al-Bawl* (Anti diuretic)
- *Dafi'-i-Ta'affun* (Anti-septic)
- *Munaqqī* (Cleanser)
- *Mudammil-i- Qurūḥ* (Cicatrizant)
- *Munaffith-i-Balgham* (Expectorant)

(Khān, 2018; Ibn Sīnā, 1987; Ibn Baytār, 2003; Al-Harawi, 2002; Kabīruddin, 2000; Ghani, YNM)

Therapeutic Uses

- *Ḍu'f-i-Ḥarārat Gharīziyya* (Innate heat insufficiency)
- *Ḍu'f-i-Dimāgh* (Cerebrasthenia)
- *Ḍu'f-i-Qalb* (Cardiac insufficiency)
- *Ḍu'f-i-Bāh* (Sexual debility)
- *Kasrat-e-Bawl* (Polyuria)
- *Salas al-Bawl* (Urinary incontinence)
- *Qurūh Khabīsā* (Putrid ulcers)
- *Waja' al-Mafāṣil* (Polyarthritis)
- *Su'āl Balghamī* (Phlegmatic cough)

(Khān, 2018; Ibn Sīnā, 1987; Ibn Baytār, 2003; Al-Harawi, 2002; Kabīruddin, 2000; Ghani, YNM)

Important formulations

Jawārish Kundur, Majūn Kundur, Dawa-i-Salasul Bawl, Jawārish-i-Haḍim, Majūn-i-Nisyān, Sufūf-i-Masikul Bawl (Anonymous, 2010)

Pharmacological / Clinical studies (evidence based)

Immunomodulatory activity

- Cell mediated and humoral components of the immune system and the immunotoxicological properties of BA, was a subject of investigation by many studies. A detailed study on the structural requirements for BAs indicated that of all the six acids, AKBA shows most pronounced inhibitory activity against 5-LO. (Gupta et. al., 2011; Syrovets et.al. , 2000; Makare et.al., 2001; Farah et.al., 2017)

- Studies also showed anti-anaphylactic and mast cell stabilizing or inhibiting mast cell degranulation activity in passive paws anaphylaxis and induced mast cell degranulation of BA. Henkel et al. identified that functional target of BAs is the Anti-microbial peptide LL-37. It is the only member of the human cathelicidin family that have immune system-modulating properties and believed to play an important role in autoimmune disease development. MALDI-TOF mass spectrometry technique was used to study the binding of BAs to the target source, LL-37 in human neutrophils. This binding lead to inhibition of the functionality of LL-37 and thus could be used for developing agents to LL-37 related disorders (Pungle et.al., 2003; Henkel et.al., 2015; Farah et.al., 2017)

- Acetyl-11-keto-b-Boswellic acid (AKBA), KBA and *B. serrata* gum resin extracts exhibit variable actions in the immune system. A mixture of BAs in higher doses can reduce primary antibody titers in the humoral defense system while lower doses show enhanced secondary antibody titers after treatment with sheep erythrocytes. BAs appear to increase lymphocyte proliferation in the cellular defense but in higher concentration effects are inhibitory. The production or release of cytokines is affected by the BAs in addition to their increase activity of phagocytosis of macrophages. Suppressions of the classic way of the complement system was found to be due to inhibition of the conversion of C3 into C3a and C3b (Ammon, 2010; Farah et.al., 2017).

Clastogenic activity

- In Indian and Chinese traditional medicine, consumption of *Boswellia* species is believed to improve learning, memory, performance and cognitive skills. Traditionally it is used in the elderly for enhancement of memory and advised to be taken by pregnant women to increase the memory and intelligence of their offspring. Aqueous extract of *B. serrata,* Spirulina alga and *Withania somnifera* produce clastogenic effect and has potential to be used in stress relief, memory enhancement and memory boost. BA fraction of *B. papyrifera* also enhances spatial memory retention in male rats after systemic administration. These effects were observed to be dose dependent and could be due to the interaction of BAs with neurotransmitter signaling cascades or protein kinase pathways in the brain (Hosseini et.al., 2010; Mahmoudi et.al., 2011; Farah et.al., 2017)

- Mahboubi et al. found that combined treatment with Melissa officinalis and *B. serrata* extracts could prevent memory loss in scopolamine treated rats. They hypothesized that the protective actions of extracts on damaged brain cells could be due to multiple mechanisms of actions including anti-inflammatory effect (Mahboubi et.al., 2016; Farah et.al., 2017).

Neuro-protective activity

- Progression of several neurodegenerative disorders including Alzheimer's disease (AD) to cognitive, behavioral and functional impairment is mainly due to neuro-inflammation. *Boswellia* species and their active constituents BAs have been thoroughly investigated for their possible role in neuroprotection owing to their potent anti-inflammatory actions. Frankincense (oilbanum) is reported to protect against the streptozotocin induced AD in a rat model by virtue of their Anti-oxidant, anti-inflammatory and anti-acetylcholinesterase activities.(Zaker et.al., 2015; Beheshti and Aghaie, 2016)

- Ding et al. in 2015, evaluated the neuro-protective effects of AKBA and KBA against ischemic brain injury. They provided clear cut evidence that neuroprotection by both BAs in oxidative stress induced ischemic injury is via their activating effect on nuclear factor erythroid-2-related factor 2 (Nrf2)/ heme oxygenase-1 (HO-1) pathway (Ding et.al., 2014; Ding et.al., 2015).

- An study by Sayed and Sayed investigated the effect of monotherapies with AKBA and a selective cyclooxygenase-2 (COX-2) inhibitor (celecoxib) and

compared the effects with the combination therapy of AKBA, a 5- lipoxygenase (5-LO) inhibitor and celecoxib as dual enzyme inhibitors. An intraperitoneal injection of lipopolysaccharide (LPS) was used to induce cognitive dysfunction in mice. Molecular changes resulted following LPS and drug treatment were assessed by measuring glutamate, tumor necrosis factor-alpha (TNF-a) levels and by performing immuno-histochemical investigations of amyloid beta peptide (Ab). It was observed that co-administration of AKBA and celecoxib have a potentiating protective effect in cognitive impairment in mice induced by LPS. The combination therapy was able to reverse the behavioral and molecular changes caused by LPS cognitive dysfunction in mice. The study provides evidence that anti-inflammatory and anti-glutamatergic pathways are possibly implicated in this neuro-protective effect of AKBA (Sayed and Sayed, 2016)

Anti-inflammatory, anti-atherosclerotic activity and anti-arthritic activity

- Boswellia species have been used a folkloric medicine since ancient time to treat the inflammatory diseases. The data of numerous scientific studies clearly support the claim that *B. serrata* possess potent anti-inflammatory, anti-atherosclerotic activity and anti-arthritic activity. In one of the clinical trials, have also shown fair to excellent anti-inflammatory results in 88% of the patients, with no adverse side effects . (Mishra et.al., 2011; Kuo et.al., 2009; Farah et.al., 2017)

- The anti-inflammatory actions of BAs are observed due to the inhibition of leukotriene synthesis via 5-LO, however, it has no effect on the activities of 12-lipoxygenase (12-LO) and the cyclooxygenase (COX) enzymes. In addition to this, peroxidation of arachidonic acid by iron and ascorbate was also not impaired by BAs. Authors have proposed that BAs inhibit leukotriene synthesis either by blocking the translocation or interacting directly with 5-LO and anti-hyper-lipidemic activity of Boswellia. Salai gum maintains the serum cholesterol and triglycerides levels of animals in optimum range, which are fed on high cholesterol and saturated fat containing diet (Zutshi et.al., 1980;)

- AKBA showed to inhibit the activity of NF-kB in atherosclerosis. AKBA is also known to have anti-adipocity property by virtue of which it induces lipolysis in mature human adipocytes as shown by an *in-vitro* study carried out by Liu et al. Further, it was noticed that this phenomenon was accompanied

by downregulation of PPAR-g2 expression and loss of phenotypic markers (Cuaz-Perolin et.al., 2008; Liu et.al., 2013; Farah et.al., 2017).

Anti-cancer / anti-tumor activity

- Boswellia is a source of one of the most potent anti-cancerous agent occurring naturally. Methanolic extract of the gum resin exudates of B. serrata Boswellin (BE) showed presence of triterpenoids, b-Boswellic acid and its analogs. Huang et al. indicated that b-BA and its derivatives (the major constituents of Boswellin) have anti-carcinogenic, anti-tumor and anti-hyper-lipidemic activities. (Huang et.al., 2000)

- A number of researchers have also reported that pentacyclic triterpenes of Boswellia are one of the most promising anti-cancer agents. The BAs (AKBA, KBA) exerts their cytotoxic effects by inhibiting topoisomerase I & IIa leading to inhibition of cell growth and proliferation, by inducing apoptosis via a caspase-8 dependent pathway in human leukemia, colon, hepatoma and in various other cancer cell lines (Yuan et.al., 2013; Yadav et.al., 2011; Park et.al., 2011; Xia et.al., 2005; Suhail et.al., 2011; Farah et.al., 2017)

- A mass spectrometry based chemoproteomic approach have revealed that b-BAs inhibits protein synthesis by interacting with the ribosomal proteins and thus modulates cancer progression. When HL-60 cells were treated with Acetyl-11-keto-b-Boswellic acid (AKBA), prominent morphological changes were observed indicating that the cells underwent apoptosis. b-boswellic acid, 3-O-acetyl-b-Boswellic acid, 11-keto-b-Boswellic acid, and 3-O-acetyl-11-keto-boswellic acid when examined for their *in-vitro* antitumor activity they were found to inhibit the synthesis of DNA, RNA and protein in human leukemia HL60 cells in a dose dependent manner. Its effect on DNA synthesis was found to be irreversible. (Casapullo et.al., 2016; Shao Yet.al., 1998; Hoerlein et.al., 1999; Farah et.al., 2017)

- Pang et al. in 2009 evaluated the role of AKBA obtained from Indian frankincense on the growth of prostate tumor in humans. They found that AKBA significantly inhibited the growth of prostate tumor via inhibition of angiogenesis induced by activation of VEGFR2 and mTOR signaling pathways. An insight into the mechanism of chemo preventive actions of BAs especially AKBA in colorectal cancer cells (CRC) was provided by Takashi et al., 2012, They found significantly upregulation of the expression of the two putative tumor suppressive miRNAs such as let-7 and miR-200 families

(CDK6, vimentin and E-cadherin) in various CRC cell lines treated with AKBA. The results of their study confirmed that anti-tumor effects of AKBA are partly due to up regulation of certain miRNA pathways which make BA an ideal candidate for further studies in the treatment of CRC. (Pang et.al., 2009; Farah et.al., 2017)

- In a study oral administration of *Boswellia serrata* gum resin hydrodistillates (BSGRH) has showed to possess chemopreventive effects on urothelial cell carcinoma (Xia et.al., 2016). Similarly, the results of another study showed that supplementation with BAs can augment the antitumor effects of doxorubicin in solid tumors of Ehrlich's ascites carcinoma and can also protect mice against doxorubicin induced cardiotoxicity. (Ali et.al., 2015;; Farah et.al., 2017)

- Schneider and Weller studied the effect of AKBA and b-BA on nine long term human Glioma stem like cells, five glioma-initiating cell lines and examined the mechanism of acute growth inhibitory, anticlonogenic properties and assessed the potential synergy with temozolomide (TMZ) or irradiation. The results supported the earlier findings that BA are cytotoxic at low molecular concentration in glioblastoma and their use with irradiation and TMS lead to potential synergistic action. AKBA was found to have the highest activity in six out of nine LTCs and four out of five GICs in testing of acute growth inhibitory and anticlonogenic properties (Schneider and Weller, 2016;; Farah et.al., 2017).

Additional activities

- Exudate/gum of *Boswellia serrata* has also been reported to possess anti-diarrhoeal, analgesic psycho-pharmacological, anti-microbial, anti-asthmatic, hepato-protective, hypo-glycemic and hypo-lipidemic activities. (Farah et.al., 2017)

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Maṣṭagī
(Resin)
Pistacia lentiscus L.

Introduction

The drug of *Maṣṭagī* is a resin obtained from *Pistacia lentiscus* L. (Family-Anacardiaceae), a shrub or small tree indigenous to the countries bordering on the Mediterranean. (Anonymous, 2008)

Fig. *Maṣṭagī*

Vernacular Names

English: Mastich, Lentisco; Hindi: *Maṣṭagī*; Urdu: *Maṣṭagī*; Arabic: *'Ālk Rowmī*; Persian: *Kundur Rowmī*. (Khān, 2018; Ibn Sīnā, 1987; Ibn Baytār, 2003; Kabīruddin, 2000; Ghani, YNM; Anonymous, 2008)

Temperament

Ḥār (Hot)^2 *Yābis* (Dry)^2 (Khān, 2013; Ibn Sīnā, 1987)

Chemical Constituents

Terpinene-4-ol, α-terpineol , α–pinene , limonene , β-myrcene, p-cymene and α-phellandrene , β-caryophyllene, catechin tannins, flavonoids, saponins, sugar, volatile oil, a bicyclic terpenoid and fatty acids are the main constituents present in *Maṣṭagī* (Abdelkader *et al.*, 2016; Anonymous, 2008).

Pharmacological Actions

- *Muqawwī-i-Ḥarārat Gharīziyya* (Tonic for innate heat)
- *Muqawwī-i-Mi'da* (Stomachic)
- *Kāsir-i-Riyāḥ* (Carminative)
- *Muqawwī-i-Kabid* (Hepato tonic)

- *Muḥallil-i-Waram* (Anti-inflammatory)
- *Munaffith-i-Balgham* (Expectorant)
- *Mulaṭṭif* (Demulcent)
- (Khān, 2018; Ibn Sīnā, 1987; Ibn Baytār, 2003; Al-Harawi, 2002; Kabīruddin, 2000; Ghani, YNM; Anonymous, 2008)

Therapeutic Uses

- *Ḍu'f-i-Ḥarārat Gharīziyya* (Innate heat insufficiency)
- *Ḍu'f-i-Mi'da* (Gastric debility)
- *Nafkh-i-Shikam* (Flatulence)
- *Humūḍat-i- Mi'da* (Hyperacidity)
- *Ḍu'f-i-Kabid* (Hepatic insufficiency)
- *Ishāl* (Diarrhoea)
- (Khān, 2018; Ibn Sīnā, 1987; Ibn Baytār, 2003; Al-Harawi, 2002; Kabīruddin, 2000; Ghani, YNM)

Important Formulations

Jawārish Maṣṭagī, Jawārish Jālinūs, *Anoshdārū*, *Dawā ul Misk Mo'ātadil* (Anonymous, 2008; Kabīruddīn, 200)

Pharmacological / Clinical studies (evidence based)

Anti-oxidant activity

- The Anti-oxidant potential of the aqueous extract of *Pistacia lentiscus* was, measured by different chemical assays: DPPH radical scavenging activity, H2O2 scavenging activity, ferric reducing anti-oxidant power [FRAP] assay and total anti-oxidant assay by phosphomolybdate method. The study concluded that the aqueous extract of *Pistacia lentiscus* contained a high level of phenolic compound and has an effective anti-oxidant in different assay including DPPH radical, hydrogen peroxide scavenging, reducing power and total anti-oxidant capacity. (Ghenima et.al., 2015).
- In another study, anti-oxidant properties of galloyl quinic derivatives isolated from P. lentiscus, have been investigated by means of Electron Paramagnetic Resonance spectroscopy (EPR) and UV-Vis spectrophotometry. Anti-oxidant

properties were also estimated using the biologically relevant LDL test. The scavenger activities of gallic acid, 5- O-galloyl, 3, 5-O-digalloyl, 3, 4, 5- O-trigalloyl quinic acid derivatives, were estimated against 1, 1 diphenyl-2-picrylhydrazyl (DPPH) radical, superoxide radical, and hydroxyl (OH) radical. On the whole, the scavenger activity increased as the number of galloyl groups on the quinic acid skeleton increased. The half-inhibition concentrations (IC50) of di- and tri-galloyl derivatives did not exceed 30 mM for all the tested free radicals. All the tested metabolites strongly reduced the oxidation of low-density lipoproteins (LDL), following a trend similar to that observed for the scavenger ability against OH radical (Baratto et.al., 2003; Botsaris et al., 2015)

- Hemma et al. (2018) carried out the study of anti-oxidant activity of methanolic extracts of a plant from the Algerian flora: *Pistacia lentiscus*. The anti-oxidant activity of the methanolic extracts of *Pistacia lentiscus* has shown a significant reducing activity. These extracts could therefore be a source of natural anti-oxidant molecules as an alternative to the use of synthetic anti-oxidants.

- Saliha et al. (2013) reported the *Pistacia lentiscus* L. extracts contain high amounts of phenolics and exhibited high anti-oxidant activity.

Immunomodulatory activity

- Bouriche et al. (2016) carried out the immunomodulatory activity of *P. lentiscus* extracts by neutrophil migration and elastase release tests. The results showed that *P. lentiscus* extracts inhibited significantly the fMLP-stimulated neutrophils chemotaxis and elastase activity.

- Selloum et al. (2003) studied the immunomodulatory effect of *P. lentiscus* extracts on human's isolated neutrophils as a cellular model *ex vivo*. Similarly, Neutrophil elastase activity assay was conducted to study the immunomodulatory effect of *P. lentiscus* extracts which result showed having immunomodulatory activity.

Anti-cancer activity

- Balan et al., (2007) reported that a 50% ethanol extract of the plant-derived product, Chios mastic gum (CMG), contains compounds which inhibit proliferation and induce death of HCT116 human colon cancer cells *in-*

vitro. CMG treatment induces cell arrest at G1, detachment of the cells from the substrate, activation of pro-caspases-8, -9 and -3, and causes several morphological changes typical of apoptosis in cell organelles. These events, furthermore, are time and dose-dependent, but p53- and p21-independent. Apoptosis induction by CMG is not inhibited in HCT116 cell clones expressing high levels of the anti-apoptotic protein, Bcl-2, or dominant-negative FADD, thereby indicating that CMG induces cell death via a yet-to-be identified pathway, unrelated to the death receptor- and mitochondrion dependent pathways. (Balan et.al., 2007)

Additional activities

- The Resin of *Pistacia lentiscus* has also been reported to possess activities like anti-arthritic, anti-bacterial, anti-microbial, anti-fungal, hepato-protective, hypotensive, wound healing, anti-gout and antidiarrhoeal. (Rahman et.al., 2020)

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Muqil
(Exudate/Gum)
Commiphora wightii (Arn.) Bhandari

Introduction

The drug of *Muqil* consists of exudate of *Commiphora wightii* (Arn.) Bhandari, synonyms *Commiphora mukul* (Stocks) Hook. (Family-Burseraceae), a small perennial tree or shrub measuring up to 1.2-1.8 m, occurring in rocky tracts of Rajasthan and Gujrat. The exudate is collected during winter season by making incisions in the bark while in summer it exudes from the bark itself. (Anonymous, 2007a)

Fig. *Muqil*

Vernacular Names

English: Gum guga, Indian bedlellium; Hindi: Guggal; Urdu: *Muqil*; Arabic: *Muqil Azraq, Qifr*; Persian: *Bū i-Jahūdān*. (Khān, 2018; Ibn Sīnā, 1987; Ibn Baytār, 2003; Kabīruddin, 2000; Ghani, YNM)

Temperament

Ḥār (Hot)[3] *Yābis* (Dry)[2] (Khān, 2018; Ghani, YNM; Kabīruddīn, 2000)

Chemical Constituents

- *C. wightii* contains diterpenoids, triterpenoids, steroids, longchain aliphatic tetrols, aliphatic esters, ferulates, lignans, carbohydrates, and a variety of inorganic ions besides minor amounts of sesamin and other unidentified constituents. (Bhardwaj and Alia, 2019)
    - **Monoterpenoids:** The gum resin of *C. wightii* yields about 0.4% of essential oil which chief components are myrcene, dimyrcene, and polymyrcene.

- ***Diterpenoids:*** Diterpenoid constituents from guggulu include α-camphorene, cembrene-A, cembrene21 and other cembrenoids. Cembrene-A is one of the most elementary tetraenes derived from geranylgeranyl pyrophosphate by C-1 to C-14 cyclization. Mukulol (allylcembrol) is a new cembrane alcohol which was isolated from the aerial parts and also from the resin of guggulu.

- ***Triterpenoids:*** Polypodane-type triperpenes, myrrhanol A, B, and C, myrrhanone A, myrrhanone B, myrrhanone A acetate, commipherol, commipherin, and octanordammarane triperpenoid, epimansumbinol have been isolated from the gum resin. (Saxena and Sharma, 1998; Rucker, 1972; Prasad and Dev 1976.; Patil, 1973; Francis, 2004)

- **Steroids:** Isolation of several steroidal constituents has been reported from the gum resin. The major constituents include E-guggulsterone, Z-guggulsterone, guggulsterol-1, guggulsterolII, guggulsterol-III, guggulsterol-IV, guggulsterol-V and guggulsterol-VI. Cholesterol has also been reported. Three new and recently isolated steroids are guggulsterone-M, dihydro guggulsterone-M and guggulsterol-Y. The steroidal constituents have been related with hypo-lipidemic and anti-inflammatory activities of the drug. (Bhardwaj and Alia, 2019;; Francis, 2004)

- **Flavonoids:** An ethanolic extract of trunk of *C. wightii* was separated on column packed with silica gel to give a new Anti-fungal flavone named muscanone along with known naringenin. Muscanone was found to be active against *C. albicans* in microbial sensitive assay. The major flavonoid components of the flowers of *C. wightii* were identified as quercetin, quercetin-3-O-α-L-arabinose), quercetin 3-O-β-D-glucuronide, quercetin-3-O-β-Dgalactoside, quercetin-3-O-α-L-rhamnoside and pelargonidin-3, 5, di-O-glucoside. (Bhardwaj and Alia, 2019; Fatope et al., 2003)

- **Guggultetrols:** A crystalline material was isolated from the saponified gum resin which was characterized as a mixture of octadecan-1, 2, 3, 4-tetrol, nonadecan1, 2, 3, 4-tetrol and eicosan-1, 2, 3, 4-tetrol with minor amount of other components, possibly lower (C-16 and C-17) and higher (C-21 and C-22) homologous tetrols. These compounds constitute a new class of naturally occurring lipids, guggultetrols. (Saxena, & Sharma, 1998; Bhardwaj and Alia, 2019)

- **Lignans:** Two lignans, sesamin29 and diayangambin36 have been reported from guggulu. Also, 5, 5-tetrahydro-1*H*, 3*H*-furo[3, 4-c]furan-1, 4-diylbis[7-(methoxy)-1, 3-benzodioxole] has been reported from methanolic extract of guggulu. (Bhardwaj and Alia, 2019)
- **Sugars:** Complete hydrolysis of gum part of resin yielded L-arabinose, D-galactose, L-fructose (traces) and 4-O-methyl-D-glucuronic acid. Graded hydrolysis of the gum furnished an aldobiouronic acid [6-O-(4-O-methyl-β-D-glucopyranosyluronic acid)-D-galactose]. The provisional structure showed the gum to be a highly branched polysaccharide containing 1-6, 1-3, - and 1-5 type of linkage. (Bhardwaj and Alia, 2019)
- **Amino Acids:** The amino acids detected were cystine, histidine, lysine, arginine, aspartic acid, serine, glutamic acid, threonine, alanine, proline, tyrosine, tryptophan, valine, leucine, and isoleucine. (Bhardwaj and Alia, 2019)

Pharmacological Actions

- *Muḥallil-i-Waram* (Anti-inflammatory)
- *Muqawwī-i-Miʿda* (Stomachic)
- *Mulayyin* (Laxative)
- *Kāsir-i-Riyāḥ* (Carminative)
- *Muqawwī-i-Aʿṣāb* (Nervine tonic)
- *Mufattiḥ-i- Sudad* (Deobstruent)
- *Munaffith-i-Balgham* (Expectorant)
- *Muqawwī-i-Bāh (Aphrodisiac)*

(Khān, 2018; Ibn Sīnā, 1987; Ibn Baytār, 2003; Kabīruddin, 2000; Ghani, YNM Anonymous, 2007a)

Therapeutic Uses

- *Ḍuʿf-i-Miʿda* (Gastric debility)
- *Qabḍ* (Constipation)
- *Ḍuʿf-i-Aʿṣāb* (Nervine weakness)
- *Fālij* (Hemiplegia)

- *Laqwa* (Bell's palsy)
- *Ri'sha* (Tremor)
- *'Irq al-Nasā* (Sciatica)
- *Waja' al-Mafāṣil* (Polyarthritis)
- *Waja' al-Qaṭan* (Lumbago)
- *Ḍīq al-Nafas* (Bronchial asthma)
- *Bawāsīr* (Heamorrhoides)

(Khān, 2018; Ibn Sīnā, 1987; Ibn Baytār, 2003; Kabīruddin, 2000; Ghani, YNM Anonymous, 2007a)

Important Formulations

Habb-i-Muqil, Majun Muqil, Majun Jograj Gugal, Itrifa Muqil Mulaiyin, Habb-i-Shabyar, Iyarij Loghaziya (Anonymous, 2007a)

Pharmacological / Clinical studies (evidence based)

Anti-oxidant activity

- Siddiqui et al. (2013) reported physicochemical characterization and anti-oxidant activity of essential oils extracted from guggul (*Commiphora wightii*) exudates collected from different places in Madhya Pradesh, India. The guggul exudates were hydrodistilled for 3-4 h in Clevenger apparatus. The oil obtained was dried over anhydrous Na_2SO_4 and stored at 4° until testing. physico-chemical characterization of the extracted oils was carried out to determine their solubility, yield%, acid value (mg/KOH/g), saponification value (mg/KOH/g), ester value, iodine value (g/g), peroxide value (mEq/kg) and Fourier transformed infrared analyses. The Anti-oxidant potential of extracted oils was evaluated by free radical scavenging activity using 1, 1-diphenyl-2-picryl hydrazyl assay.
- The anti-oxidant property of guggulu helped stop the oxidation of cholesterol and subsequent hardening of the arteries, reduced the stickiness of platelet, and also lowered the risk of coronary artery disease. It also enhanced the production of thyroxin and triiodothyronine; the hormones that increase the metabolism of carbohydrates and protein synthesis and help in lowering the lipid activity (Panda and Kar, 1999).

- The anti-oxidant activity was attributed to the presence of guggulsterones. It was tested *in-vitro* against the formation of oxygen free radicals. The oxidation of human LDL induced by Fe2+ or by rat peritoneal macrophages caused marked formation of lipid peroxidation products. Guggulsterone (50 µM) prevented the generation of thiobarbituric acid reactive substances and lipid hydroperoxide of low density lipoprotein in above system. However, it did not protect lipids against the formation of conjugated dienes, the initial step of lipid peroxidation cascade. The protective action of guggulsterone might also be due to free radical scavenging property. The metal chelating capacity of guggulsterone might be contributing to its Anti-oxidant activity (Bellamkonda et.al., 2011)

Immuno-stimulatory activity

- Immuno-stimulatory, anti-oxidant, anti-cancer activities of *Commiphora wightii* have reported by Bhagyasree *et al.,* (2019).
- Diayangambin of *Commiphora wightii* has immunomodulatory and anti-inflammatory activity and also used to reduce the ear swelling (De Leon et al., 2002).

Cytotoxic activity

- Treatment with gugulipid significantly inhibited the viability of human prostate cancer cell line LNCaP (androgendependent) and its androgen-independent variant (C-81) with IC50 of 1 µM(24 h treatment), thus indicating its possible role in apoptosis and cancer prevention. The results of this study indicated that guggulsterone inhibited proliferation of PC-3 cells in culture by causing apoptosis, whereas a normal prostate epithelial cell line is resistant to growth inhibition and apoptosis induction by this phytoconstituent. These observations provided rationale for further preclinical and clinical evaluation of *Gugglu* (Zhu et.al. 2001. Xiao et.al. 2011).
- Ferulate compounds are used in the method for prevention and treatment of abnormal cell growth and proliferation of inflammation, neoplasia, and cardiovascular disease. Ethyl acetate extract showed significant *in-vitro* cytotoxicity. A fraction showing cytotoxic activity was characterized as a mixture of two ferulates with an unusual skeleton by spectral and chemicalmethods. This fraction also showed moderate scavenging effect against 2, 2-diphenyl-1- picryl hydrazyl (DPPH) radicals. (Zhu et.al. 2001).

Anti-obesity and hypo-lipidemic/ hypo-cholesterolaemic activity

- Crude Guggulu was found to reduce the body weight of hydrogenated ground-nut oil treated rabbits (Satyavati et al; 1969)
- Preliminary clinical trials on 22 patients of hypercholestrolaemia associated with obesity, IHD, HTN, DM etc. Guggulu crude was administrated orally (6.12mg in three divided doses for 15 days to one month. A fall in total serum cholesterol and serum lipidphosphorus was found in all the cases treated with Guggulu. The body weight of 10 patients of obesity also found to be reduced significantly (Satyavati, 1969)
- Crude Guggulu was reported to possess highly encouraging hypolipaemic activity in rabbits Anion exchange property detected by means of chloride retention and bile acid sequestrating activity in the oleoresin fraction hypocholesterolaemic activity. (Satyavati et al; 1988; Bhardwaj M and Alia, 2019).
- Crude drug as well as its two fractions (alcohol soluble and alcohol insoluble) were found to cause a significant fall in serum cholesterol and serum turbidity with a concomitant increase in the coagulation time and prothrombin time. The alcohol insoluble fraction was slightly more potent in this respect than alcohol soluble fraction as well as crude Guggulu.PE fraction A (petrol-soluble), B (alkali washed neutral portion) and C (petrol-insoluble) were given to 8 week old male white leg horn chicks for 2-3 weeks in hypercholesterolaemia induced by atherogenic diet. All fractions lowered the serum cholesterol, but fraction A was most potent and B was the least potent57. (Mehta, et.al., 1968;; Bhardwaj M and Alia, 2019)
- Alcohol extract and two pure fractions (a terpenoid and a steroid) isolated from the PE extract showed that the steroid fraction was highly potent as hypolipaemic agent lowering the serum cholesterol by 69.3% as well as the c/p ratio. The alcohol extract could lower the cholesterol by 59.2% whereas the Terpenoid lowered it by 54.3%. (Malhotra et.al., 1970; Bhardwaj M and Alia, 2019)
- The alcohol extract of Guggulu when orally administrated to Indian domestic pigs kept on standard atherogenic diet over a period of six weeks effectively reduced the total serum cholesterol and also serum beta-lipoprotein fraction and significantly altered the lipoprotein ratio.(Khanna, et.al., 1969)

- The steroidal compound isolated from fraction A of PE extract reduced the lipid content (Viz., total lipids, cholesterol, TG and phospholipids) of both hepatic and aortic tissues. The response was doses-dependent and the maximum effect was noted at 10mg/kg.(Malhotra, et.al., 1972; Bhardwaj M and Alia, 2019)
- Fraction A of PE extract of C. mukul, effectively lowered serum lipids, cholesterol, phospholipids and triglycerides in monkeys fed with cholesterol diet. (Das, et.al., 1973;; Bhardwaj M and Alia, 2019)
- Alcoholic extract (25-50 mg/kg orally), reduced serum cholesterol level in normal and hyperlipaemic rats and rabbits. Further, a resin fraction, a pure steroid and fraction F isolated from crude extract showed hypo-cholesterolaemic effect on normal and tritoninduced hyper-lipaemic rats (Kapoor and Nityanand 1971; Nityanand et.al., 1971; Bhardwaj M and Alia, 2019)
- The hypo-lipidemic activity was shown in animals as well as in patients of obesity and hyper-cholesterolemia (Satyavati, 1988; Bhardwaj M and Alia, 2019)
- A number of clinical studies were carried out to confirm hypo-lipidemic activity of guggulu and gugulipid (Nityanand, et.al., 1989; Verma and Bordia, 1988)
- In another study, highly significant reduction in levels of mean serum cholesterol and triglyceride was observed in groups of animals receiving high-fat diet for one month along with guggulu, which clearly demonstrated its hypo-lipidemic activity. Additionally, administration of guggulu partially reversed the atherosclerosis in the aorta that was induced by high fat diet (Baldwa, et.al., 1981; Bhardwaj M and Alia, 2019)
- Clinical studies on *C. mukul* showed its hypo-lipidemic effect and the outcome of change in lipid profile upon its administration. This study showed significant decrease in total cholesterol and LDL cholesterol after treatment with guggulu (Hasani et.al., 2010; Bhardwaj M and Alia, 2019).
- The hypo-lipidemic activity of the isomers *E*- guggulsterone and *Z*-guggulsterone has also been studied in animal models. Administration of guggulsterone (*E* and *Z*) significantly lowered serumlipid levels of rats with either triton (WR-1339) or cholesterol-induced hyperlipidemia (Chander et.al., 1996; Bhardwaj M and Alia, 2019)

Additional activities

- The Resin of *Commiphora wightii* has also been reported to possess activities like platelet aggregation, fibrinolytic, thyroid stimulatory, anti-bacterial, anti-inflammatory & anti-arthritic, hypo-glycaemic, anti-fertility, anti-microbial, cardio-protective and anti-atherosclerotic. (Bhardwaj M and Alia, 2019)

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Raiḥān
(Leaf)
Ocimum tenuiflorum L.

Introduction

The drug of *Raiḥān* consists of dried leaf of *Ocimum tenuiflorum* L., Syn. *Ocimum sanctum L.* (Family-Lamiaceae), an erect, 30-60 cm high, much branched, annual herb, found throughout the country. (Anonymous, 2008)

Fig. Raiḥān

Vernacular Names

English: Holy Basil, Thai Basil; Hndi: *Tulsi*; Urdu: *Raiḥān*, Tulsi; Arabic: *Shāhasfaram*; Persian: *Raiḥān*. (Khān, 2013; Ibn Sīnā, 1987; *Ibn Baytār*, 1999; Ghani, YNM; Anonymous, 2008)

Temperament

Ḥār (Hot)[1] *Yābis* (Dry)[1] (Khān, 2013; Ibn Sīnā, 1987)

Chemical Constituents

The phenolic compounds present in the crude extract and its fractions of *Ocimum tenuiflorum* leaves were 3, 4-dimethoxycinnamic acid, caffeic acid, permethrin, and rosmarinic acid; other compounds reported include kaempferol, luteolin (flavonoid), kaempferide (flavonol), chrysoeriol (flavon), xanthomicrol (flavonoid), isosakuranetin (Flavanone) and robinetin trimethyl ether (flavonoids). Some more compounds such as peonidin, diosmetin, nevadensin, anthocyanidins, flavone glycoside, flavones, and glycosides were identified from *Ocimum tenuiflorum* leaves crude extract and its fractions.

The novel compounds identified in *Ocimum tenuiflorum* leaves crude extract and its fractions for the first time were pedunculin, 3, 4, 5-trimethoxycinnamic acid, di

(ethylhexyl) phthalate and 4, 4'-methylene-bis (2-methyl aniline), isosakuranetin, and robinetin trimethyl ether frequently.

Leaves also contain tannin, flavonoid, and glycoside, ursolic acid, apigenin, saponin orientin, molludist (Joshi *et al.*, 2011; Mousavi *et al.,* 2018; Anonymous, 2008).

Pharmacological Actions

- *Muqawwī-i-Qalb* (Cardio tonic)
- *Mufarriḥ* (Exhilarant)
- *Muqawwī-i-Miʻda* (Stomachic)
- *Munaffith-i-Balgham* (Expectorant)
- *Muḥallil-i-Waram* (Anti-inflammatory)
- *Muddir-i-Bawl* (Diuretic)
- *Mulaṭṭif* (Demulscent)

(Khān, 2013; Ibn Sīnā, 1987; *Ibn Baytār*, 1999; Ghani, YNM; Anonymous, 2008; Kabīruddīn, 2000)

Therepeutic Uses

- *Ḍuʻf-i-Qalb* (Cardiac insufficiency)
- *Khafaqān* (Palpitation)
- *Ḍuʻf-i-Miʻda* (Gastric debility)
- *Suʻāl* (Cough)
- *Nazla* (Catarrh)
- *Zukām* (Coryza)
- *Ḍīq al-Nafas* (Bronchial asthma)
- *Ishāl* (Diarrhoea)
- *Tap-i-Balghamī* (Phlegmatic fever)
- *Yarqān* (Jaundice)

(Khān, 2013; Ibn Sīnā, 1987; *Ibn Baytār*, 1999; Ghani, YNM; Anonymous, 2008; Kabīruddīn, 2000)

Important formulations

Khamīra Ābresham ʻŪd Maṣṭagiwālā, ʻĀrq Māul laḥam ʻĀmbarī (Anonymous, 2008)

Pharmacological / Clinical studies (evidence based)

Anti-oxidant activity

- Anti-oxidant activity of *Ocimum sanctum* was carried out performing total phenolic content test and DPPH to identify the percentage of scavenging by the chemical constituents. The total phenolic contents and DPPH radical scavenging showed anti-oxidant result. (Khān *et al.,* 2018; Sood et al., 2010)

- Harichandan et al. (2019) observed that *Ocimum sanctum* L. has been suggested to possess, anti-cancer, anti-diabetic, anti-fertility, anti-fungal, anti-microbial, cardio-protective, analgesic, anti-spasmodic and adaptogenic actions with Eugenol (1-hydroxy-2methoxy-4-allylbenzene) as active constituent. They revealed that *O. sanctum* may heal many chronic diseases due to its chemical constituent that is believed to have anti-ageing, immunomodulatory, anti-microbial and anti-cancer properties. They also observed that the plant is known to possess antiseptic, analgesic, anti-inflammatory, anti-stress, hypoglycemic, hypertensive and anti-oxidant properties.

Immunomodulatory activity

- Godhwani et al. (1988) investigated the immune-regulatory profile of methanolic extract and aqueous suspension of *O. sanctum* L. leaves to antigenic challenge of *Salmonella typhosa* and sheep erythrocytes by quantifying agglutinating antibodies employing the Widal agglutination and sheep erythrocyte agglutination tests and E-rosette formation in albino rats. The study data indicated an immune-stimulation of humoral immunogenic response as represented by an increase in antibody titre in both the Widal and sheep erythrocyte agglutination tests as well as by cellular immunologic response represented by E-rosette formation and lymphocytosis.

- Basil polysaccharides has anti-tumor, anti-oxidant, anti-aging activity with anti-bacterial effects, anti-atherosclerotic effects, immunity enhancement effect and useful in treatment of diabetes mellitus (Feng *et al*., 2019)

- *Shahrajabian et al.,* (2020) reported pharmacological activities of *Ocimum tenuiflorum* as anti-cancer, radio-protective, anti-microbial, anti-inflammatory, immunomodulatory, anti-stress, anti-diabetic, anti-pyretic, anti-arthritic and anti-oxidant besides, it may be used as a prophylactic agent and in cardiovascular disease.

- *Jeba et al.,* (2011) studied that aqueous extract of *Ocimum sanctum* at the oral doses of 100, 200 mg/kg/day in rats enhanced the production of RBC, WBC, haemoglobin and also enhanced the production of antibodies without affecting biochemical parameters.
- *Ocimum tuniflorum* shows anti-oxidant activities like scavenging superoxide anion radicals, 1, 1-diphenyl-2-picrylhydrazyl radicals (DPPH), hydroxyl radicals, hydrogen peroxide, chelating ferrous iron, and ferric ion reducing potential (*Hakkim et al.*, 2007).
- *In-vitro* method with hot aqueous extracts (HAE) of *O. sanctum* leaves had proliferative as well as inhibitory effect on splenocytes. In comparison to negative control, 42.17, 55.42 and 47.38% increase in the proliferation of spleen cells were reported when splenocyte culture was treated with 31.25, 62.5 and 125 µg/ml HAE of O. sanctum, respectively. However, 33.73 and 45.78% inhibitions were reported when splenocyte culture was treated with 250 µg/ml and 500µg/ml HAE of O. sanctum, respectively. In comparison to positive control, spleen cells with HAE of *O. sanctum* leaves in presence of Con-A exhibited 1.25 and 12.36% increase in the proliferation of spleen cells when splenocyte culture was treated with 31.25µg/ml and 62.5 µg/ml HAE of O. sanctum, respectively. However 17.78, 63.61 and 75.55% inhibitions were observed when splenocyte culture was treated with 125, 250 and 500 µg/ml HAE of *O. sanctum* leaves with Con-A, respectively (*Kumar* et al., 2013).
- Cytokines are the biomolecules released by the cells during the process of immunomodulation thus when HAE of *O. sanctum* leaves were used to study in-vitro cytokine IL-10 secretion, splenocytes treated with HAE of *O. sanctum* leaves compared with negative control (only spleen cells) revealed 3.48, 9.76, 5.23 and 0.23% induction of the IL-10 secretion at dose rate of 31.25, 62.5, 125 and 250µg/ml of *O. sanctum* leaves extract, respectively, whereas 9.41% reduction in cytokine secretion was reported at dose rate of 500 µg/ml of extract. The maximum induction of 9.76% was observed with 62.5µg/ml of *O. sanctum* leaves extract in absence of Con-A. splenocytes treated with HAE of *O. sanctum* leaves and Con-A were also compared with positive control (spleen cells + Con-A) and it was observed that IL-10 secretion was induced by 11.45 and 10.44% at dose rate of 31.25 and 62.5µg/ml of *O. sanctum* leaves extract, respectively, whereas IL-10 secretion was decreased by 5.82, 37.95 and 45.58% when spleen cells were treated with 125, 250 and 500 µg/ml of plant extract, respectively. The maximum induction of 11.45% was observed

with 31.25µg/ml of *O. sanctum* leaves extract in presence of Con-A (*Kumar* et al., 2013)

Antianxiety and anti-depressant activity

- Chatterjee et al in 2011 studied the effect of ethanolic extract of leaves of *Ocimum sanctum* in Swiss albino mice against both anxiety and depressive disorder. Depression was studied through tail suspension test and forced swim test. Anxiety experiments included light dark test, elevated plus maze test and Hole-board test. The *Ocimum sanctum* extracts shows antianxiety and Anti-depressant properties at the same dose and can be a potential therapeutic agent against mixed anxiety and depressive syndrome.

Anti-convulsant activity

- Different extracts of stem, leaf and leaves of OS were tested for anti-convulsant activity by maximal electroshock model using phenytoin as standard. It was observed that ethanol and chloroform extract of leaf and stem were effective in preventing toxic convulsions induced by trans corneal electroshock. 22 OS fixed oil (2-3 ml/kg ip) has been reported to show Anti-convulsant property in pentobarbitone-induced rats. (Jaggi et al., 2003).

Memory enhancer activity

- Alcoholic extract of *Ocimum sanctum* (OS) L. ameliorated the amnesic effect of scopolamine (0.4 mg/kg) and aging-induced memory deficits in mice. OS extract increased step-down latency (SDL) and acetylcholinenesterase inhibition significantly. Hence, OS can be employed in the treatment of cognitive disorders such as dementia and Alzheimer 's disease. (Joshi and Parle, 2006).

Anti-cancer activity

- *Kadian and Parle* (2012) suggested that erythrocytes from cancer patients responded to oxidative stress by elevating glutathione levels, while a decrease in glutathione levels in OS flavonoids treated patients, could be due to the free radical scavenging effect of OS flavonoids, sparing the glutathione. The *O. sanctum* L. has also been suggested to possess antifertility, anti-cancer, anti-diabetic, anti-fungal, anti-microbial, hepato-protective, cardio-protective, anti-emetic, anti-spasmodic, analgesic, adaptogenic, and diaphoretic actions (Lavanya *et al.*, 2019).

- The cytotoxic effect of root extract of *Ocimum tenuiflorum* against breast cancer cell lines MCF-7 was determined by a rapid colorimetric assay using MTT (methyl-thiazolyl-tetrazolium bromide) assay by *Melanathuru et al.* (2019). The results indicated that the maximum MCF7 cell death was 87.39 ± 0.62% at 250 µg/mL concentration of root extract of *Ocimum tenuiflorum* and the IC50 was 12.88 µg/mL concentrations. The previous studies reported anti-proliferative activity of phenolics but the mechanism of action was not clearly understood. The various mechanisms include metabolite activation of promutagen which acts as blocking agents and results in formation of adducts with the help of mutagens, free radical scavenging, suppression of tumour cell invasiveness and finally inhibition of matrix metalloproteinase-2/-9 activity. (Lavanya *et al.*, 2019).

Additional activities

- Leaf of *Ocimum sanctum* has also been reported to possess activities like anti-viral, analgesic, anti-inflammatory, anti-asthmatic, expectorant, anti-bacterial, anti-fungal, anti-convulsant, anti-emetic, anti-helminthic, anti-arthritic, anti-hyperlipidemic, cardio-protective, anti-hypertensive, anti-stress, hepato-protective, neuro-protective, radio-protective and wound healing. (Siva et al., 2016; Triveni et al., 2013)

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Raṭab
(Fruit)
Phoenix dactylifera L.

Introduction

The drug of *Raṭab* consists of ripe and mature fruit of *Phoenix dactylifera* L. (Family-Arecaceae), a tall palm tree up to 36m high, cultivated in Delhi, Punjab, Rajasthan, Gujrat, Uttar Pradesh and Karnataka (Anonymous, 2009a)

Fig. *Raṭab*

Vernacular Names

English: Dates, Date Palm; Hindi: *Khajūr,* Pinda; Urdu: *Khajūr,* Arabic: *Raṭab*, *Tamar, Tamar Raṭab; Persian; Khurmā-i- Tar*. (Khān, 2018; Khān, 2013; Ibn Sīnā, 1987; *Ibn Baytār*, 1986; Ghani, YNM; Anonymous, 2009a)

Temperament

Ḥār (Hot)[2] *Raṭb* (Moist)[1] (Khān, 2018; Ibn Sīnā, 1987)

Chemical Constituents

Phytochemical analysis of whole plant shows carbohydrates, alkaloids, steroids, flavonoids, vitamins and tannins. The phenolic profile of the plant revealed the presence of mainly cinnamic acids, flavonoid glycosides, and flavanols. The Thin layer chromatography (TLC) analysis showed the presence of steroids namely cholesterol, stigmasterol, campesterol and α-sitosterol. While fresh dates contain anthocyanins (Vembu et al., 2012). Dates are rich source nutrients as carbohydrates (44-88%), Dietary fibers (6.4-11.5%), fats (0.2-0.5%) and proteins (2.3-5.6%). Dates also contain fatty acids e.g. Palmitolieic acid, Oleic, Linoleic and Linolenic acid. There are 23 types of amino acids in date`s proteins and some of

them are not present in nutritious fruits like bananas, oranges and apples. Besides this vitamin A, B1, B2 and nicotinic acid are also constituents of dates (Abdu, 2011; Mallhi et al., 2014).

Ascorbic acid, carotene, nicotinic acid, riboflavin, thiamine, sugars, protein, vitamins, carbohydrates, calcium phosphorus, iron, rhamnose, ribose, xylose, galactose, galacturonic acid etc. are the common constituents present in the fruit of dates. (Husain et al.1992; Anonymous, 2009a)

Pharmacological Actions

- *Muqawwī-i-Ḥarārat Gharīziyya* (Tonic for innate heat)
- *Muqawwī-i-ʻĀm* (General tonic)
- *Musammin-i-Badan* (Adipogenic)
- *Muqawwī-i Bāh* (Aphrodisiac)
- *Muwallid-i-Mani* (Spermatogenic)
- *Muqawwi-i-Aʻṣāb* (Nervine tonic)
- *Muwallid-i-Dam* (Haemopoietic)

(Khān, 2018; Ibn Sīnā, 1987; *Ibn Baytār*, 1986; Al-Harawi, 2002; Ghani, YNM; Anonymous, 2009a; Kabīruddīn, 2000)

Therapeutic Uses

- *Ḍuʻf-i-Ḥarārat Gharīziyya* (Innate heat insufficiency)
- *Ḍuʻf-i-ʻĀm*`(General debility)
- *Ḍuʻf-i-Bāh* (Sexual debility)
- *Ḍuʻf-i-Aʻṣāb* (Nervine weakness)
- *Faqr al-Dam* (Anaemia)
- *Yarqān* (Jaundice)

(Khān, 2018; Ibn Sīnā, 1987; *Ibn Baytār*, 1986; Al-Harawi, 2002; Ghani, YNM; Anonymous, 2009a)

Important Formulations

Majūn Aarad Khurmā, Majūn Supārīpāk (Anonymous, 2009b)

Pharmacological/Clinical studies (evidence based)

Anti-oxidant activity

- Al-Turki in 2008, analyzed anti-oxidant properties of date palm cultivars from the United States and Saudi Arabia for their total phenolic content and Anti-oxidant activity for two years. The amount of phenolic compound and Anti-oxidant activity in all date fruit and pit cultivars tested in this study. Results showed that total polyphenolic content of fruit ranged from 507.03 to 2225.02 mg gallic acid equivalent and found that it has Anti-oxidant activity. (Al- Turki, 2008)

- Saryono et al. (2019) analysed second-grade dates (*Phoenix dactylifera* L.), with hard texture, from three selected Tunisian cultivars (Allig, Deglet Nour, and Bejo) from their anti-oxidant activities using DPPH radical scavenging activity, FRAP assay, H_2O_2 scavenging activity, and metal chelating activity. Dates extracts showed strong and concentration-dependant activity in all tested methods. The results showed that all three selected Tunisian cultivars had Anti-oxidant activity.

- El Abed et al. (2018) evaluated the anti-oxidant, the anti-inflammatory, and the anti-tumoral activities of the aqueous ethanolic extract from *Phoenix dactylifera* L. parthenocarpic dates. The Anti-oxidant activity was carried ouit using DPPH radical scavenging activity. The result showed that parthenocarpic dates had strongly scavenging activity on DPPH reaching 94% with an IC_{50} value of 0.15 ± 0.011 mg/mL ($p < 0.05$). The anti-inflammatory potential was determined by the inhibitory effect of the aqueous ethanolic extract on phospholipase A_2 activity as well as on carrageenan-induced paw edema in mice. The *in-vitro* study showed that the extract inhibited the phospholipase A_2 activity with an IC_{50} value of 130 µg/mL and the *in-vivo* study showed a significantly decrease in the paw edema after 1 h compared to the control group. Finally, the anti-proliferative activity of the aqueous ethanolic extract was assessed by MTT test against MCF-7 and MDA-MB-231 cancer cell lines. This extract was found effective in inhibiting MDA-MB-231 and MCF-7 cancer cells growth with IC_{50} values of 8 and 18 mg/mL, respectively, after 72 h treatment. These results confirm the ethnopharmacological significance of *Phoenix dactylifera* L. parthenocarpic dates, which could add support for its pharmaceutical use.

- Ramchoun et al. (2017) determined the functional composition and anti-oxidant activities of eight major date fruit varieties grown in Morocco. The analysis shows that date fruit contains a high amount of sugar (66.03–83.05% DW) but a low content of fat (0.218–0.363% DW) and protein (2.2–3.45% DW). Among the eight studied minerals; potassium, calcium and magnesium were the predominant. Moreover, the niacin is the major B vitamin of all analyzed varieties. The total phenolic content was found between 331.86 and 537.07 mg GAE/100 g DW, the flavonoid between 68.88 and 208.53 mg of RE/100 g DW and condensed tannins between 57.56 and 92.141 mg CE/100 g DW, the Anti-oxidant activity ranged between 383.90 and 846.94 µmol TE/100 g DW for ABTS, 6.255 and 2.046 g of date/l for DPPHIC50 and 406.614 and 860.89 µmol TE/100 g DW for FRAP assays.

- The anti-oxidant activities of extracts of different varieties obtained with solvents of different polarity were investigated using assays of 2, 2-diphenyl-2-picrymhydrasyl hydrate radical-scavenging activity, total phenolics and flavonoids amount, condensed tannins, reducing power, and total Anti-oxidant capacity. The results showed that all the extracts exhibited Anti-oxidant and radical-scavenging activities at different magnitudes and potency. The decreasing order of anti-oxidant and radical-scavenging activities among the extracts assayed were found to be methanol (MeOH) fraction > ethyl acetate fraction > hexane fraction > water extract. Correlation analysis indicated that there is a linear relationship between anti-oxidant potency, free radical-scavenging ability, and the content of phenolic and flavonoids compounds of *Phoenix dactylifera* extracts. These results showed that *Phoenix dactylifera* extracts are a valuable natural Anti-oxidant (Kriaa et al., 2012).

- Samad et al. (2016) aimed to study the effect of fruit chilling at 4°C for 8 weeks, extract storage at –20°C for 5 weeks, and extraction solvents (methanol) on total phenolic content (TPC), anti-oxidant activity and anti-bacterial properties of *P. dactylif*. Methanol was a better solvent compared to acetone for the extraction of phenolic compounds in dates. The results showed methanolic extract exhibited anti-oxidant activity, and anti-bacterial activity against all four bacteria tested: *Staphylococcus aureus*, *Bacillus cereus*, *Serratia marcescens* and *Escherichia coli*.

Immunomodulatory activity

- Eddine et al. (2014) evaluated *in-vivo* the immuno-stimulatory properties

of *Phoenix dactylifera* .The immuno-stimulant potential of the plant extract of *Phoenix dactylifera* on the phagocytic activity was measured by the carbon clearance rate test. The anti-oxidant activity was measured by spectrophotometric determination of glutathione from liver's homogenate. The results showed that phagocytic and the anti-oxidant activities weres increased significantly in animals injected with *Phoenix dactylifera* extract at doses (30, 50 and 100mg/kg).

- Elhemeidy et al. (2018) investigated the immunomodulatory effects of *Ajwa* date fruit extract to determine whether it stops the progression of breast cancer. Using rats induced with single dose 20 mg DMBA subcutaneously, they examined whether administration of Ajwa date fruit (Phoenix dactylifera) extract (at 400, 800 mg/kg body weight/d) post-DMBA induction for 30 days modulate NK cells, TNF-alpha, and development of breast cancer. ELISA, FACS, immunohistochemistry, and histologic observation were employed. Compared to positive control group (DMBA-induced only), the results showed that Ajwa date fruit extract normalized the level of circulatory CD161 NK cells and breast tissue TNF-alpha, cell size and proliferation, and improved overall survival rates. It was concluded that Ajwa date fruit extract may be used to modulate NK cells and TNF-alpha against progression of breast cancer.

Prevention of peripheral neuropathy activity

- Peripheral neuropathy is another common adverse effect of chemotherapy. Taxanes such as docetaxel and paclitaxel, vinca alkaloids such as vincristine and vinblastine, oxaliplatin, thalidomide, and irinotecan are all commonly used agents that cause peripheral neuropathy. A study on streptozocin-induced diabetes in rats probed Phoenix dactylifera's ability to prevent neuropathy, Rats used in the study were screened for fasting blood glucose levels of 200 mg/dL, well over the standard for diagnosis in humans. Date fruit extract at 4 ml/kg was administered orally over a six-week timeframe post-confirmation of diabetic status. Measurements included rearing status, total distance moved, mobility duration, and grooming frequency using Ethnovision software, and motor nerve conduction velocity via direct stimulation at the right sciatic notch and ankle. No significant difference was found in rearing status, total distance moved, or mobility duration in the group receiving 4 mL/kg/day of date fruit extract orally, but a significant reduction from control was noted in grooming frequency and sciatic motor nerve conduction velocity. (Zangiabad et.al., 2011)

Anti-cancerous activity

- The glucans prepared from the dates fruit possessed anti-neoplastic effects in experimental study. The author observed a dose dependent anti-cancer activity, with an optimum activity at a dose of 1 mg/kg , in mice bearing Sarcoma-180 solid tumors. It was hypothesized that the observed antitumor activity could be correlated to their (1 → 3)-*β*- d-glucan linkages. (Ishurdaet. al., 2005)
- The polysaccharides (glucans) prepared from grape fruits exhibited dose dependent anti-cancer activity with an optimum activity at 1 mg/kg in tumor induced by subcutaneously transplanting allogenic solid sarcoma-180 tumor cells into the right side of female CD1 mice. In another study, date fruit extracts showed anti-angiogenic, anti-proliferative and and anti-oxidant actions in different cell line studies. (Saad et.al., 2016)

Additional activities

- The fruit of *Phoenix dactylifera* has also been reported to possess hepato-protective, nephro-protective, gastro-intestinal protective, anti-inflammatory, anti-hyper-lipidemic, anti-fungal, gonadotropic and anti-diarrhoeal activities. (Ateeq et al., 2013)

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Rummān
(Fruit)
Punica granatum L.

Introduction

The drug *Rummān* consists of fruit of *Punica granatum* L. (Family-Lythraceae). A large deciduous shrub or a small tree, found growing wild in the warm valley, outer hills of Himalayas between 900-1800 m and cultivated throughout India. (Anonymous, 2007d)

Fig. *Rummān*

Vernacular Names

English: Pomegranate; Hindi: *Anār*: Urdu; *Anār*; Arabic: *Rummān*; Persian: *Anār*. (Khān, 2012; Ibn Sīnā, 1987; *Ibn Baytār*, 1986; Anonymous, 2007d)

Temperament

Bārid (Cold)[1] *Raṭb* (Moist)[1] (Khān, 2012; Ibn Sīnā, 1987)

Chemical Constituents

Anthocynin and flavonoides: The seeds contain glycosides of malvidine and petunidine and petargonidine 3, 5- diglucoside was found to be the main pigment of flowers. Leaf extracts have yieldedapegenin-4, O-β glucopyranosides, luteoline 4, O-β glucopyranoside, luteoline -3-O-β xylopyranoside and isoquerctine. **Alkaloids:** Punicalin, punicalagine, granatine β, gallagyldilaclene casuarine, pedunculagine and tellimagrandine.

Sugars, vitamin C, sitosterol, ursolic acid, protein, fat and mineral matters, nicotinic acid, pectin, riboflavin, thiamine, delphinidin diglycodise, aspartic, citric, ellagic, gallic and malic acids, glutamine, isoquercetine, estrone and punicic acid. (Arun and Singh, 2012; Nadkarni, 1989; Chopra, *et al.*, 1956)

Pharmacological Actions

Anār Shīrīn

- *Muqawwī-i-Ḥarārat Gharīziyya* (Tonic for innate heat)
- *Muqawwī-i-Qalb* (Cardio tonic)
- *Muqawwī-i-Kabid*(Hepato tonic)
- *Musakkin-i-ʻAṭash* (Allaying thirst)
- *Muwwalid-i-Dam* (Haematogenic)
- *Muddir-i-Bawl* (Diuretic)

Anār Tursh

- *Muqawwī-i-Ḥarārat Gharīziyya* (Tonic for innate heat)
- *Qābiz* (Constipative)
- *Muqawwī-i-Qalb* (Cardio tonic)
- *Muqawwī-i-Kabid* (Hepato tonic)
- *Musakkin-i-Safra* (Yellow bile attenuating agent)
- *Musakkin-i-Dam* (Blood attenuating agent)
- *Mudirr-i-Bawl* (Diuretic)

(Khān, 2012; Ibn Sīnā, 1987; *Ibn Baytār*, 1986; Al-Harawi, 2002; Anonymous, 2007d; Ghani, YNM; *Kabīruddīn*, 2000)

Therapeutic Uses

Anār Shīrīn

- *Ḍuʻf-i-Ḥarārat Gharīziyya* (Innate heat insufficiency)
- *Ḍuʻf-i-ʻĀm* (General debility)
- *Ḍuʻf-i-Qalb* (Cardiac insufficiency)
- *Ḍuʻf-i-Jigar* (Hepatic insufficiency)
- *Ḍuʻf-i-Miʻda* (Gastric debility)
- *Ḍuʻf-i-Bāh* (Sexual debility)
- *ʻAṭash-i- Mufriṭ* (Polydipsia)
- *Faqruddam* (Anaemia)

Anār Tursh

- *Ḍu'f-i-Ḥarārat Gharīziyya* (Innate heat insufficiency)
- *Ḍu'f-i-Qalb* (Cardiac insufficiency)
- *Ḍu'f-i-Jigar* (Hepatic insufficiency)
- *Sozish-e-Ṣadr* (Burning in the chest)
- *Ghathayān* (Nausea)
- *Qay'* (Vomitting)
- *Yarqān* (Jaundice)

  (Khān, 2012; Ibn Sīnā, 1987; *Ibn Baytār*, 1986; Al-Harawi, 2002; Anonymous, 2007d; Ghani, YNM; *Kabīruddīn*, 2000)

Important formulations

Jawārish Anārayn, Sharbat Anār, Qurṣ Gulnār, Qurṣ Zayābīṭus, Qurṣ Ṭabāshīr, Jawārish Pudīna (Alam *et al.*, 2018; Anonymous, 2007d)

Pharmacological / Clinical studies (evidence based)

Anti-oxidant activity

- An *in-vitro* assay using four separate testing methods demonstrated thatpomegranate juice and seed extracts have 2-3 times the anti-oxidant capacity ofeither red wine or green tea. (Alam *et al.*, 2018; Gil, *et al.*, 2000)
- Pomegranate extracts have beenfound to scavenge free radicals and decrease macrophage oxidative stress and lipid peroxidation in animals and increase plasma anti-oxidant capacity in elderlyhumans. (Rosenblat *et al.*, 2006; Guo *et al.*, 2008)
- Studies in rats and mice confirm the anti-oxidant properties of a pomegranate by-product (PBP) extractmade from whole fruit minus the juice, showing 19% reduction in oxidativestress in mouse peritoneal macrophages (MPM), 42% decrease in cellular lipidperoxide content, and 53% increase in reduced glutathione levels. (Rosenblat *et al.*, 2006)
- *In-vitro* assay of fermented pomegranate juice (FPJ) extract andcold pressed seed oil (CPSO) extract found that Anti-oxidant capacity of both aresuperior to red wine as well as green tea extract (Schubert, 1999). A

separatestudy in rats with CCl4 induced liver damage demonstrated that pre-treatmentwith a pomegranate peel extract (PPE) enhanced or maintained the free-radicalscavenging activity of the hepatic-enzymes catalase, superoxide dismutase andperoxidase, and resulted in 54% reduction of lipid peroxidation values comparedto controls. (Chidambara, *et al.,* 2002)

- Research in humans has shown a juice made from pomegranate pulp (PPJ) has superior anti-oxidant capacity to apple juice. Using the FRAP assay (ferric reducing/Anti-oxidant power), Guo et al. found that 250 mL PPJ given to healthy elderly subjects in the dose of 250ml PPJ daily for four weeks increased plasma Anti-oxidant capacity from 1.33 mmol to 1.46 mmol, while subjects consuming apple juice experienced no significant increase in anti-oxidant capacity. In addition, subjects consuming the PPJ exhibited significantly decreased plasma carbonyl content (a biomarker for oxidant/Anti-oxidant barrier impairment in various inflammatory diseases) compared to subjects taking apple juice. Plasma vitamin E, ascorbic acid and reduced glutathione values did not differ significantly between groups, leading researchers to conclude that pomegranate phenolics may be responsible for the observed results (Alam *et al.* 2018; Guo *et al.* 2008)

Immunomodulatory activity

- A study carried out to investigate the immunomodulatory activity of *Anār* by Ross G et al. revealed that aqueous suspension of fruit rind powder, administered orally to rabbits at a dose of 100 mg/kg, stimulated the cell-mediated and humoral components of the immune system. There was an increase in antibody titre to typhoid-H antigen. (Haque *et al.,* 2015)

Anti-obesity and hyper-lipidaemic activity

- A pilot study in type 2 diabetic patients with hyperlipidaemia found that concentrated PJ decreased cholesterol absorption, increased faecal excretion of cholesterol, had a beneficial effect on enzymes involved in cholesterol metabolism, significantly reduced total and LDL cholesterol, and improved total/ HDL and LDL/HDL cholesterol ratios. (Alam *et al.,* 2018; Esmaillzadeh, *et al.,* 2006).

Anti-carcinogenic activity

- *In-vitro* assays utilizing three prostate cancer cell lines (DU-145, LNCaP, and PC-3) demonstrated that various pomegranate extracts (juice, seed oil, peel)

potently inhibit prostate cancer cell invasiveness and proliferation, cause cell cycle disruption, induce apoptosis and inhibit tumor growth. These studies also demonstrated that combinations of pomegranate extracts from different parts of the fruit were more effective than any single extract (Lansky, *et al.,* 2005; Albrecht, *et al.,* 2004).

- Several animal studies have elucidated pomegranate's potential anti-cancer mechanisms. Two studies in mice implanted with prostate cancer PC-3 cell line demonstrated that pomegranate fruit extract (PFE; edible parts of the fruit, excluding the peel) inhibits cell growth and induces apoptosis via modulation of proteins regulating apoptosis (Malik *et al.,* 2006; Malik *et al.,* 2005)

- In an open-label phase II clinical trial in 46 men with recurrent prostate cancer, 16 patients (35%) showed significant decrease in serum prostate specific antigen (PSA) levels (average=27%) during treatment with eight ounces of pomegranate juice. Corresponding *in-vitro* assays using patient plasma and serum demonstrated significant decrease in prostate cancer cell line proliferation and increased apoptosis. Nitric oxide preservation via ingestion of pomegranate polyphenols significantly correlated with lower PSA values. These results indicate pomegranate may affect prostate cancer because of anti-proliferative, apoptotic, anti-oxidant and possibly anti-inflammatory effects (Pantuck, *et al.,* 2006). Recent research also indicates pomegranate constituents inhibit angiogenesis via down regulation of vascular endothelial growth factor in MCF-7 breast cancer andhuman umbilical vein endothelial cell lines (Alam *et al.,* 2018; Toi *et al.,* 2003)

Additional activities

- The fruit of *Punica granatum* has also been reported to possess anti-inflammatory, analgesic, anti-convulsant, anti-bacterial, hypo-glycaemic, anti-hypertensive, anti-atherosclerotic and heamatopoitic activities. (Alam *et al.,* 2018; Haque *et al.,* 2015)

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Shūnīz
(Seed)
Nigella sativa L.

Introduction

The drug of *Shūnīz* consists of seeds of *Nigella sativa* L. (Family- Ranunculaceae). Drug yielding plant is a small herb. 45-60 cm high, mostly cultivated in Punjab, Himachal Pardesh, Bihar and Assam. (Anonymous, 2007 a)

Fig. *Shūnīz*

Vernacular Names

English: Small Fennel Nigella Seed, Black Cumin, Black Caraway; Hindi: *Kalaunjī*, *Mangaraila*; Urdu: *Kalonjī*; Arabic: *Habbat al-Sawda*, *Shūnīz*; Persian: *Shūnīz* (Khān, 2014; Ibn Sīnā, 1987; *Ibn Baytār*, 1999; Ghani, YNM; Anonymous, 2007a)

Temperament

Ḥār (Hot)^2 *Yābis* (Dry)^2 (Khān, 2014; *Ibn Baytār*, 1999; *Kabīruddīn*, 2000)

Chemical Constituents

Black Cumin contains: Essential oil, fixed oil, steroid, melanthin, mucilage, resins, sugars, alkaloids, tannins, linoleic acid, palmitic acid, stearic acid, palmitoleic acid and oleic acid, nigellidine, nigellicine, dithymoquinone, volatile oils (active constituents) 1.5%. It consists of Carvone (45-60), Terpene or d-limonene (carvene) andcymene. Fixed oil (Fattyacids) 3.7%, Tannins, Resins, Proteins, Carbohydrate, Sugars (glucose), Saponins, Arachidic acid, Arachidonic acid, other alcohol soluble organic acids. The seeds contain the following amino acids (cystine, aspartic acid, glutamic acid, alanine, tryptophan, valine and leucine and lysine) and also enzyme lipase. Recently Nigellimine is also isolated from the seeds. Minerals such as calcium, phosphorus and iron are present in higher amounts while zinc,

magnesium, manganese and copper in lesser amounts in *Nigella sativa* seeds. Fat soluble vitamins such as DL-a-tocopherol, DL-y- tocopherol, and all trans-retinol in *Nigella sativa* seeds. Water soluble vitamins like B1, B6, niacin and folic acid are also present in black seed. (Nasir *et al.,* 2014; Rastogi *et al.,* 1998; Masood *et al.,* 2010; Khan *et al.,* 1999; Ali and Blunden, 2003; Ismail, 2009)

Pharmacological Actions

- *Mu'mmir* (Longevity promoting agent)
- *Muqawwī-i-Ḥarārat Gharīziyya* (Tonic for innate heat)
- *Muqawwī-i-A'ṣāb* (Nervine tonic)
- *Muqawwī-i-Mi'da* (Stomachic)
- *Kāsir-i-Riyāḥ* (Carminative)
- *Muḥallil* (Resolvent)
- *Musakkin* (Analgesic)
- *Munaffith-i-Balgham* (Expectorant)
- *Jāli* (Detergent)

  (Khān, 2014; Ibn Sīnā, 1987; *Ibn Baytār*, 1999; Al-Harawi, 2002; Ghani, YNM; Anonymous, 2007a; *Kabīruddīn*, 2000)

Therapeutic Uses

- *Ḍu'f-i-Ḥarārat Gharīziyya* (Innate heat insufficiency)
- *Ḍu'f-i-A'ṣāb* (Nervine weakness)
- *Shaqīqa* (Migraine)
- *Nisyān* (Forgetfulness)
- *Fālij* (Hemiplegia)
- *Ri'sha* (Tremor)
- *Ḍu'f-i-Mi'da*(Gastric debility)
- *Ḍīq al-Nafas* (Bronchial asthma)
- *Waja' al-Mafāṣil* (Polyarthritis)
- *Amrāḍ-i- Jild* (Skin Diseases like *Bahaq* (Pityriasis), *Baraṣ* (Vitiligo), *Qūbā* (Tinea/Ring worm)

  (Khān, 2014; Ibn Sīnā, 1987; *Ibn Baytār*, 1999; Al-Harawi, 2002; Ghani, YNM; Anonymous, 2007a; *Kabīruddīn*, 2000)

Important Formulations

Ma'jūn Kalkalānaj, Ma'jūn Fanjnosh, Ma'jūn Kundur (Anonymous, 2007a)

Pharmacological / Clinical studies (evidence based)

Anti-oxidant activity

- The seed oil and its main active constituent, thymoquinone, are reported to inhibit peroxidation in ox brain phospholipid liposomes. Similarly, thymoquinone was shown to exhibit protective effect against tert-butyl-hydro-peroxide induced hepato-toxicity and also Hepato-protective effect against carbon tetrachloride induced toxicity in mice, rats and rabbits. Furthermore, thymoquinone was found to exhibit renal protective effect in rats through its Anti-oxidant action. The essential oil of *Nigella sativa* seeds was tested for a possible anti-oxidant activity. The essential oil, thymoquinone and other components; carvacrol, anethole and 4-terpineol demonstrated respectable radical scavenging property. The free radical scaveng ing effects of thymol, thymoquinone and dithymoquinone were studied on the reactions generating reactive oxygen species such as superoxide anion radical (O,), hydroxyl radical (HO) and singlet oxygen (1O,) using the chemiluminescence and spectrophotometric methods. The Hepato-protective effects of Nigella oil and thym oquinone were found via the Anti-oxidant mechanism. Similarly, the protective effect of thymoquinone against doxorubicin-induced nephropathy and that against doxorubicin-induced cardiotoxicity was also found to be due to its anti-oxidant activity. In some other studies, the modulating effect of thymoquinone on benzopyrene-induced for stomach tumors in mice and its antitumor effect on 20- methyl cholanthrene -induced fibrosarcoma tumorigenesis were found to be partly through its anti-oxidant effect. The possible mechanism of the protective effect of thymoquinone against acetic acid- induced colitis in rats was also supposed to be partly its anti-oxidant action. (Gilani *et al.,* 2004; Nagi *et al.,* 1999; Burits *et al.,* 2008; Mansour *et al.,* 2002)

Immunomodulatory activity

- In an *in-vitro* study, the potential immunomodulatory effects of *N. sativa* were investigated in light of splenocyte proliferation, macrophage function, and NK anti-tumor activity using BLAB/c and C57/BL6 primary cells. Results demonstrated that the aqueous extract of *N. sativa* significantly enhances

splenocytes proliferation in a dose-responsive manner. In addition, the aqueous extract of *N. sativa* favors the secretion of Th2, versus Th1, cytokines by splenocytes. The secretion of IL-6, TNF-α, and NO; key pro-inflammatory mediators, by primary macrophages is significantly suppressed by the aqueous extract of *N. sativa*, indicating that it exerts anti-inflammatory effects. (Zaidi *et al.,* 2015; Majdalawieh, 2010)

Effects on immune system and cancer

- *Nigella sativa* seeds and its oil have been traditionally used as a tonic to promote health and prevent diseases. They were reported to exhibit immuno-potentiating, immunomodulating and interferon-like activities. The ethanolic extract was found to inhibit cancer cells and endothelial cells progression *in-vitro* . The protective effect of *Nigella* grains as nutraceuticals was studied on the oxidative stress and carcinogenesis induced by methyl nitrosourea in Sprague Dawley rats and it was found to produce about 80% protection against methyl nitrosourea-induced oxidative stress, inflammatory response and carcinogenesis. The alcoholic extract also showed the cytotoxic activity and was found to cure oral cancers. In a study, a crude gum, a fixed oil and two purified components of *Nigella* seed, thymoquinone and dithymoquinone were assayed in-vitro for their cytotoxicity for several parental and multi drug resistant human tumor cell lines. Although as much as 1% w/v of the gum or oil was devoid of cytotoxicity, both thymoquinone and dithymoquinone were found to be cytotoxic for several types of human tumor cells. (Mabrouk *et al.,* 2002; Salomi *et al.,* 1989)

- The proteins of *Nigella sativa* fractionated by ion-exchange chromatography were also found to possess immunomodulatory effect. The effect of these proteins on the production of cytokines was further evaluated by using specific enzyme-linked immunosorbant assay (ELISA). The results, however, showed that the fractionated *Nigella sativa* was less effective when compared with whole *Nigella* proteins. (Gilani *et al.,* 2004; Haq *et al.,* 1999)

- The active principle of *Nigella sativa* seeds containing certain fatty acids was studied for anti-tumor activities against Ehrlich ascites carcinoma, Dalton's lymphoma ascites and Sarcoma-180 cells *in-vitro* and *in-vivo*. The active principle showed complete inhibition *in-vivo* and 50% cytotoxicity *in-vitro* studies. In mice bearing Ehrlich ascites carcinoma xenograft, thymoquinone (from volatile oil) significantly enhanced the anti-tumor effect of ifosfamide

(analogue of eyelophosphamide). There was also less weight loss and lower mortality rate compared to ifosfamide single therapy, thus thymoquinone was found to improve the therapeutic efficacy of ifosfamide by both decreasing ifosfamide-induced nephrotoxicity and improving its anti- tumor activity. In another study, thymoquinone inhibited the benzopyrene-induced forestomach carcinogenesis in mice. The possible modes of action were discussed to be through its anti-oxidant and anti-inflammatory activities coupled with enhancement of detoxification process. (Gilani *et al.,* 2004; Salomi *et al.,* 1991)

- Thymoquinone-induced cytotoxicity was investigated in a study using canine osteosarcoma, its cisplatin-resistant variant, human breast adenocarcinoma, human ovarian adenocarcinoma and Madin-Darby canine (MDCK) cell lines. Thymoquinone-induced cytotoxicity was determined using a proliferation assay (MTT assay) and apoptosis assays. Effects on the cell cycle were determined using flow cytometry and thymoquinone was found to produce cell cycle arrest. In another study, the aqueous and alcoholic extracts of *Nigella sativa* alone or in combination with HCO, as an oxidative stressor, were found to be effective in-vitro in inactivating MCF-° breast cancer cells. (Gilani *et al.,* 2004)

- The fresh aqueous extract augmented Natural Killer Cells (62.3%) in developing cytotoxicity against YAC *in-vitro* . Fresh aqueous extracts appeared to be more potent than old dried extracts or ethanolic extracts. Aqueous extract of *Nigella sativa* seeds was also found to significantly augment the splenic natural killer cells in generating cytotoxicity in mice against YAC tumor targets. (Gilani *et al.,* 2004; Salomi *et al.,* 1992)

- In a study using murine Cytomegalovirus as a model, intra-peritoneal administration of oil substantially decreased the viral load in liver and spleen. There was an increase in interferon-y, macrophages and CD4 T cells and decrease in both number and function of NK cells. On day 10, the virus titer was undetectable in the spleen and liver of infected mice, while positive in controls. (Gilani *et al.,* 2004; Worthen *et al.,* 1998)

- A fraction of the ethanolic extract of *Nigella sativa* seeds was studied in mice against intra-peritoneally implanted murine P388 leukemia and subcutaneously implanted Lewis lung carcinoma cells. The life span of treated mice increased by 153% as compared to dimethyl sulphoxide-treated control

mice. n- Hederin, a triterpene saponin isolated from this fraction produced significant tumor inhibition rates; while, the underlying mechanism(s) of anti-tumor activity of n-Hederin remained to be established. (Gilani *et al.,* 2004)

- In a study, the stimulating effect of n-hederin on the release of nitric oxide and upregulation of inducible nitric oxide synthase gene expression in mouse macrophages were examined. Thus showing a mechanism responsible for its biological effects including its anti-tumor activities. (Gilani *et al.,* 2004)
- In another study, the anti-tumor effect of thymoquinone was investigated both in-vivo and in-vitro in male Swiss albino rats on fibro sarcoma induced by 20- methyl cholanthrene and it was found to inhibit tumor incidence and tumor burden significantly. The possible modes of action were discussed as its Anti-oxidant activity and interference with DNA synthesis coupled with enhancement of detoxification processes. (Gilani *et al.,* 2004)

Anti-cancer activity

- It is documented that methanolic extract of *N. sativa* exhibits potent inhibition of cancerous cell growth against HL-60 and U- 937 with IC50Value 13.70 µg/ml, and 28.31 µg/ml respectively. (Raval, 2010). Another study showed that essential oil of *N. sativa* has an anti-metastatic activity in mice or that it inhibits or delays metastasis by rapid reduction of primary tumor volume at the site of induction. (Mbarek, 2007) Another study showed that ethanolic extract of *N sativa* exhibit antitumor activity in ehlrich ascites tumor in mice. (Musa *et al.,* 2004)

Additional activities

- The seed of *Nigella sativa* has also been reported to possess anti-bacterial, anti-spasmodic, anti-diabetic, mutagenic, analgesic, anti-fungal, hepato-protective activity, nephro-protective, neuro-protective and anti-hyperlipidemic activities. (Nasir *et al.,* 2014)

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Sīr
(Bulb)
Allium sativum L.

Introduction

The drug of *Sīr* consists of bulb of *Allium sativum* L. (Family-Liliaceae), a perennial bulbous plant, cultivated as an important condiment crop in the country. The bulb is odoriferous and contains outer layers of thin sheathing leaves surrounding an inner sheath that encloses the clove. Often the bulb contains 10 to 20 cloves that are asymmetric in shape, except for those closest to the center. (Anonymous, 2008)

Fig. *Sīr*

Vernacular Names

English: Garlic; Hindi: *Lahasun*; Urdu: *Lahsan*, *Sīr*; Arabic: *Thawm, Fawm,* ; Persian: *Sīr*. (Khān, 2014; Ibn Sīnā, 1987; Ibn Baytār, 1985; Ghani, YNM; Anonymous, 2008)

Temperament

Ḥār (Hot)^3 *Yābis* (Dry)^3 (Khān, 2014; Ibn Sīnā, 1987; Kabīruddīn, 2000)

Chemical Constituents

- Bulbs of *A. sativum* are reported to contain hundreds of phytochemicals including sulfur-containing compounds such as ajoenes (E-ajoene, Z-ajoene), thiosulfinates (allicin), vinyldithiins (2-vinyl-(4H) -1, 3-dithiin, 3-vinyl-(4H)-1, 2-dithiin), sulfides (diallyl disulfide (DADS), diallyl trisulfide (DATS)) and others that accounted 82% of the overall garlic sulfur content (*Al-Snafi,* 2013).

- Alliin, the main cysteine sulfoxide is transformed to allicin by allinase enzyme after cutting off the garlic and breaking down the parenchyma (Zeng et al., 2017). S-propyl-cysteine-sulfoxide (PCSO), allicin and S-methyl cysteine-sulfoxide (MCSO) are the main odoriferous molecules of freshly milled garlic homogenates (Zeng *et al.*, 2017). PCSO can produce more than fifty metabolites depending on water content and temperature as well as allinase enzyme that can act on the mixture of MCSO, PCSO, and alliin to produce other molecules, such as allyl methane thiosulfinates, methyl methanethiosulfonate, and further corresponding thiosulfinates (R-S-S-R0). (*El-Saber Batiha et al.*, 2020).

  The main constituents present in bulb of *A. sativum* are volatile oil, allyl disulphide, dially disulphide, allin, allicin, mucilage, albumin etc. (Anonymous, 2008).

Pharmacological Actions

- *Mu'mmir* (Longevity promoting agent)
- *Muqawwī-i-Ḥarārat Gharīziyya* (Tonic for innate heat)
- *Musakhkhin-i-Badan* (Calorific)
- *Muqawwī-i-Mi'da* (Stomachic)
- *Muqawwī-i-Bāh* (Aphrodisiac)
- *Muḥallil-i-Waram* (Anti-inflammatory)
- *Qāti' Akhlāt-i-Ghalīza* (Breaking agent for viscous humours)
- *Muqarreḥ* (Ulcerative)
- *Jālī* (Detergent)
- *Munaffith-i-Balgham* (Expectorant)
- *Musakkin* (Analgesic)
- *Mudirr-i-Bawl* (Diuretic)

  (Khān, 2014; Ibn Sīnā, 1987; *Ibn Baytār*, 1985; Al-Harawi, 2002; Ghani, YNM; Anonymous, 2008)

Therapeutic Uses

- *Ḍu'f-i-Ḥarārat Gharīziyya* (Innate heat insufficiency)

- *Amrāḍ-i-Bārida Balghamiyya* (Cold phlegmatic disorders) such as *Laqwa* (Bell's palsy), *Istirkhā'* (Atony/flaccidity), *Ri'sha* (Tremor) *etc.*
- *Fālij* (Hemiplegia)
- *Waja' al-Mafāṣil* (Polyarthritis)
- *'Irq al-Nasā* (Sciatica)
- *Ḍīq al-Nafas* (Bronchial asthma)
- *Su'āl* (Cough)
- *Ḍu'f-i-Bāh* (Sexual debility)
- *Amrāḍ-i- Jild* (Skin Diseases like *Bahaq* (Pityriasis), *Baraṣ* (Vitiligo)

(Khān, 2014; Ibn Sīnā, 1987; Ibn Baytār, 1985; Al-Harawi, 2002; Ghani, YNM; Anonymous, 2008; Kabīruddīn, 2000)

Important Formulations

Ma'jūn Sīr, Majūn Sīr Alvi Khānī, Rawghan Sīr (Anonymous, 2008)

Pharmacological / Clinical studies (evidence based)

Anti-oxidant activity

- The anti-oxidant potential garlic extracts was determined by using methanol, hexane and ethyl acetate at different time intervals (35, 50 and 65 min) followed by their polyphenols and flavonoid content determination. The result revealed that the methanolic extracts obtained at 50 min extraction time showed maximum total phenolics as 60.38±0.23 mg GAE/100g and flavonoids as 58.45±1.24 mg/100g. Similarly, the highest DPPH activity (61.59±1.58%) and β-carotene and linoleic acid potential (64.96±1.72%) were also observed for methanolic extract. (*Awan* et al. (2019)

- *Shrestha* et al. (2016) carried out the study to evaluate the anti-oxidant and anti-bacterial activities of fresh extracts of garlic and onion. Activities of enzymatic anti-oxidants (superoxide dismutase and catalase) and non-enzymatic anti-oxidant (ascorbic acid content) activities were measured and compared in between garlic and onion extracts. Superoxide dismutase and catalase activities in garlic were found noticeably high ($p < 0.05$) compared to onion but significantly reverse in case of the ascorbic acid content ($p < 0.05$). Likewise, six bacteria were chosen to study anti-bacterial activities of

garlic and onion. The zones of inhibitions exhibited by the extracts against *B. cereus, S. aureus*, *Micrococcus* sp., *E. coli, Klebsiella* sp. and *Proteus* sp. were compared with the reference antibiotic chloramphenicol (1%). Anti-bacterial activity of the garlic extract singly and its mixture with onion extract in the ratio 1:1 against the tested bacteria were found significantly higher ($p < 0.05$) than the onion extract. They concluded that the anti-oxidant activities of garlic are higher than onion and also the anti-bacterial activities of garlic and its mixture are more potent than onion alone.

- *Liu* et al. (2014) compared the anti-oxidant activity of garlic aqueous and methanol extracts processed before and after boiling to mimic the cooking process. By testing the anti-oxidant activities of the extracts in different chemical mimic systems *in-vitro* , namely, ABTS [2, 2'-azino-bis (3-ethylbenzthiazoline-6-sulfonic acid)] and DPPH (2, 2-diphenyl-1-picrylhydrazyl) radical scavenging activities, reducing power, and metal chelating ability, they found the following data: (1) no significant difference was observed on the ABTS radical scavenging activities of garlic aqueous and methanol extracts before and after boiling process; (2) the reducing power of garlic aqueous and methanol extracts decreased by 25.9% and 14.1%, respectively, whereas the metal chelating activity of boiled garlic aqueous extracts increased by 54.7%; and (3) DPPH radical scavenging test may not be suitable to examine the garlic extracts. In addition, the ABTS radical scavenging activities of garlic extracts were very stable at pH ranges similar in human bodies, and both sulfhydryl and phenolic compounds were probably responsible for the Anti-oxidant ability of garlic. The boiling process destroyed only a small part of garlic bio-ingredients related to anti-oxidant activity properties.

Immunomodulatory activity

- Moutia et al. (2018) reported different bioactive molecules and formulations of Garlic which were extensively probed in *in-vitro* and *in-vivo* studies to examine anti-inflammatory and immunomodulatory properties. One of the main mechanisms observed was through modulation of cytokine profiles and, on the other hand, direct instruction and stimulation of immune cells. It was suggested that the garlic beneficial effects are attributed, in particular, to sulfur-containing compounds, some polyphenols, and flavonoids. The synergistic effect of the different compounds present in garlic preparations might be responsible for the biologic activities revealed in different pathological situations. However, the identification of the potential compound(s), which

could eventually mediate efficient antitumor immunity, would be of major interest.

- The immunomodulatory properties of garlic could be useful in clinical applications, since it enhances innate and specific cell immunity and also improves host resistance. It was also reported that allicin modulates T cells and adhesion molecules and exerts an inhibitory effect on NF-κB activation and hence prevents liver damage (*Bruck et al., 2005; Dorhoi et al.,* 2006)
- Immunomodulation is among innumerable biological activities of *A. sativum*. Aged garlic extract has showed superior immunomodulatory properties over raw garlic extract. This effect of garlic is attributed to the transformed organosulfur compounds. Aged garlic fructans have recently showed to possess immunomodulatory activities *in-vitro* . Garlic extract is concentration-dependently effective on the proliferation of interleukin (IL)-2 and interferon (INF)-γ gene expression of stimulated lymphocytes. The extracts reduced macrophage infection through induction of nitric oxide (NO) production *in-vitro* .
- A study demonstrated that immune-mediated liver damage in mice can be prevented by allicin, probably because of its immunomodulatory effects on T cells and adhesion molecules and inhibition of NF-kappaB activation. Another observation indicated that allicin exerts an inhibitory immunomodulatory effect on intestinal epithelial cells and it may have the potential to attenuate intestinal inflammation. Allicin exerted an *in-vitro* immunomodulatory effect on certain functions of the peripheral blood cells. (*El-Saber Batiha et al.*, 2020).

Anti-Alzheimer's disease activity

- Alzheimer's disease (AD) is the main cause of dementia in the elderly with neurodegenerative and cerebrovascular disorders. Acetylcholinesterase (AChE) is the main enzyme that converts the acetylcholine (ACh) in the nervous system to acetate and choline. ACh depletion in the central nervous system has been involved in the pathophysiology noticed in AD; therefore, donepezil (AChE inhibitor) was effective in the management/prevention of AD. Surprisingly, oil from garlic bulbs suppressed AChE activity of cerebral cortex synaptosome and exhibits Anti-oxidant properties, thus, inhibiting AChE activity *in-vitro* as well as their ability to scavenge diphenyl-1-picrylhydrazyl (DPPH) free radical. (Akinyemi et.al., 2018; Singh et al., 2010)

- *Borek* evaluated the neuro-protective effect of AGE using an animal model and showed that AGE protected brain from neurodegenerative diseases by preventing brain injury following ischemia, saving neurons toward apoptosis, and inhibiting oxidative death caused by β-amyloid. (Borek, 2006; Jackson et al., 2003)

- *Mbyirukira* and Gwebu reported that AGE or SAC inhibits the brain's frontal lobe degeneration, promotes memory and learning retention, and prolongs the lifespan. Based on the amyloid hypothesis, aggregated β-amyloid (Aβ) accumulation in the brain is believed to be the pathological factors that drive the onset of AD. It has been suggested that the formation of the neurofibrillary tangles contain τ-protein and synaptic degradation caused by the imbalance consequences between Aβ clearance and Aβ production. (*Mbyirukiraet al.*, 2003)

- *Haider* et al. reported that the prolonged garlic uptake is related to promoting the memory function by affecting the levels of the neurotransmitter, serotonin. The *in-vivo* consumption of *A. sativum* extracts showed that it improves memory by eliminating free radicals that cause oxidative damage and inhibit AChE enzyme. It was noted that allicin inhibits AChE and butyrylcholinesterase (BuChE) enzymes (enzymes that break down neurotransmitter choline) which successively increased ACh concentration in the brain. Thus, delayed cognitive decline and dementia. (*Haider* et. al., 2008; *Mukherjee et.al., 2013)*

- Combination therapy of allicin with cholinesterase inhibitors (ChEIs) including; rivastigmine, galantamine, and donepezil are now the most commonly used for the treatment of AD as they have the ability to correct the cholinergic deficiency seen with AD. Anti-oxidants such as tocopherol, selegiline, and ascorbic acid (vitamin C) were examined as a possible preventive therapy for AD, and they show delayed functional deterioration in AD patients. (*Hogan* et al., 2007; *Schmitt* et.al., 2004)

- *Millard* et al. reported that AChE incubated with allicin produced rapid inactivation that was concentration and time-dependent. Many results showed concentration-dependent inhibition of bovine AChE by allicin complementing the previous finding. However, different cholinesterase inhibitors such as donepezil, rivastigmine, and tacrine are used to treat AD, and their side effects are becoming increasingly remarkable Therefore, the search for new derivatives extracted from the natural product with a dual function and lower

side effects could be useful for patients with AD. Allicin is a small lipophilic molecule that can suppress BuChE and AChE, and therefore, enhances ACh concentration, which is decreased remarkably in AD patient's brains. Recently, allicin has also shown to have a protective effect on ischemic or traumatic neuronal damage controlled by apoptosis and oxidative stress pathways. (*Millard* et al., 2003; *Inglis*, 2002; *Jann* et.al., 2002; *Liu* et al., 2015)

Effect on dyslipidemia

- In various experimental and clinical trials, the garlic was found to have an important effect on dyslipidemia by significantly decreasing serum TC, TG, and LDL levels and moderately increasing HDL cholesterol. (*Iweala* et al., 2005; *El-Saber Batiha et al*., 2020)
- *Sobenin* et al. revealed that garlic administration at a dose of 300 and 60 mg/day for 12 months and 12 weeks, respectively decreased TC, TG, and LDL while increased HDL. (*Sobenin et al., 2008; Sobenin, etal., 2010;; El-Saber Batiha et al., 2020)*
- *Ashraf* et al. reported that garlic tablets administration at a dose of 600 mg/day for 12 weeks in diabetic patients with dyslipidemia results in high HDL and low LDL and TC levels. (*Ashraf* et al., 2005; *El-Saber Batiha et al*., 2020)

Anti-cancer activity

- *Petrovic* et al. (2018) examined the molecular and cellular activities of a simple homemade ethanol-based garlic extract (GE) for the anti-cancer activities in epidemiological studies. They found that GE inhibits growth of several different cancer cells *in-vitro* , as well as cancer growth *in-vivo* in a syngeneic orthotopic breast cancer model. Multiple myeloma cells were found to be especially sensitive to GE. The GE was fractionated using solid-phase extractions, and allicin was identified in one GE fraction; however, growth inhibitory activities were found in several additional fractions. These activities were lost during freeze or vacuum drying, suggesting that the main anti-cancer compounds in GE are volatile. The anti-cancer activity was stable for more than six months in –20°C. They further reported that GE enhanced the activities of chemotherapeutics, as well as MAPK and PI3K inhibitors. Furthermore, GE affected hundreds of proteins involved in cellular signalling, including changes in vital cell signaling, cascades regulating proliferation, apoptosis, and the cellular redox balance. The data indicated that the reduced

proliferation of the cancer cells treated by GE is at least partly mediated by increased endoplasmic reticulum (ER) stress.

- *Thomson and Ali* (2003) reported two major compounds in aged garlic, S-allylcysteine and S-allylmercapto-L-cysteine had the highest radical scavenging activity. In addition, some organosulfur compounds derived from garlic, including S-allylcysteine, have been found to retard the growth of chemically induced and transplantable tumors in several animal models. Therefore, the consumption of garlic may provide some kind of protection from cancer development.

- *Nouroz et al.* (2015) reported that compounds of garlic like Alliin, Ajoene and Allicin acts as efficient Anti-cancer agents.

- *Li et al.* (2018) suggested a possibility that the anti-cancer property of garlic is more effective only when exposed directly to cancer cells than absorbed first by the normal epithelial cells of the gastro-intestinal tract wall. They tested this possibility in two mouse models of highly aggressive malignancies that cannot yet be cured by conventional therapies: sarcoma 180- and EL4-induced lethal ascites. Daily oral gavages of raw garlic extract (RGE; equivalent to 100 mg wet weight) for 21 days failed to offer any meaningful effect in the mice with malignancies. However, the daily injection of the same amounts of the same materials for 21 days completely cured all the mice of cancer. This novel Anti-cancer activity of RGE was present entirely in the size fraction of the molecules smaller than 3000 Dalton rather than the larger molecules and was completely partitioned into the organic phase rather than into the aqueous phase. One half of the anti-cancer activity was inactivated by heating at 100 °C for 10 min, suggesting that multiple components were concertedly involved. In a direct comparison, the RGE was significantly more effective in killing the cultured cancer cells *in-vitro* than the extracts from other 21 raw vegetables and fruits. In cell culture, RGE killed a wide variety of different cancer cells regardless of species of origin and cell types. The most-effective way of treating cancer by RGE may be the direct injection instead of eating the cooked garlic.

Additional activities

- Bulb of *Allium sativum* has also been reported to possess anti-viral, anti-inflammatory, anti-bacterial, anti-fungal, anti-protozoal, anti-hyperlipidemic,

cardio-protective, anti-hypertensive, anti-obesity, anti-atherosclerotic and anti-thrombotic activities. (El-Saber Batiha et al., 2020)

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Sumbul al-Ṭīb
(Rhizome)
Nardostachys jatamansi (D.Don) DC.

Introduction

The drug of *Sumbul al-Ṭīb* consists of the dried root rhizome of *Nardostachys jatamansi* (D.Don) DC (Family-Caprifoliaceae). It is a flowering plants grows in the Himalayas, primarily in a belt through Kumaon, Nepal, Sikkim and Bhutan. (Anonymous, 2007a)

Fig. *Sumbul al-Ṭīb*

Vernacular Names

English: Muskroot, Indian Spikenard, Spikenard; Hindi: *Bālchhaṛ*, *Jatāmāsi*; Urdu: *Sumbul al-Ṭīb*; Arabic: *Sumbul al-Ṭīb, Sumbul al-'Aṣāfīr;* Persian: *Āyak (Khān,* 2014*; Ibn Sīnā,* 1987*; Ibn Baytār,* 1999*; Kabīruddin,* 2000*; Ghani,* YNM; Anonymous, 2007a)

Temperament

Ḥār (Hot)[2] *Yābis* (Dry)[1] *(Khān,* 2014*; Ibn Sīnā,* 1987*; Ibn Baytār,* 1999*; Kabīruddin,* 2000*)*

Chemical Constituents

The main active constituents of *Nardostachys jatamansi* are sesquiterpenes, coumarins and valeranone or jatamansone. The other sesquiterpenes includes alphapatcho-ulense, *β*-eudesemo, *β*-sitosterol, elemol, angelicin, jatamansin, jatamansinol, calarene, jatamansone *β*atchoulense, n-hexaco- sanyl, n-hexacosane, oroselol, valeranal, valeranone, seychelane, nardostachnol, nardostachone, nardin,

nardal, jatamnsic acid, b-maline. Volatile oil, essential oil, resin, sugar, starch, bitter extractive matter, gum, ketone, jatamansic acid, jatamansone, lupelol, malliene, calarenol, coumarin jatamansin, propionate, cyclohexanal ester, heptacosanyl pentanoate are isolated from rhizomes. The phytochemical investigation of hydro alcoholic extract of *Nardostachys jatamansi* showed the presence of steroids, alkaloids, sterols, tannins, mucilage, flavonoids, carbohydrates, gums, terpenes and glycosides An alkaloid named actinidine has also been reported. (Nakoti et al., 2017; Jha et al., 2012; Sharma et al.2016)

Pharmacological Actions

- *Muqawwī-i-Ḥarārat Gharīziyya* (Tonic for innate heat)
- *Muqawwī-i-Qalb* (Cardiotonic)
- *Muqawwī-i-Dimāgh* (Brain tonic)
- *Muqawwī-i-Kabid* (Hepatotonic)
- *Muqawwī-i-Miʿda* (Stomachic)
- *Muqawwī-i Bāh* (Aphrodisiac)
- *Muḥallil-i-Waram* (Anti-inflammatory)
- *Kāsir-i-Riyāḥ* (Carminative)
- *Muddir-i-Bawl* (Diuretic)
- *Mudirr-i-Ḥayḍ* (Emmenagogue)
- *Mufattiḥ* (Deobstruent)
- *Jāli* (Detergent)
- *Muṭīb-i Dahan* (Mouth freshener)

  (*Khān,* 2014; *Ibn Sīnā,* 1987; *Ibn Baytār,* 1999; Al-Harawi, 2002; *Kabīruddin,* 2000; *Ghani,* YNM; Anonymous, 2007a)

Therapeutic Uses

- *Ḍuʿf-i-Ḥarārat Gharīziyya* (Innate heat insufficiency)
- *Ḍuʿf-i-Qalb* (Cardiac insufficiency)
- *Ḍuʿf-i-Dimāgh* (Cerebrasthenia)
- *Ḍuʿf-i-Kabid* (Hepatic insufficiency)
- *Ḍuʿf-i-Qalb* (Cardiac insufficiency)
- *Ḍuʿf-i-Bāh* (Sexual debility)

- *Ṣudā'* (Headache)
- *Nafkh-i-Shikam* (Flatulence)
- *Waram-i-Kabid* (Hepatitis)
- *Yarqān* (Jaundice)
- *Istisqā'* (Ascites)
- *Waram-i-Raḥim* (Metritis)
- *Waram-i-Mathāna* (Cystitis)
- *Amrāḍ-i- Jild* (Skin diseases)

(Khān, 2014; Ibn Sīnā, 1987; Ibn Baytār, 1999; Al-Harawi, 2002; Kabīruddin, 2000; Ghani, YNM; Anonymous, 2007a)

Important Formulations

Jawārish Fanjnawsh, Barsh'ashā, Anawshdārū, Anawshdārū Lawlawī, Koḥal Rawshna'i, Sufūf-e- Mohazzil, Iyarij Fayaqra, Rawghan Bābūna Qawī, Ḍimād Sunbul-ut-Ṭīb (Anonymous , 2007a)

Pharmacological / Clinical Studies (evidence based)

Anti-oxidant activity

- Sharma and Singh (2012) carried out the study to evaluate the anti-oxidative potential of a hydroalcoholic extract of *Nardostachys jatamansi* (NJE) rhizomes by various anti-oxidant assays, including anti-oxidant capacity by the phosphomolybdenum method, total anti-oxidant activity in linoleic acid emulsion systems, 1, 1-diphenyl-2-picrylhydrazyl (DPPH), superoxide, hydroxyl radicals, nitric oxide (NO) scavenging, metal chelating and reducing power activity. These various Anti-oxidant activities were compared with standard anti-oxidants such as butylated hydroxytoluene, tocopherol, catechin, and L-ascorbic acid. Total phenolic and flavonoid content of NJE was also determined by a colorimetric method. The extract exhibited high reduction capability and powerful free radical scavenging, especially against DPPH and superoxide anions as well as a moderate effect on NO. Moreover, the peroxidation inhibiting activity of NJE was demonstrated in the linoleic acid emulsion system. The results revealed that the antioxidative potency of NJE, which may account for some of the medical claims attributed to this plant.

- Razack et al. (2015) conducted the study aimed at analyzing the metabolite profile of *Nardostachys jatamansi* using RP-HPLC, GC-MS and also its Anti-oxidant, biomolecule protective and cyto-protective properties. The 70% ethanolic extract of *Nardostachys jatamansi* (NJE) showed the presence of polyphenols and flavonoids (gallic acid, catechin, chlorogenic acid, homovanillin, epicatechin, rutin hydrate and quercetin-3-rhamnoside) analyzed by RP-HPLC, whereas hexane extract revealed an array of metabolites (fatty acids, sesquiterpenes, alkane hydrocarbons and esters) by GC-MS analysis. The anti-oxidant assays showed the enhanced potency of NJE with a half maximal inhibitory concentration (IC_{50}) value of 222.22 ± 7.4 µg/mL for 2, 2-diphenyl-1-picrylhydrazyl (DPPH), 13.90 ± 0.5 µg/mL for 2, 2'-azino-bis (3-ethyl benzothiazoline-6-sulfonic acid) diammonium salt (ABTS), 113.81 ± 4.2 µg/mL for superoxide, 948 ± 21.1 µg/mL for metal chelating and 12.3 ± 0.43 mg $FeSO_4$ equivalent/g of extract for ferric reducing Anti-oxidant power assays and was more potent than hexane extract.The study suggested that the herb unequivocally is a potential source of Anti-oxidants and could aid in alleviating oxidative stress-mediated disorders.

- Ahmed et al. (2009) evaluated the free radical scavenging and anti-cholinesterase activity of the methanolic extracts of *Acorus calamus* (ACME) and *Nardostachys jatamansi* (NJME) rhizomes *in-vitro* . In addition, total phenolics (TP) were also estimated. NJME contained significantly higher (p =0.05) phenolics (37 µg GAE/mg) than ACME (23µg GAE/mg). Consequently, NJME exhibited significantly higher (p =0.05) radical scavenging activity than ACME and BHT, a synthetic anti-oxidant. Further, the IC50 values were 704, 237 & 335 µg/ml for ACME, NJME and BHT respectively. In case of anti-cholinesterase activity also NJME exhibited significantly higher (p =0.05) activity with lower IC50 value than ACME. However, the anti-cholinesterase activity of both ACME and NJME were significantly lower (p =0.05) than neostigmine, a standard drug wherein, neostigmine exhibited significantly lower (p =0.05) IC50 value than ACME and NJME. Furthermore, a significant correlation between the total phenolic content, anti-oxidant and anti-cholinesterase activities of both the extracts indicating that total phenolics might be responsible for the observed anti-oxidant and anti-cholinesterase activities.

Anti-oxidant and stress relieving activity

- The anti-stress effect of hydro-ethanolic extract of *N. jatamansi* was evaluated

in reference to its anti-oxidant property. Wistar rats were divided into four groups nañve, stressed, T-200 and T-500 stressed with oral pre-treatment of *N. jatamansi* extract 200 and 500 mg/kg, respectively. Restraint of rats on metallic chambers for 4 h at 4°C was followed by sacrifice and assessment of stress-induced alterations in biochemical parameters, incidence and severity of ulcers. The In-vitro anti-oxidant activity of *N. jatamansi* was studied by measuring the free radical scavenging activity. *N. jatamansi* showed potent Anti-oxidant activity and significantly reversed the stress-induced elevation of LPO and NO levels and decrease in catalase activity in the brain. The *N. jatamansi* possesses significant anti-stress activity, which may be due to its anti-oxidant activity. (Lyle et al., 2009; Sahu et al., 2016)

Immunomodultory activity

- Gulati et al. (2002) described *N. jatamansi* as effective immunomodulatory plant, involved in the prevention and treatment of disease and stresses upon the role of diet, life style and drugs as cornerstones of therapy.
- Salim et al. (2003) reported the protective effect of *Nardostachys jatamansi* (NJ) on neurobehavioral activities, thiobarbituric acid reactive substance (TBARS), reduced glutathione (GSH), thiol group, catalase and sodium-potassium ATPase activities was studied in middle cerebral artery (MCA) occlusion model of acute cerebral ischemia in rats. The right MCA of male Wistar rats was occluded for 2 h using intraluminal 4-0 monofilament and reperfusion was allowed for 22 h. MCA occlusion caused significant depletion in the contents of glutathione and thiol group and a significant elevation in the level of TBARS. The activities of Na (+)K(+) ATPase and catalase were decreased significantly by MCA occlusion. The neuro-behavioral activities (spontaneous motor activity and motor coordination) were also decreased significantly in MCA occlusion group. All the alternations induced by ischemia were significantly attenuated by 15 days pretreatment of NJ (250 mg/kg po) and correlated well with histopathology by decreasing the neuronal cell death following MCA occlusion and reperfusion. The study provides first evidence of effectiveness of NJ in focal ischemia most probably by virtue of its Anti-oxidant property.

Anti-depressant activity

- The efficacy of the extract at the dose of 200 and 400 mg/kg, p. o. was compared with the standard drug imipramine [10 mg/kg, p. o.] in normal

and sleep deprived mice. *N. jatamansi* at the dose of 200 and 400 mg/kg, p.o produced significant [P<0.001] anti-depressant like effect in normal and sleep deprived mice in both TST and FST and their efficacies were found to be comparable to imipramine at the dose of 10 mg/ kg, p.o. It did not show any significant change in locomotor functions of mice as compared to normal control. However it significantly [P<0.01] improves the locomotors activity in case of sleep deprivation which is comparable to normal control. This finding suggests that *N. jatamansi* has dose dependent anti-depressant activity and can also be used in patients suffering from depression due to sleep disturbances. (Rahman & Muralidharan, 2010; Sahu et al., 2016)

Anti-convulsant activity

- Ethanolic extract of of *N. jatamansi* was studied for its anti-convulsant activity. The results showed a significant increase in the seizure threshold by *N. jatamansi* root extract against maximal electro shock seizure model as indicated by a decrease in the extension/flexion ratio. However the extract was ineffective against pentylenetetrazole induced seizures. Further, pre-treatment of rats with phenytoin at a dose of 12.5, 25, 50 and 75 mg/kg in combination with 50 mg/kg of *N. jatamansi* root extract resulted in a significant increase in the protective index of phenytoin from 3.62 to 13.17. The dose response studies of phenytoin alone and in combination with *N. jatamansi* extract in the serum levels of phenytoin clearly demonstrated the synergistic action of both the drugs. (Rao et al., 2005; Sahu et al., 2016)

Anti-cancer activity

- Chaudhary et al., (2015) evaluated anti-cancer activities of extract of *Nardostachys jatamansi* in breast carcinoma. Petroleum ether (NJPE), methanol extract (NJM) and subsequent diethyl ether (NJDE), ethyl acetate (NJEA) and aqueous (NJAQ) fractions of roots and rhizomes of *N. jatamansi* were prepared. Anti-proliferative activity was assessed in estrogen receptor (ER)-positive (MCF-7) and ER-negative breast carcinoma (MDA-MB-231) cells by MTT and SRB assay. Cell cycle analysis, Hoechst staining, and clonogenic assay were employed to determine the mode of anti-proliferative and pro-apoptotic activity in MDA-MB-231 cells. The result showed that the NJM exhibited the highest anti-proliferative activity (IC50: 58.01 ± 6.13 and 23.83 ± 0.69 µg/mL in MCF-7 and MDA-MB-231 respectively). Among the fractions, NJPE and NJDE were found to be most potent in MCF-7 (IC50: 60.59 ± 4.78 µg/mL)

and MDA-MB-231 (IC50: 25.04 ± 0.90 µg/mL) cells respectively. Statistical analyses revealed NJM and NJDE exhibited significantly higher ($P < 0.05$) cytotoxicity in MDA-MB-231 cells. Cell cycle analysis demonstrated that NJM, NJPE and NJEA caused G2/M arrest while NJDE caused G0/G1 phase arrest in MDA-MB-231 cells. Further, NJM/fractions induced significant ($P < 0.001$) cell death by apoptosis characterized by apoptotic morphological changes in Hoechst staining and inhibited long-term proliferation ($P < 0.001$) of MDA-MB-231 cells in clonogenic assay. Lupeol and β-sitosterol were identified as Anti-cancer principles in NJM/fractions by HPTLC.

- Bhagat et al. (2013) explored the anti-proliferative tumor potential of roots extracts of *Nardostachys jatamansi* against human cancer cell lines as well as *in-vivo* activity of active fraction against Sarcoma 180 murine tumor (solid) model. The results revealed that the alcoholic extract (ACE) and its n-butanol faction showed significant and dose-dependent inhibitory effect on proliferation of various human cancer cell lines i.e., A54-9 (lung), Hep-2 (liver), OVCAR-5 (ovary) and prosate (PC-3). Similarly the active n-butanol (BTF) fraction of *N. jatamansi* also exhibit significant antitumor activity in Sarcoma 180 solid tumor bearing mice and is comparable to the reference standard, 5- fluorouracil. The results suggested that the 95% alcoholic extract and its n-butanol fraction of *N. jatamansi,* had strong *In-vitro* as well as *in-vivo* antitumor potential.

- Suryavanshi et al. (2017) evaluated the effect of ethanolic extract of *Nardostachys jatamansi* roots (NJ_{et}) on MYCN mediated regulation of expression of MDM2 and p53 proteins in neuroblastoma cell lines, IMR-32 and SK-N-MC. The effect of NJ_{et} on cell viability was determined by MTT; and on growth kinetics was evaluated by trypan blue dye exclusion method and soft agar assay. The expression of p53, MDM2 and MYCN proteins in response to NJ_{et} treatment was evaluated by immunoblotting. The results showed that the NJ_{et} decreased the viability of neuroblastoma cells without affecting the viability of non-cancerous, HEK-293 cells. It altered the growth kinetics of the cancer cells in a dose-dependent manner. NJ_{et} down regulated the expression of MYCN and MDM2 proteins with a simultaneous increase in the expression of tumor suppressor protein p53. The findings of present data demonstrated that NJ_{et} regulated the growth of IMR-32 and SK-N-MC through reduction in MYCN expression that lead to down regulation of MDM2 protein and increase in p53 expression.

- The roots of *N. jatamansi* was explored for *in-vitro* anti proliferative potential against two neuroblastoma human cancer cell lines viz., IMR-32 and SK-N-SH using SRB assay. Three extract like 95% alcoholic [ACE], 50% hydro-alcoholic [HAE] and aqueous [AQE] extracts and four fractions viz., hexane [HXF], chloroform [CHF], butanol [BTF] and aqueous [AQF] were evaluated. The 95% alcoholic extract showed significant and dose-dependent inhibitory effect for proliferation of both the cell lines of neuroblastoma. The percent growth inhibition was found to be 71% against IMR-32 and 85% against SK-N-SH at 100 µg/ml respectively. It showed growth inhibition of 54% and 91% against IMR-32 and 45% and 82% against SKN- SH at 30 mg/ml and 100 µg/ml against neuroblastoma cancer cell lines respectively.(Middleton & Kandaswami, 2000; Sahu et al., 2016)

Additional activities

- The *Nardostachys jatamansi* has also been reported to possess hepato-protective, cardio-protective, neuro-protective, hypo-lipidemic, anti-fungal, anti-bacterial, anti-microbial, anti-ulcer, anti-hypertensive, anti-diabetic, anti-inflammatory, insecticidal, heamatopoetic, anti-depressant, radio-protective, anti-cataleptic and anti-anxiolytic activities. (Nakoti et al., 2017; Sahu et al., 2016)

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Z'afrān
(Style & Stigma)
Crocus sativus L.

Introduction

The drug of *Z'afrān* consists of dried style and stigma of *Crocus sativus* L., Syn. *Crocus officinalis* (L.) Honck. (Family-Iridaceae). A small, bulbous, perennial, 15 to 25 cm high. It is cultivated in the Kashmir valley, especially in the Pampor plateau, at about 1600 m. (Anonymous, 2009).

Fig. *Zafran*

Vernacular Names

English: Saffron; Hindi:, *Kaysar*; Urdu: *Z'afrān*; Arabic: *Kurkum, Z'afrān, Ḥalūq, Jād;* Persian: *Kīmās. (Khān,* 2013*; Ibn Sīnā,* 1987*; Ibn Baytār,* 1986*; Kabīruddin,* 2000*; Ghani,* YNM*)*

Temperament

Ḥār (Hot)[2] *Yābis* (Dry)[1] *(Khān,* 2013*; Ibn Sīnā,* 1987*; Ibn Baytār,* 1986*; Kabīruddin,* 2000*)*

Chemical Constituents

- The characteristic components of saffron are crocin-(responsible for the color), picrocrocin- (responsible for the bitter taste), and safranal- (responsible for odor and aroma) (Evans, 2009). Saffron contains more than 150 volatile and aroma-yielding compounds. It also has many non-volatile active components, many of which are carotenoids including zeaxanthin, lycopene, and various α- and β-carotenes (Liakopoulou-Kyriakides and Kyriakidis, 2002).The volatiles with a very strong odor are consistent of more than 34

components that are mainly terpenes, terpene alcohols, and their esters. Non-volatiles include crocins 14 that are responsible for the red or reddish brown color of stigmas together with carotenes, crocetin, picrocrocin (a glycosidic precursor of safranal), the bitter substance and safranal the major organoleptic principle of stigmas (Wallis, 1946). However saffron's golden yellow-orange color is primarily due to α-crocin. This crocin is *trans*-crocetin di-(β-D-gentiobiosyl) ester. This means that the crocin underlying saffron's aroma is a digentiobiose ester of the carotenoid crocetin. Crocins themselves are a series of hydrophilic carotenoids that are either monoglycosyl or di-glycosyl polyene esters of crocetin (Liakopoulou-Kyriakides and Kyriakidis, 2002). Meanwhile crocetin is a conjugated polyene dicarboxylic acid that is hydrophobic and thus oil soluble. When crocetin is esterified with two water-soluble gentiobioses (which are sugars), a product results that is itself water soluble. The resultant α-crocin is a carotenoid pigment that may comprise more than 10% of dry saffron's mass. The two esterified gentiobioses make α-crocin ideal for coloring waterbased (nonfatty) foods such as rice dishes (Wallis, 1946).

- A hypothetical protocrocin of the fresh plant is decomposed on drying into one molecule of crocin and two molecules of picrocrocin. Crocin on hydrolysis yields gentiobiose and crocetin, while picrocrocin yields glucose and safranal (Evans, 2009). The bitter glucoside picrocrocin is responsible for saffron's flavor. Picrocrocin is a union of an aldehyde sub-element known as safranal and a carbohydrate. It has insecticidal and pesticidal properties and may comprise up to 4% of dry saffron. Safranal is less bitter than picrocrocin and may comprise up to 70% of dry saffron's volatile fraction in some samples. A second element underlying saffron's aroma is 2-hydroxy-4, 4, 6-trimethyl-2, 5-cyclohexa-dien-1-one, the scent which has been described as "saffron, dried hay-like (Hosseinzadeh *et al.,* 2003).
- Crocetin, riboflavin, picrotoxin, thiamine, picrocrocin, crocin, carotenoids, essential oil, bitter glycoside are the main constituents present in *Crocus sativus L.* (Anonymous, 2009).

Pharmacological Actions

- *Muʿmmir* (Longevity promoting agent)
- *Muqawwī-i-Ḥarārat Gharīziyya* (Tonic for innate heat)

- *Muqawwī-i-Qalb* (Cardio tonic)
- *Muqawwī-i-Dimāgh* (Brain tonic)
- *Muqawwī-i-Baṣar* (Eye tonic)
- *Muqawwī-i-Kabid* (Hepato tonic)
- *Muqawwī-i Bāh* (Aphrodisiac)
- *Muḥallil-i-Waram* (Anti-inflammatory)
- *Mufarriḥ* (Exhilarant)
- *Muḥarrik-i-Bāh* (Libido stimulant)
- *Mudirr-i-Bawl* (Diuretic)
- *Mudirr-i-Ḥayḍ* (Emmenagogue)
- *Qābiḍ* (Astringent)
- *Dāfi'-i-Ta'ffun* (Antiseptic)
- *Jāli* (Detergent)

(*Khān*, 2013; *Ibn Sīnā*, 1987; *Ibn Baytār*, 1986; Al-Harawi, 2002; *Kabīruddin*, 2000; *Ghani*, YNM; Anonymous, 2009)

Therapeutic Uses

- *Ḍu'f-i-Ḥarārat Gharīziyya* (Innate heat insufficiency)
- *Amrāḍ-i-Qalb* (Cardiac diseases)
- *Ḍu'f-i-Qalb* (Cardiac insufficiency)
- *Ḍu'f-i-Kabid* (Hepatic insufficiency)
- *Ḍu'f-i-Dimāgh* (Cerebrasthenia)
- *Ḍu'f-i-Baṣar* (Poor eyesight)
- *Ḍu'f-i-Bāh* (Sexual debility)
- *Nisyān* (Forgetfulness)

(*Khān*, 2013; *Ibn Sīnā*, 1987; *Ibn Baytār*, 1986; Al-Harawi, 2002; *Kabīruddin*, 2000; *Ghani*, YNM; Anonymous, 2009)

Important Formulations

Dawa ul Kurkum, Dawa ul Misk Mo'tadil sada, Dawa ul Misk Mo'tadil Jawāhar wālā, M'ajūn Dabīd ul Ward, Jawarish Zar'ūni. (Anonymous, 2009)

Pharmacological / Clinical studies (evidence based)

Anti-oxidant activity

- The imbalance between reactive oxygen species (ROS) production and anti-oxidant level is directly linked to the pathogenesis of diseases. The enhancement of anti-oxidant level or reduction of reactive species level is maintained through anti-oxidant properties of plants or their derivatives. Numerous studies based on *in-vivo* and *in-vitro* have confirmed that *Crocus sativus* has a significant anti-oxidant activity. Anti-oxidant activity of saffron has been observed in extract of stigma and such extract shows role in the reduction of chlorophyll damage, lipid peroxidation, and protein oxidation. Similarly, other finding has confirmed that saffron stigma contains superior anti-oxidant activity. Earlier findings have demonstrated that active and inactive constituents of saffron extract have high anti-oxidant activity and saffron petal extract showed anti-oxidant activity. (Rahmani et al., 2017; Assimopoulou et al., 2005; Goli et al., 2012)

- More studies demonstrated that constituent of saffron such as crocin has a potent anti-oxidant activity. Lebanon based finding demonstrated that saffron notably decreased lipid peroxidation as well increased superoxide dismutase activity when compared to control group. Crocin showed role in the inhibition of lipid peroxidation and restored SOD activity. Stigma of *Crocus sativus* contains more anti-oxidant activity as compared to tomatoes and carrots.(Rahmani et al., 2017; Asdaq et al., 2010; Makhlouf et al., 2011; Ochiai et al., 2004)

- Baba et al (2015) study was conducted to evaluate and compare the chemical composition and anti-oxidant activity of three different tissue types of *Crocus* viz: stigma, corm, and leaf. The phytochemical analysis carried out using LC-MS showed that the major constituents identified were flavonoids like kaempferol, taxifolin, naringenin, etc. and apocarotenoids including crocin, crocetin, and their derivatives. Also the total phenolic, flavonoid, and carotenoid contents were determined. The anti-oxidant property of these tissue types was also investigated and compared by biochemical assays like, DPPH, NBT, and FRAP. The ethanolic fraction of stigma demonstrated the strongest anti-oxidant activity which could be attributed to its highest content of phenolics and flavonoids. Stigma extract was further evaluated for its role in alleviating oxidative stress in plants, yeast, and bacteria. The results revealed

that stigma extract reduced methylviologen induced chlorophyll damage, lipid peroxidation, and protein oxidation in plants thereby rendering them more tolerant to stress. It also showed to alleviate H_2O_2 mediated oxidative stress tolerance in bacteria and yeast.

Immunomodulatory activity

- Samarghandian et al. (2017) investigated the immunomodulatory effects of the aqueous saffron extract on streptozotocin (STZ)-induced diabetic rats. During the study, rats were divided into the following groups of 9 animals each: control, untreated diabetic, three saffron extract-treated diabetic groups. Diabetes was induced by STZ in rats. Saffron was administered 3 days after STZ administration; these injections were continued to the end of the study (4 weeks). At the end of 4-week period, blood was drawn for biochemical assays and the abdominal aorta was removed for detecting the inflammatory cytokines expression. As result, the saffron decreased blood glucose, malondialdehyde, nitric oxide, total lipids, triglycerides, cholesterol levels significantly ($p < 0.01$) and increased glutathione level, catalase, and superoxide dismutase activities in the saffron-treated diabetic groups compared with the untreated groups, in a dose dependent manner ($p < 0.05$, $p < 0.01$, $p < 0.001$). On the other hand, saffron-treated diabetic rats inhibited the expression of inflammatory cytokines in the abdominal aorta versus the untreated diabetic rats.

- Kianbakht and Ghazavi (2011) reported immunomodulatory activities of *Crocus sativus* without any adverse effects.

- Zeinali et al. (2019) summarized the protective roles of *C. sativus* and its constituents against the pathogenesis of immune diseases and understanding a better management of the same. The study indicated that the compounds with immunoregulatory properties may be effective for prevention and treatment of such diseases.

Activity in memory impairment

- Saffron extract improved ethanol-induced impairments of learning behaviours in mice, and prevented ethanol-induced inhibition of hippocampal long-term potentiation, a form of activity-dependent synaptic plasticity that may underlie learning and memory. Accordingly, saffron extract or its active constituents, crocetin and crocin, could be useful as a treatment for neuro-degenerative

disorders accompanying memory impairment (Esmail Al-Snaf, 2016; Abe and Saito, 2000)

- Alzheimer's disease was characterized pathologically by deposition of amyloid beta-peptide (Abeta) fibrils. Oxidation was thought to promote Abeta fibril formation and deposition. To identify agents inhibiting the pathogenesis of Alzheimer's disease, the anti-oxidant properties of extract of *Crocus sativus* stigmas and its effect on Abeta (1-40) fibrillogenesis was investigated *in-vitro*. The anti-oxidant properties were determined by measuring the ferric-reducing anti-oxidant power and Trolox-equivalent Anti-oxidant capacity, while its effects on Abeta-aggregation and fibrillogenesis were studied by thioflavine T-based fluorescence assay and by DNA binding shift assay. The water: methanol (50:50, v/v) extract of *Crocus sativus* stigmas possessed good Anti-oxidant properties, higher than those of tomatoes and carrots, and inhibited Abeta fibrillogenesis in a concentration and time-dependent manner. The main carotenoid constituent (trans-crocin-4) the digentibiosyl ester of crocetin, inhibited Abeta fibrillogenesis at lower concentrations than dimethylcrocetin, revealing that the action of the carotenoid was enhanced by the presence of the sugars. The result suggested the possible use of *Crocus sativus* stigma constituents for inhibition of aggregation and deposition of Abeta in the human brain (Papandreou etal., 2006)

- Saffron extract was investigated in preventing D-galactose and NaNO2 induced memory impairment and improving learning and memory deficits in amnestic mice. The learning and memory functions in ovariectomized mice were examined by the one way passive and active avoidance tests. In active avoidance test, training in amnestic treated (AT) and amnestic prophylaxis (AP) groups, was improved, there was a significant difference between them and the amnestic control (AC) group. In passive avoidance test, animal's step through latency, as an index for learning, in all test groups was significantly greater than control group. Total time spent in dark room (DS), which opposed the memory retention ability, in AC was significantly greater than AT group at 1 and 2 hours after full training, while there was no significant difference in this parameter between AP and AT (Esmail Al-Snaf , 2016;; Dashti et al., 2012)

- The acute effects of an alcohol extract of *Crocus sativus* (CS-extract) were studied on learning and memory in step through (ST) and step down (SD) tests in normal, trained and memory-impaired mice. A single oral administration of

CS-extract had no effects on memory registration consolidation or retrieval in normal mice. CS-extract reduced the ethanol-induced impairment of memory registration both in ST and SD tests and the ethanol-induced impairment of memory retrieval in SD test. CS extract decreased the motor activity (MA) and prolonged the sleeping time induced by hexobarbital (Esmail Al-Snaf , 2016; Zhang et al., 1994)

- Long-term potentiation (LTP) was thought as a generative mechanism underlying learning and memory via storing information in central nervous system. Electro-neurophysiological assay for LTP was generally used in screening the drugs that can facilitate learning and memory. Methanol extract of saffron (MES) being able to facilitate LTP-induction, and can antagonize the inhibiting effect of 30% ethanol on LTP induction (30 pulses/60 Hz) (Esmail Al-Snaf , 2016; He et al., 2009)

- The effects of *Crocus sativus*, and its active constituent crocin was evaluated on learning and memory loss and the induction of oxidative stress in the hippocampus by chronic stress. Rats were injected with saffron extract, crocin or vehicle over a period of 21 days while being exposed to chronic restraint stress (6 h/day). Then, animals were trained and tested on a water-maze spatial memory task. They performed four trials per day for 5 consecutive days, and this was followed by a probe trial two days later. At the end of the behavioral testing, several parameters of oxidative stress in the hippocampus were measured. Treatment with saffron extractor crocin blocked the ability of chronic stress to impair spatial learning and memory retention. Crocin significantly decreased plasma levels of corticosterone, as measured after the end of stress. Thee results indicated that saffron and its active constituent crocin can prevent the impairment of learning and memory as well as the oxidative stress damage to the hippocampus induced by chronic stress (Esmail Al-Snaf , 2016; Ghadrdoost et al., 2011)

- The effect of aqueous extracts of saffron was investigated in morphine-induced memory impairment. On the training trial, the mice were subjected to an electric shock on entering into the dark compartment. Twenty-four and forty-eight hours later, the time latency for entering the dark compartment was recorded and defined as the retention trial. The mice were divided into (1) control, (2) morphine which received morphine before the training in the passive avoidance test, (3-5) three groups treated by 50, 150 and 450 mg/kg

of saffron extract before the training trial, and (6 and 7) the two other groups received 150 and 450 mg/kg of saffron extract before the retention trial. The time latency in morphine-treated group was lower than control ($p<0.01$). Treatment of the animals by 150 and 450 mg/kg of saffron extract before the training trial increased the time latency at 24 and 48 hours after the training trial ($p<0.05$ and $p<0.01$). Administration of both 150 and 450 mg/kg of the extract before retention trials also increased the time latency ($p<0.01$). The results revealed that the saffron extract attenuated morphine-induced memory impairment (Esmail Al-Snaf , 2016; Naghibi et al., 2012)

- Inhibitors of acetylcholine breakdown by acetylcholinesterase (AChE) constituted the main therapeutic modality for Alzheimer's disease. The inhibition of AChE activity of saffron extract and its constituents was studied by *in-vitro* enzymatic and molecular docking studies. Saffron extract showed moderate AChE inhibitory activity (up to 30%), but IC50 values of crocetin, dimethylcrocetin, and safranal were 96.33, 107.1, and 21.09 µM, respectively. Kinetic analysis showed mixed-type inhibition, which was verified by in silico docking studies. Safranal interacted only with the binding site of the AChE, but crocetin and dimethylcrocetin bind simultaneously to the catalytic and peripheral anionic sites (Esmail Al-Snaf , 2016; Geromichaloset al., 2012)

- The efficacy of *Crocus sativus* was studied in the treatment of patients with mild-to-moderate Alzheimer's disease. Fifty-four Persian adults, 55 years of age or older were participated in a 22-week, double-blind study of parallel groups of patients with AD. The main efficacy measures were the change in the Alzheimer's disease Assessment Scale-cognitive subscale and Clinical wztia Rating Scale-Sums of Boxes scores compared with baseline. Adverse events (AEs). Participants were randomly assigned to receive a capsule saffron 30 mg/day (15 mg twice per day) or donepezil 10 mg/day (5 mg twice per day). Saffron at this dose was found to be effective similar to donepezil in the treatment of mild-to-moderate AD after 22 weeks. The frequency of AEs was similar between saffron extract and donepezil groups with the exception of vomiting, which occurred significantly more frequently in the donepezil group (Esmail Al-Snaf , 2016; Akhondzadeh et al., 2010)

Cardio-protective activity

- Saffron and its constituents have also supported the evidences of cardio-protective effects. Rat model based study has confirmed that whole saffron

pretreatment or its individual constituents such as safranal pretreatment considerably decrease the serum LDH and CK-MB level, as well as myocardial lipid peroxidation as compared to isoproterenol – induced animals. Crocin, an ingredient of saffron revealed its protective effects of cardio-toxicity through reducing lipid peroxidation as well as alleviating apoptosis. In a similar study based on rat models, it was concluded that crocin improves toxic effects of diazinon through decreasing lipid peroxidation and restoring altered contractile and relaxant responses in aorta. The cardio-protective effect of saffron active constituents including crocin has been confirmed through regulation of oxidative stress. The finding concluded that *Crocus sativus* perfused during electrolysis might trap radical oxygen species and significantly improve myocardial function. (Rahmani et al., 2017).

Anti-obesity activity

- Saffron showed anti-obesity and anorectic effects in the obese rat models. It's property of reducing the leptin level in obese cases indicates that saffron reduces fat mass and increases insulin sensitivity. In an experimental protocol, it was performed to assess the anti-obesity effects of ethanolic extracts of saffron and crocin. Results of this study demonstrated that saffron extract notably decrease the food consumption by obese rats as compared to control groups. Furthermore, crocin showed a noteworthy decrease on rate of body weight gain, total fat deposition and regulates the weight ratio of epididymal fat to body. (Rahmani et al., 2017).

Anti-convulsant activity

- The results of the experiments performed on mice to evaluate the anti-convulsant activities of safranal and crocin, indicated that safranal reduced the seizure duration, delayed the onset of convulsions as well as protected mice from death. This study further investigated that crocin did not show this anti-convulsant activity at all. (Rahmani et al., 2017; Hosseinzadeh & Talebzadeh, 2005)

Anti-cancer activity

- Abdullae (2002) demonstrated that saffron extract itself and its main constituents, the carotenoids, possess chemo-preventive properties against cancer.

- Chemoprevention using readily available natural substances from vegetables, fruits, herbs and spices is one of the significantly important approaches for cancer prevention in the present era. Among the spices, *Crocus sativus* L. has generated interest because pharmacological experiments have established numerous beneficial properties including radical scavenging, anti-mutagenic and immuno-modulating effects. Studies in animal models and with cultured human malignant cell lines have demonstrated antitumor and cancer preventive activities of saffron and its main ingredients. This review provides a brief insight into the Anti-cancer properties of saffron and its components. (Bhandari, 2015).

- The topical application of a saffron extract has been shown to inhibit both the initiation and the promotion of cancer by a common carcinogen, DMBA, which is used to induce skin cancer for experimental purposes. The saffron extracts have been shown to significantly prolong-almost by three-fold-the life spans of mice undergoing experimental chemotherapy with the toxic Anti-cancer drug, cisplatin. Saffron also partially prevented the decrease in body weight, hemoglobin levels and leukocyte counts associated with that form of chemotherapy (Nair, 1991).

- Oral administration of saffron extract inhibited the growth of mouse tumors that were derived from three different kinds of cancer cells and significantly increased the life spans of treated tumor-bearing mice (Chermahini *et al.*, 2010).

Additional activities

- The style & stigma of *Crocus sativus* L. has also been reported to possess anti-depressant, antianxiety, anti-diabetic, anti-inflammatory, analgesic activity, anti-microbial, anti-viral, anti-hypertensive, anti-hyperglycemic, anti-nociceptive, gastro-protective, nephro-protective, hepato-protective, CNS protective, anxiolytic, aphrodisiac and neuro-protective activities. (Esmail Al-Snaf , 2016; Rahmani et al., 2017)

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Zaytūn
(Fruit's oil & Leaf)
Olea europaea L.

Introduction

The drug of *Zaytūn* consist leaf and mature fruit of *Olea europaea* L. (Family-Oleaceae). It is an evergreen tree or shrub native to Mediteranean Europe, Asia and Africa. The fruit is a drupe harvested in the green to purple stage. The fruits when just ripe contain the largest amount of oil. (Nadkarni; 1976)

Fig. Zaitūn

Vernacular Names

English: Olive; Arabic: *Zaytūn, Zayt*; Persian: *Zaytūn* (Khān, 2013; Ibn Sīnā, 1987; Ibn Bayṭār, 1986; Kabīruddīn, 2000; Ghani, YNM)

Temperament

Ḥār (Hot) *Raṭb* (Moist) (Khān, 2012; Ibn Sīnā, 1987)

Chemical Constituents

- Olive tree includes secoiridoids, carbohydrates, sugar alcohols, and terpenoids as biochemicals (Guinda *et al.*, 2015). Basic components in olive leaf are secoiridoids such as oleuropein, ligstroside, I methyloleuropein, and oleoside; flavanoids such as apigenin, kaempferol, luteolin, and chrysoeriol; and phenolic compounds such as caffeic acid, tyrosol, and hydroxytyrosol (Servili *et al.*, 2009; Gariboldi *et al.*, 1986). Secoiridoids, chemical components of leaf, are glycosidically bound and produced by secondary metabolisms of terpenes as the pioneers of various indole alkaloids. Secoiridoids are generally derived

from an oleoside type of glucoside oleosides that are characterized with the combination of elenolic acid and glucoside residues (Soler-Rivas *et al.*, 2000).

- Oleuropein (Oleuropein-1), one of the secoiridoids, is a basic phenolic compound found in olive leaf and the reason of characteristic bitter taste of olive cultivars (Soler-Rivas *et al.,* 2000). Oleuropein is an ester of 2-(3, 4-dihydroxyphenyl) ethanol (hydroxytyrosol) and has the oleosidic skeleton that is common to the secoiridoid glucosides of Oleaceae, mainly in its aglycone form, which makes the sugar moiety insoluble in oil (Soler-Rivas *et al.*, 2000; Omar, 2010).
- Hydrolysis of oleuropein can produce elenolic acid, hydroxytyrosol, tyrosol, and glucose (Hassen *et al.*, 2015). Oleuropein and hydrolysis products found in olive leaf have important biological characteristics.

Pharmacological Actions

- *Muʿmmir* (Longevity promoting agent)
- *Muqawwī-i-Ḥarārat Gharīziyya* (Tonic for innate heat)
- *Muqawwī-i-Badan* (General tonic)
- *Muqawwī-i-Aʿṣāb* (Nervine tonic)
- *Muqawwī-i-Miʿda* (Stomachic)
- *Muqawwī-i Bāh* (Aphrodisiac)
- *Muḥallil-i-Waram* (Anti-inflammatory)
- *Mufattiḥ-i-Sudad* (Deobstruent)
- *Mufattit-i-Hasāt* (Lithotriptic)
- *Mulayyin* (Laxative)
- *Mudammil-i-Qurūḥ* (Cicatrizant)
- *Musakkin* (Soothing agent)
- *Mushtahī* (Appetizer)
- *Kāsir-i-Riyāḥ* (Carminative)

(Khān, 2013; Ibn Sīnā, 1987; Ibn Bayṭār, 1986; Al-Harawi, 2002; Kabīruddīn, 2000; Ghani, YNM)

Therapeutic Uses

- *Ḍuʿf-i-Ḥarārat Gharīziyya* (Innate heat insufficiency)

- *Ḍu'f-i-'Ām* (General debility)
- *Nisyān* (Forgetfulness)
- *Ḍu'f-i-Mi'da* (Gastric debility)
- *Ḍu'f-i-Bāh* (Sexual debility)
- *Ḍu'f-i-Ishtiha* (Loss of appetite)
- *Waja' al-Mafāṣil* (Polyarthritis)
- *Su'āl* (Cough)
- *Fālij* (Hemiplegia)
- *Laqwa* (Bell's palsy)
- *Istirkhā'* (Atony/Flaccidity)
- *Ri'sha* (Tremor)
- *'Irq al-Nasā* (Sciatica)
- *Dā'al Tha'lab* (Alopecia areata)
- *Qūlanj (Colic)*

(Khān, 2013; Ibn Sīnā, 1987; Ibn Bayṭār, 1986; Al-Harawi, 2002; Kabīruddīn, 2000; Ghani, YNM)

Important Formulations

Rawghan Zaitūn (Kabīruddīn, 2000)

Pharmacological / Clinical studies (evidence based)

Anti-oxidant activity

- Dekdouk et al. (2015) studied phenolic composition and biological activities of fruit extracts from Italian and Algerian *Olea europaea* L. cultivars. Moreover 14 different phenolic compounds were identified, and their profiles showed remarkable quantitative differences among analyzed extracts. Three complementary assays were used to measure their anti-oxidant activities and consequently Relative Anti-oxidant Capacity Index (RACI) was used to compare and easily describe obtained results. Results showed that *Chemlal*, between Algerian cultivars, and *Coratina*, among Italian ones, had the highest RACI values. On the other hand all extracts and the most abundant phenolics were tested for their efficiency to inhibit α-amylase and α-glucosidase enzymes. *Leccino*, among all analysed cultivars, and luteolin, among identified

phenolic compounds, were found to be the best inhibitors of α-amylase and α-glucosidase enzymes. Results demonstrated that *Olea europaea* fruit extracts can represent an important natural source with high anti-oxidant potential and significant α-amylase and α-glucosidase inhibitory effects.

- Nicoln et al. (2019) investigated the phytochemical profiles and anti-oxidant activities in the leaves of 15 Italian *Olea europaea* L. cultivars grown in the same pedoclimatic conditions. The phenolic profiles and amounts of their seven representative compounds were analyzed using HPLC ESI/MS-TOF. The Anti-oxidant activities were determined using three different anti-oxidant assays (DPPH, ORAC, and superoxide anion scavenging assay). Wide ranges of total phenolic content (11.39–48.62 g GAE kg–1 dry weight) and anti-oxidant activities (DPPH values: 8.67–29.89 µmol TE mg–1 dry weight, ORAC values: 0.81–4.25 µmol TE mg–1 dry weight, superoxide anion scavenging activity values: 27.66–48.92 µmol TE mg–1 dry weight) were found in the cultivars. In particular, the cultivars Itrana, Apollo, and Maurino, showed a high amount of total phenols and anti-oxidant activity.

- Ferreira et al. (2007) reported that the residues of copper in olive leaves, harvested at different times, were evaluated by atomic absorption spectrometry. At all the collection times, treated olive leaves had significantly higher copper contents, compared to the control. The different copper amounts in pesticide formulations lowered the leaves contents in total phenols and hence their anti-oxidant properties. Olive leaves sprayed with copper oxychloride possessed the highest copper levels and the lowest content in phenols, which influenced its anti-oxidant activity (higher EC50 values for reducing power, scavenging effect on DPPH radicals and inhibition of erythrocyte hemolysis). Leaves without copper residues proved to be a good natural source of Anti-oxidants, giving values comparable to the reference compounds.

- De Marino et al. (2014) identified the main components in the *Olea europaea* L. leaf (cv. Leccino) preserved during the decoction preparation, in order to delineate the anti-oxidant activities of the crude extracts and its isolated compounds by using different *in-vitro* assays including DPPH radical scavenging capacity, total anti-oxidant capacity (TAC), xanthine oxidase (XO) inhibitory effect and the ability to delay the linoleic acid peroxidation process (ALP). The most active compound in the TAC evaluation, was the 3, 4 dihydro-phenyl glycol (8) (0.90 caffeic acid equiv.) while taxifolin and fraxamoside resulted as the most efficient inhibitors of XO activity (IC50 2.7

and 5.2 µM, respectively). Secoxyloganin (4), oleuropein (2) and tyrosol (6) showed the highest ALP activity. This study adds to the growing body of data supporting the bioactivities of phytochemicals and their potential impact on human health.

- Benavente-Garcıa et al. (2000) identified the main phenolic compounds present in an olive leaf extract (OL) in order to delineate the differential anti-oxidant activities of these compounds through the extent of their abilities to scavenge the $ABTS^+$ radical cation and to clarify the structural elements conferring anti-oxidant capacity in aqueous systems. The results showed that the relative abilities of the flavonoids from olive leaf to scavenge the $ABTS^+$ radical cation are influenced by the presence of functional groups in their structure, mainly the B-ring catechol, the 3-hydroxyl group and the 2, 3-double bond conjugated with the 4-oxo function. For the other phenolic compounds present in OL, their relative abilities to scavenge the $ABTS^+$ radical cation are mainly influenced by the number and position of free hydroxyl groups in their structure. Also, both groups of compounds show synergic behaviour when mixed, as occurs in the OL.

- Briante et al. (2002) reported natural substances from a vegetal source, their Anti-oxidant properties have been compared with those of the leaf extract from *Olea europaea* L. The extract possess a higher concentration of simple phenols, characterized by a stronger anti-oxidant capacity, than those available in extra virgin olive oils and in many tablets of olive leaf extracts, commercially found as dietetic products and food integrators.

Immunomodulatory activity

- Randon and Attard (2007) conducted a study to investigate the *in-vitro* effects of oleuropein and *Olea europaea* extracts on unstimulated lymphocytes. Oleuropein, a secoiridoid glycoside, is a potential anti-oxidant and anti-microbial agent. The stimulatory effects of oleuropein and extracts were concentration-dependent with a range of median stimulatory concentration 1 mm at 48 hour. The cytotoxicity effect of oleuropein and extracts increased with time resulting in a greater cytotoxic effect on already-stimulated lymphocytes at 96 hour even though dose dependence was not demonstrated. Morphological observations showed that oleuropein and extracts induced blastogenesis similar to that of phytohaemagglutinin (PHA). In fact, from lymphocyte activation studies, oleuropein exhibited a high

degree of lymphocyte aggregation, which is an indicator of cell activation and proliferation.

- Vezza et al. (2017) revealed the anti-oxidant activities of extracts from olive (*Olea europaea*) leaves. They contain antioxidative Phenolic compounds, such as oleuropeoside, which could be interesting for the treatment of inflammatory conditions associated with oxidative stress in humans, including inflammatory bowel disease. The extract showed effect in both colitis models reducing the expression of pro-inflammatory mediators (IL-1β, TNF-α, and iNOS), and improving the intestinal epithelial barrier integrity restoring the expression of ZO-1, MUC-2, and TFF-3. These effects were confirmed *in-vitro*. Furthermore, it reduced the production of pro-inflammatory mediators (IL-1β, IL-6, IL-8, and TNF-α) in intestinal mucosal samples from CD patients.

- Magrone et al. (2018) reported that the Olive leaf extracts (OLEs) exerted the cardio-protective, anti-oxidant and anti-inflammatory activities. Peripheral blood mononuclear cells from twenty-five healthy donors were cultured in the presence of 3 µg of two OLE extracts, extract A (resuspended in water) and extract B (resuspended in 70% ethanol). After harvesting, cell pellets were used for cytofluorimetric phenotyping, while supernatants were assayed for cytokine release by means of ELISA. Furthermore, in the same supernatants nitric oxide (NO) content was determined. The Results found that both extracts, but especially extract A, increased absolute numbers of CD8+ and natural killer (NK) cells. In addition, an increased production of interferon (IFN)-γ by both extracts as an expression of T helper (h)1 activation was observed. Finally, both extracts enhanced NO release. OLEs, and mostly extract A, are able to *in-vitro* modify healthy human immune response by increasing IFN-γ production which seems to be associated to the higher absolute numbers of CD8+ and NK cells and this may suggest a reinforcement of the anti-tumor activity. Furthermore, increased levels of NO may indicate the potential cardio-protective effects exerted by OLEs in virtue of their vasodilation dependent activity. In the light of these results, OLEs are potential therapeutic compounds for the treatment of chronic inflammatory disease, also preventing cardiovascular event outcome.

- Hashmi et al. (2015) reported *in-vitro* and *in-vivo* pharmacological activities like anti-diabetic, anti-convulsant, anti-oxidant, anti-inflammatory, immuno-modulatory, analgesic, anti-microbial, anti-viral, anti-hypertensive, anti-

cancer, antihyperglycemic, anti-nociceptive, gastro-protective, and wound healing activities of *Olea europaea*.

Anti-cancer activity

- Oleuropein (Ole), a secoiridoid glucoside present in *Olea europaea* leaves. Oleuropein might potentiate the cytotoxicity of conventional drugs used to treat melanoma, disclosing a potentially new therapeutic strategy. The cytotoxic action of Ole alone or in combination with chemotherapeutics was tested on A375 human melanoma cells. It was found that Ole was able, at a dose of 500 µM, to stimulate apoptosis, while at a non-toxic dose of 250 µM, it affected cell proliferation and induced the downregulation of the pAKT/pS6 pathway. A dose of 250 µM Ole did not potentiate the effect of Vemurafenib (PLX4032), but it succeeded in increasing the cytotoxic effect of Dacarbazine (DTIC). The major effect was found in the association between Ole and Everolimus (RAD001), also on PLX4032-resistant BRAF melanoma cells, which possibly cooperate in the inhibition of the pAKT/pS6 pathway. Of interest, an olive leaf extract enriched in equimolar Ole was more effective and able to further improve DTIC and RAD001 efficacy on BRAF melanoma cells with respect to Ole alone. Therefore, Ole represents a natural product able to potentiate a wide array of chemotherapeutics against BRAF melanoma cells affecting the pAKT/pS6 pathway (Ruzzolini *et al.*, 2018).

- Nashwa and Abdel-Aziz (2014) carried out study to evaluated the anti-cancer activities of the extract olive leaf by water and methanol 80%, at two extraction ratios for up to 120 min. Methanol was more efficient than water in extracting polyphenols. Polyphenols and flavonoids were analyzed by High Performance Liquid Chromatography. The anti-cancer effect of the methanolic extract of olive leaves in breast, colon, hepatocellular and cervical carcinoma cells was studied. The extract possessed high activity against hepatocellular carcinoma cells. The results pave the way for utilization of olive leaf as a source of natural Anti-cancer agents.

- Shamshoum et al. (2017) reported that the epidemiological studies suggest that olive oil intake is associated with a reduced risk of cancer. Olive oil, olives, and olive leaves contain many polyphenols, including oleuropein. Recently, several studies have demonstrated that oleuropein inhibits proliferation and induces apoptosis in different cancer cell lines. In addition, anti-cancer effects of oleuropein have been seen in animal studies. These effects are associated

with oleuropein's ability to modulate gene expression and activity of a variety of different signaling proteins that play a role in proliferation and apoptosis. This article summarizes the existing *in-vitro* and *in-vivo* studies focusing on the anti-cancer effects of oleuropein and its effects on key signaling molecules.

- Essafi Rhouma et al. (2019) characterized phenolic compounds of olive flower obtained from Olive tree cultivar *Chemlali* and to investigate their anti-cancer effect on MCF-7 cells. Phenolic characterisation was determined using LC/MS-MS. Cytotoxicity of the extract was determined using MTT. Biochemical markers of apoptosis were evaluated by immunoblotting. The results showed that olive flower contained significant amounts of phenolic compounds mainly flavonoids, secoiridoids and simple phenols. Furthermore, the phenolic extract exerted a significant reduction in MCF-7 cell viability (EC_{50} values equal to 220.8 µg/ml). Western blot analysis revealed the presence of the cleaved forms of Parp-1. The DAPI staining analysis demonstrated a significant reduction in the number of cells and a considerable change in the morphology of the treated cells. In conclusion, *Olea europaea*. L flower contained great amounts of different bio-phenols able to reduce the proliferative activity of breast cancer MCF-7 cells by the induction of apoptosis.

Additional activities

- The *Olea europaea* L. has also been reported to possess anti-diabetic, anti-convulsant, anti-inflammatory, analgesic, anti-microbial, anti-viral, anti-hypertensive, anti-hyperglycemic, anti-nociceptive, gastro-protective and wound healing activities. (Hashmi et al., 2015)

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Zanjabīl
Root (Rhizome)
Zingiber officinale Roscoe

Introduction

Zanjabīl consists of root (dried rhizome) of *Zingiber officinale* Roscoe (Family-Zingiberaceae). Drug yielding plant is widely cultivated in India, rhizomes are dug in January-February, buds and roots removed, soaked overnight in water, decorticated, and sometimes treated with lime and dried. (Anonymous, 2007a)

Fig. *Zanjabīl*

Vernacular Names

English: Ginger, Hindi: *Sonth*, *Adrak*, *Ada*: Urdu; Zanjabīl, *Sonth*; Arabic: Zanjabīl; Persian: *Shangbīiz*. (Khān, 2012; Ibn Sīnā, 1987; *Ibn Baytār*, 1986; Anonymous, 2007a)

Temperament

Ḥār (Hot)[3] *Yābis* (Dry)[3] (Khān, 2012; Ibn Sīnā, 1987; *Ibn Baytār*, 1985; *Kabīruddīn*, 2000)

Chemical Constituents

Volatile oils/ ginger essential oils	Terpenes, alcohols, aldoketone, acids- L-Bornyl acetate terpenoids, essential oils: car-3-ene, α-terpinene, α-terpineol, neurol, 1, 8-cineole, zingiberene, neral, geranial, geraniol geranyl acetate, heptane, octane, isovaleraldehyde, nonanol, ethyl pinene, camphene, β-pinene, sabinene, myrecene, limonene, β-phellandrene and 1, 8-cineole, gingediol, methylgingediol, Sesquiterpenes sequithujene, cis-sequisabinene hydrate and zingiberenol, esquiterpene hydrocarbons, sesquiterpene, monoterpenoids, zingiberol, zingiberene, βbisabolene etc.

Oleoresin	Gingerol, shogaol and zingerone
Sugars	Polysaccharides, cellulose, and soluble sugar
Organic Acids	Oxalic acid, tartaric acid, lactic acid, acetic acid, citric acid, succinic acid, formic acid, and malonic acid
Proteins and Amino Acids	Glutamate, aspartic acid, serine, glycine, threonine, alanine, cystine, valine, methionine, isoleucine, leucine, tyrosine, phenylalanine, lysine, histidine, arginine, proline etc.
Inorganic Elements	It contains more than 20 inorganic elements such as K, Mg, Ga, Mn, P, Al, Zn, Fe, and Ba etc.
In addition to above, the root (rhizome) also contains protein, fat, fibre, carbohydrate (starch, pentosans), minerals (Ca, P, Fe), trace of Iodine and fluorine, Vitamins (thiamine, riboflavin, niacin, Vitamin C, carotene), fructose, sucrose, raffinose etc. (Liu *et al.,* 2019; Tauheed *et al.,* 2017; Mao *et al.,* 2019; Bhandari and Sethiya, 2018)	

Pharmacological Actions

- *Muqawwī-i-Ḥarārat Gharīziyya* (Tonic for innate heat)
- *Munaffith-i-Balgham* (Expectorant)
- *Muqawwī-i-Miʿda* (Stomachic)
- *Muqawwī-i-Kabid* (Hepato-tonic)
- *Mushtahī* (Appetizer)
- *Kāsir-i-Riyāḥ* (Carminative)
- *Hāḍim* (Digestive)
- *Muqawwī-i Bāh* (Aphrodisiac)
- *Muḥarrik* (Stimulant)

(Khān, 2012; Ibn Sīnā, 1987; *Ibn Baytār*, 1985; Al-Harawi, 2002; *Kabīruddīn*, 2000; Ghani, YNM; Anonymous, 2007a)

Therapeutic Uses

- *Ḍuʿf-i-Ḥarārat Gharīziyya* (Innate heat insufficiency)
- *Suʿāl* (Cough)
- *Ḍīq al-Nafas* (Bronchial asthma)

- *Ḍu'f-i-A'ṣāb* (Nervine weakness)
- *Nisyān* (Forgetfulness)
- *Ḍu'f-i-Mi'da*(Gastric debility)
- *Sū'-i-Haḍm* (Indigestion)
- *Ḍu'f-i-Ishtiha* (Loss of appetite)
- *Ḍu'f-i-Kabid* (Hepatic insufficiency)
- *Waja' al-Mafāṣil* (Polyarthritis)
- *Ḍu'f-i-Bāh* (Sexual debility)
- *Sailān-ur-Raḥim* (Leucorrhoea)

(Khān, 2012; Ibn Sīnā, 1987; *Ibn Baytār*, 1985; Al-Harawi, 2002; *Kabīruddīn*, 2000; Ghani, YNM; Anonymous, 2007a)

Important Formulations

Jawārish Zanjabīl, Majūn Zanjabīl, Murabbā Zanjabīl, Majūn Suhāg Sonth, Jawārish Jalīnūs, Jawārish Kamūni, Habb-i-Hiltīt, Habb-i- Pachlona, Habb-i-Kabid Naushādri, Habb-i-Tursh Mushtahi, Jawārish Bisbāsa, Lubūb Kabīr, Majūn Falāsifa, Majūn Jograj Gugal, Majūn Supārīpak, Sufūf-i-Hāzim Kalān (Anonymous, 2007a; *Kabīruddīn*, 2000)

Pharmacological / Clinical studies (Evidence based studies)

Anti-oxidant activity

- Stoilova *et al.*, studied Anti-oxidant effect and the total phenols of ginger. Total phenols of the alcohol extract were found to be 870.1 mg/g dry extract. Ginger extract inhibited the hydroxyl radicals 79.6% at 37°C and 74.8% at 80°C, which showed a higher anti-oxidant activity than quercetin. The IC50 concentration for inhibiting OH at 37 °C was slower than that at 80 °C -1.90 and 2.78 µg / ml respectively. The ginger extract chelated Fe3+ in the solution. (Tauheed *et al.*, 2017)
- Significant anti-oxidant activity of volatile and non-volatile compounds of fresh and dried ginger (N-hexane and methanolic extract) was noted in an experiment performed on rats by using DPPH and ferric reducing anti-oxidant power (FRAP) and it is found that methanolic extract of ginger especially of fresh ginger possess appreciable amount of anti-oxidant compound within it

which showed good inhibitory property against free redicals (Tauheed *et al.,* 2017; Hassan *et al.,* 2010).

- In a model of oxidative damage to pancreatic β cells. n -hexane extract exerted antiradical capacity. Protective potential of *Zingiber officinale* in a model of cytotoxic conditions imposed by diabetes in β cells was assessed in this study (Tauheed *et al.,* 2017; Rackova *et al.,* 2013)

- Oxidation of biological molecules induces a variety of pathological diseases including atherosclerosis or cancer. These damages are caused due to the presence of free radicals. [6]- gingerol, [6]-shogaol have displayed strong anti-oxidant activity *in-vitro* . It is known that the anti-oxidant activity of plant extracts containing polyphenol components is due to their capacity to be donors of hydrogen atoms or electrons and to capture the free radicals. The ginger extract showed anti-oxidant effect in inhibiting DPPH radical, IC50 was 4.25 mg/ml. DPPH analysis is one of the tests used to prove the ability of the components of the ginger extract to act as donors of hydrogen atoms. DPPH radical does not react with flavonoids, which contains no OH-groups in B-ring as well as with aromatic acids containing only one OH-group.(Syafitri *et al.,* 2018)

Anti-oxidant & hepato-protective activity

- The current study was designed by Hasan *et al.,* 2016 to evaluate the potential hepato-protective and anti-oxidant activity of *Z. officinale* against liver injury and fibrosis induced by CCl4 in rats. To induce liver fibrosis, Wistar albino rats received CCl4 (2ml/kg diluted in corn oil) twice weekly for 8 weeks. Also rats were concurrently treated with ginger extract at two different dose (300 and 600mg/kg/day), the CCL4 induction produced a significant increase in serum aminotransferases, lipids, liver lipid peroxidation, and nitric oxide. The hepato-protective effect was evidenced by significant decrease in serum aminotransferases and liver lipid peroxidation. Through its potent anti-oxidant activity, ginger maintained the integrity of plasma membrane and increased the regenerative and reparative capacity of the liver. (Bhandari *et al.,* 2018)

- Another report has shown that administration of single dose of aqueous extract of ginger (200, 400 mg/kg prior to acetaminophen) was effective in preventing the acetaminophen-induced hepatotoxicity and also decreased

ALT, AST, and ALP levels and increased the activities of anti-oxidant enzymes levels in the liver. (Bhandari *et al.,* 2018; Gijith *et al.,* 2007)

- *Z. officinale* is effective in Parkinson's disease because zingerone, an active ingredient in ginger scavenged peroxide and hydroxyl ions as well as suppressed lipid peroxidation. (Dissanayake *et al.,* 2020)
- Ginger consists with renoprotective effect in renal failures because of anti-inflammatory properties by attenuating serum C-reactive protein levels and anti-oxidant effects by reducing lipid peroxidase marker, malondi aldehyde levels and increasing renal superoxide dismutase activity. Carbon tetra chloride and acetaminophen induced liver damages in acute liver injuries are prevented. (Dissanayake *et al.,* 2020)

Anti-oxidant and anti-cancer effect

- *Z. officinale* exhibits anti-inflammatory and anti-tumorigenic effects due to its bioactive molecules such as 6-gingerole, 6-shogaol, 6-paradol and zerumbone, as a result prevention or control from colorectal, gastric, ovarian, liver, breast and prostate cancers is possible. (Dissanayake *et al.,* 2020)
- *Z. officinale* activates enzymes such as glutathione peroxidase, glutathione s transferase and glutathione reductase and suppresses colon carcinogenesis. Oral administration of Zerumbone effects in inhibition of multiplicity of colonic adenocarcinomas through suppression of colonic inflammation due to inhibition of proliferation, induction of apoptosis and suppression of NF-κB and heme oxygenase (HO)-1 expression. In gastric carcinomas, gingerol and shogaol effect in TRAIL induced NF-κB, suppresses cIAP1 expression and increases TRAIL induced caspase-3/7 activation which promotes apoptosis as well gingerol is effect in liver cancers by arresting cell cycle and induction of apoptosis. Growth inhibition of human epidermoid carcinoma cells via reactive oxygen species (ROS) induced apoptosis is exhibited by gingerol with conciderable amount of toxicity. (Dissanayake *et al,* 2020)
- Active compounds of *Z. officinale* effect in controlling ovarian cancers via inhibition of NF-κB activation and diminished the secretion of VEGF and IL-8.Zerumbone is also effect in controlling pancreatic cancers through p53 signal pathway, formation of apoptotic bodies, condensed nuclei and the increased activity of caspase-3. (Dissanayake *et al.,* 2020)

- Maintaining, proper circulation, nervous conduction, heart functions and balancing digestive and absorptive disorders through enhancing appetite is beneficial in enhancement of the immunity of the body which supports in alleviate abnormal growths and malfunctions of physiological body. (Dissanayake *et al.,* 2020)

Cognitive enhancer activity

- Anti-oxidants plants have gained a great deal of attention due to the role of oxidative stress-induced cognitive impairment. Study aimed to determine the effect of *Zingiber officinale* extract, on the cognitive function of middle-aged, healthy women. 60 participants received a placebo or standardized plant extract at doses of 400 and 800 mg once daily randomly for 2 months. Participant were evaluated for working memory and cognitive function using computerized battery tests and the auditory oddball paradigm of event-related potentials at three different time periods: before receiving the intervention, one month, and two months. Ginger-treated groups had significantly decreased P300 latencies, increased N100 and P300 amplitudes, and exhibited enhanced working memory. It is a potential cognitive enhancer for middle-aged women. (Tauheed *et al.,* 2017; Saenghong *et al.,* 2011)

- Study done by Wattanathorn J *et al.,* suggests that *Z. officinale* possessed the protective effect against focal cerebral ischemia induced by the occlusion of right middle cerebral artery. Cognitive enhancing effect and neuro-protective effect appeared to show almost the same magnitude as the positive control groups used in this study. The cognitive enhancing and neuro-protective effect occurred partly via the Anti-oxidant activity of the extract. Study shows beneficial effect of ginger rhizome to protect against focal cerebral ischemia. (Tauheed *et al.,* 2017)

- Study was conducted to evaluate the effect of alcoholic extract of Ginger on the testes in rats in busulfan induced infertility in rat model. It showed that *Zingiber offiicinale* increased the semen volume of seminiferous tubules in test group treated with 100mg/kg of the extract of ginger compared to control group. Sperm count and level of testosterone were also increased in test group treated with alcoholic extract of ginger in dose of 100 mg/kg and 150 mg/kg body weight of rat, in comparision to control group. (Bordbar, 2013)

- Study conducted on 30 male Sparague Dawley rats allotted in 3 groups 10 in each, for evaluation of androgenic activity of ginger. It showed significant increase in testicular weight and body weight gain, serum testosterone in test group treated with 200mg/kg of aqueous extract of *Zingiber officinale* for 28 and 56 days as compared to control group without any toxic effect on spermatogenesis in the testes. (Memudu, 2012)

- A study reported in which aqueous extract of *Zingiber officinale* was administered orally in the Broiler breeder male in dose of 5 % and 10 % has demonstrated that aqueous extract of ginger has an anti-oxidant and androgenic activity and has good effects on spermatogenesis and sperm parameters as well as increase in ejaculatory volume, sperm concentration, count, movement, decrease in motility and abnormality. There was also significant increase in semen plasma cholesterol, glucose, and significant decrease in protein, increase in testosterone, LH, FSH hormone level (P<0.05%). (Saeid, 2011)

- In an experiment, aqueous extract of *Zingiber officinale* was given orally to 2 groups of rats in dose of 500 mg / kg b.w. and 1000 mg / kg b.w. for 14 and 28 days, then test groups were investigated for effect of ginger on reproductive functions in the male rats in comparison to control group. It was revealed by the study that there was significant increase (P<0.05%) in the weight of the testis and epididymis, and dose and duration dependent increase in sperm count and motility (P<0.05%). There was significant increase (P<0.05%) in serum testosterone level noted.(Bashir and Afrin, 2019; Morakinyo, 2008)

Neuro-protective activity

- Ginger and their constituents play a vital role as a neuro-protector. The exact mechanism of action of ginger in this vista is not known fully. But it is thought ginger shows neuro-protector effect due to the phenolic and flavonoid compounds. An important study has shown that 6-shogaol has neuro-protective effects in transient global ischemia via the inhibition of microglia. (Bhandari *et al.,* 2018; Ha *et al.,* 2012)

- Another finding in the support of ginger as neuro-protector suggests that it exhibits neuro-protective effect by accelerating brain anti-oxidant defense mechanisms and down regulating the MDA levels to the normal levels in the diabetic rats. (Bhandari *et al.,* 2018; Shanmugam *et al.,* 2011)

Additional activities

- The root (Rhizome) of *Zanjabīl* has also been reported to possess gastro-protective, hepato-protective, cardio-protective, anti-bacterial, anti-hyperlipidaemic, anti-diabetic, anti-emetic, anti-tussive, antibiotic, cyto-protective, anti-ulcer, anti-allergic, anti-arthritic, anti-inflammatory, analgesic, aphrodisiac, androgenic and spermatogenic activities. (Dissanayake *et al.,* 2020; Bashir and Afrin, 2019; Bhandari *et al.,* 2018; Syafitri *et al.,* 2018; Tauheed *et al.,* 2017)

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Zard Chob
(Rhizome)
Curcuma longa L.

Introduction

The drug of *Zard Chob* consists of the dried rhizome of *Curcuma longa* L. (Family-Zingiberaceae) that is yielded from a perennial herb extensively cultivated in all parts of the country. The crop is harvested after 9-10 months, when lower leaves turn yellow. Rhizomes carefully dug up with handpicks between October-April. (Anonymous, 2007 a)

Fig. *Zard Chob*

Vernacular Names

English: Turmeric; Hindi: *Haldi*, *Hard*; Urdu: *Haldī*, Arabic: *'Ārūq al-Ṣifr*; Persian: *Zard Chob*. (Khān, 2013; Ibn Sīnā, 1987; Ibn Baytār, 1999; Kabīruddin, 2000; Ghani, YNM Anonymous, 2007a)

Temperament

Ḥār (Hot)^3 *Yābis* (Dry)^3 (Khān, 2013; Ibn Sīnā, 1987)

Chemical Constituents

- **Eugenol;** Epiprocurcumenol, Eucalyptol; Feruloyl-p-coumaroyl-methane, Gamma-atlantone, Germacrone, Germacrone13-al; Guaiacol, Isoborneol, L-alphacurcumene
- **1, 8-cineole;** 2-bornanol, 2-hydroxymethyl-anthraquinone, 4-hydroxybisabola
- **10-diene-9-one**; 4-methoxy-5- hydroxybiosabola; 4-hydroxy-cinnamoyl-(Feruloyl)-methane, Alpha-atlantone, Alphapinene, Alphaterpineol, Ar-turmerone, Arabinose

- **Ascorbic-acid**, Ash, Azulene, Betacarotene, Beta-pinene, Beta sesquiphellandrene, Bis-(Para-hydroxycinnamoyl)-methane
- **Bis-desmethoxycurcumin**; Bisabolene, Bixin, Borneol, Boron, Caffeic-acid, Calcium, Caprylic-acid, Caryophyllene, Chromium, Cineole, Cinnamic-acid, Cuminyl-alcohol, Curcumene, Curcumenol, Curcumin, Curdione, Cobalt, Copper
- **L-beta-curcumene**; Limonene, Manganese, Monodesmethoxycurcumin, Niacin, Nickel, norbixin; O-coumaric-acid, P-coumaric-acid, P-methoxycinnamic-acid, Pcymene, Ptolymethylcarbinol, Phosphorus, Protocatechuic-acid, Procurcumadiol
- **Acidic polysaccharides**; utonan A, B, C, D
- **Volatile Oil**; (4.2%), its main content is turmerone, arturmerone, curcumene, germacrone, ar-curcumene
- **Other constituents**; protein (6.3%), fat (5.1%), minerals (3.5%), carbohydrates (69.4%) and moisture (13.1%). Phenolic diketone, curcumin (diferuloylmethane) (3-4%) is responsible for the yellow colour, and comprises curcumin I (94%), curcumin II (6%) and curcumin III (0.3%). Copper, zinc, campesterol, stigmasterol, betasitosterol, cholesterol, fatty acids and metallic elements; potassium, sodium, magnesium, calcium, manganese, iron. (Chanda & Ramachandra, 2019; Anonymous, 2007)

PharmacologicalActions

- *Muḥallil-i-Waram* (Anti-inflammatory)
- *Musakkin* (Soothing agent)
- *Munaffith-i-Balgham* (Expectorant)
- *Muqawwī-i-Kabid* (Hepatotonic)
- *Dāfi'-i-Tashannuj* (Anti-spasmodic)
- *Mujaffif* (Desiccant)
- *Mufattiḥ-i-Sudad* (Deobstruent)
- *Jāli* (Detergent)
- *Muṣaffī-i-Dam* (Blood purifier)

(Khān, 2013; Ibn Sīnā, 1987; Ibn Baytār, 1999; Kabīruddin, 2000; Ghani, YNM Anonymous, 2007a)

Therapeutic Uses

- *Ḍīq al-Nafas* (Bronchial asthma)
- *Su'āl (Cough)*
- *Nazla* (Catarrh)
- *Zukām* (Coryza)
- *Waja' al-Mafāṣil* (Polyarthritis)
- *Ḍu'f-i-Kabid* (Hepatic insufficiency)
- *Ḍu'f-i-Baṣar* (Poor eyesight)
- *Amrāḍ-i- Jild* (Skin diseases)
- *Qurūḥ* (Ulcers)

  (Khān, 2013; Ibn Sīnā, 1987; Ibn Baytār, 1999; Kabīruddin, 2000; Ghani, YNM Anonymous, 2007a)

Important Formulations

Sanūn-i-Zard, Safūf-i-Ṭihāl, Rawghan Aurāq Qawī, Marham-i-Jadwār, Raughan-i-Sanan (Anonymous, 2007a)

Pharmacological/Clinical studies (evidence based)

Anti-oxidant activity

- Water and fat soluble extracts of turmeric and its curcumin component possess strong anti-oxidant activity, when it is comparable to vitamins C and E. Curcumin pre-treatment has effective result which decreases ischemia induced changes in the heart. An *in-vitro* study was conducted utilizing bovine aortic endothelial cells for measuring the effect of curcumin on endothelial hemeoxygenase-1, an inducible stress protein. The cellular resistance to oxidative damage was also enhanced, when curcumin incubated for 18 h. Curcumin have anti-oxidants properties so it can significantly inhibit the generation of reactive oxygen species (ROS) such as H2O2, superoxide anions and nitrite radical generation by activated macrophages. Its derivatives can prevent and treat cholelithiasis besides having anti-oxidant activities (Velayudhan, 2012; Chanda & Ramachandra, 2019)

- Sharma et.al. (1976) supported anti-oxidant property of curcumin; it acts as a scavenger of oxygen free radicals and can protect hemoglobin from oxidation.

Curcumin can significantly reduce speed of the production of reactive oxygen species such as superoxide anions, hydrogen peroxide, and nitrite radical production. This is done by activated macrophages which role is crucial in inflammation. (Sharma, 1976; Ruby et.al., 1995; Subramanian et.al., 1994; Rao et.al., 1982; Joe et.al., 1994; Dikshit et.al., 1995; Ashraf and Sultan, 2017).

- Different extracts of turmeric such as water and fat soluble and its curcumin component exhibited strong anti-oxidant activity. Pre-treatment of curcumin causes and decreases ischemia-induced changes in the heart. In another study *in-vitro* measuring, the effect of curcumin on endothelial heme oxygenase-1, an inducible stress protein, was carried out by utilizing bovine aortic endothelial cells. (Motterlini et.al., 2000 Ashraf and Sultan, 2017)

- Curcumin was found to reduce the testicular damage caused by exposure to di-n-butyl phthalate, by an increase in glutathion (GSH), testosterone levels, and glucose-6-phosphate dehydrogenase activity and decrease in malondialdehyde (MDA) levels. These properties may be due to intrinsic ant-oxidative abilities of curcumin. (Ranjan et.al., 1998; Ashraf and Sultan, 2017)

- Curcumin is only anti-mutagenic against mutagens which require metabolic activation. Curcumin was found to block cyclosporine A-resistant phorbol myristate acetate + anti-CD28 pathway of T-cell proliferation. Clinical research on curcumin's therapeutic advantage for pancreatitis is inadequate and has mainly focused on its anti-oxidant properties. However, research indicates that the inflammatory response plays a critical role in the development of pancreatitis and subsequent tissue damage. Consequently, it appears likely an anti-inflammatoryagent like curcumin, effective against a variety of inflammatory molecular targets, and shown to decrease inflammatory markers in an animal model of pancreatitis. (Okamoto et.al. 2002; Ashraf and Sultan, 2017).

- One pilot study examined the effect of curcumin for tropical pancreatitis in patients. Action consequence on pain patterns as well as erythrocyte MDA (MDA; an indicator of lipid peroxidation) and GSH was evaluated at baseline and after 6 weeks. In the curcumin group, there was a significant drop in MDA levels. Further research is needed to determine the role of lipid peroxidation in pain and other symptomology associated with pancreatitis. (Gukovsky et.al., 2003; Durgaprasad et.al., 2005; Ashraf and Sultan, 2017)

- Kumar et al. (2016) evaluated the curcumin content, anti-oxidant activity and total phenol content of *Curcuma longa* flower. The Anti-oxidant activity of the flower was determined by free radical scavenging activity of DPPH, and the total phenol content was determined using the Folin-Ciocalteu reagent through standard protocols. The results showed the flowers having about (3.87±0.5µg/g) of curcumin during HPLC-PDA analysis.

- Priyanka et al. (2017) studied on methanolic extract of eight turmeric cultivars in three different forms and in eight levels for free radical scavenging activity [DPPH (1, 1-diphenly-2-picrylhydrazyl)]. Among the eight cultivars, Prathibha variety exhibited higher radical scavenging activity of 59.58±2.82 with observation of statistical significance in radical scavenging activity of all varieties. All the extracts notably reduced the concentration of DPPH free radical due to their hydrogen donating ability irrespective of processing methods. The higher anti-oxidant activity of Prathibha variety may be due to the presence of phenolics, flavonoids and natural anti-oxidants such as Curcuminoids in higher percentage. The findings thus, highlighted the importance of the cultivars, method of processing and its anti-oxidant potential.

- Tanvir et al. (2017) investigated the aqueous and ethanolic extracts of different forms (local names: *Mura* and *Chora*) of turmeric (*Curcuma longa*) for their anti-oxidant properties and polyphenol, flavonoid, tannin, and ascorbic acid contents. The anti-oxidant activity was determined using the 1, 1-diphenyl-2-picrylhydrazyl (DPPH) free radical scavenging activity and ferric reducing anti-oxidant power (FRAP) values. The ethanolic extract of Chittagong's mura contained the highest concentrations of polyphenols (16.07%), flavonoids (9.66%), and ascorbic acid (0.09mg/100 g) and chora resulted in high yields (17.39%). The ethanolic extract of Khulna's *Mura* showed a higher DPPH radical-scavenging activity with the lowest 50% inhibitory concentration (IC50) (1.08 µg/mL), while *Khulna's chora* had the highest FRAP value (4204.46 ± 74.48 µM Fe [II] per 100 g). Overall, the ethanolic extract had higher anti-oxidant properties than those in the aqueous extract. However, the tannin concentration was lower in the ethanolic extract. It was concluded that the turmeric varieties investigated in the study were found as useful sources of natural anti-oxidants, which confer significant protection against free radical damage.

Immunomodulatory activity

- Antony et al. (1999) analyzed an active ingredient present in *Curcuma longa*, for the immunomodulatory activity in Balb/c mice. Curcumin administration was found to increase the total WRC count (15, 290) significantly on the 12th day. The group of animals treated with vehicle alone showed results similar to that of normal animal (10, 130 on 12th day). Curcumin increased the circulating antibody titre (512) against SRBC and increased the plaque forming cells (PFC) in the spleen and the maximum number of PFC was observed on the 6th day (1, 130 PFC/10(6) spleen cells) after immunization with SRBC. Bone marrow cellularity (16.9x10(6) cells/femur) and alpha-esterase positive cells (1, 622/4000 cells) were also enhanced by curcumin administration. A significant increase in macrophage phagocytic activity was also observed in curcumin treated animals ($P<0.001$). These results indicated that the curcumin has immunostimulatory activity.

- Mehrotra et al. (2013) reported that curcumin, one of major curcu-minoids of *Curcuma longa*, possesses several pharmacological properties including anti-inflammatory, anti-cancer, immunomodulatory activities. Curcumin blocks inflammatory enzymes cyclooxygenase (COX), lipooxy-genase (LOX), matrix metalloproteinase (MMP) and suppresses the proliferation of a wide variety of tumour cells, including breast carcinoma, colon carcinoma, and renal cell carcinoma through cell cycle arrest. It induced apoptosis by downregulation of antiapoptotic protein (Bcl-2 and Bcl-xL). Curcumin modulates immune system by suppressing T-cells, proliferating number of B-cells and reducing proliferation of immature B-cell lymphoma cells. It also inhibited the production of cytokines (IL-8, MIP-1α, MCP-1, IL-1β, TNF-α) and dimerization of TLR's. Immuno-regulatory activity of curcumin is by inhibiting phosphorylation of IKKβ which ultimately leads to suppression of NF-κB (transcriptional activator protein). This activity of curcumin has renewed scientific interest in its potential to prevent and treat diseases such as arthritis, allergy, asthma & cancer.

- In a study, it was suggested that the modulation of immune responses by curcumin plays a dominant role in the treatment of inflammation and metabolic diseases. Observations from both in-vitro and in-vivo studies have provided strong evidence towards therapeutic potential of curcumin. These studies have also identified a plethora of biological targets and intricate mechanisms of action that characterize curcumin as a potent 'drug' for numerous ailments.

During inflammation the functional influence of lymphocytes and the related cross-talk can be modulated by curcumin to achieve the desired immune status against diseases. (Chanda & Ramachandra, 2019)

Anti-depressant properties and effect on nervous system

- The Anti-depressant effect of curcumin was explored in chronic mild stress (CMS) model. In assessment with normal rats, rats suffering from the CMS procedure have a considerable lower consumption of sucrose, increased interleukin (IL-6), tumor necrosis factor alpha (TNF-α) levels, CRF, and cortisol levels. Ethanolic extract of turmeric caused to increase the sucrose intake to normal control levels, reduced CMS induced increase in serum IL-6 and TNF-α level, and reduced the CRF levels in serum and medulla oblongata to lower than normal. It also lowered the cortisol levels in serum to normal levels. (Yu et.al., 2002; Kulkarni and Dhir, 2010)

- Ethanolic extract of *C. longa* causes to reverse the decrease in serotonin, noradrenaline, and dopamine concentrations as well as increase in serotonin turnover, cortisol levels, and serum corticotrophin-releasing factor. Xu et al. examined the consequence of orally directed curcumin on behavior in a long-lasting stress model of depression in rats. The Anti-depressant imipramine was used as control. Administration of curcumin exhibited similar properties as imipramine. The findings propose that the properties of chronic administration of curcumin on the conduct of chronic stressed rats may be connected to the controlling properties of the dysfunction of the hypothalamic-pituitaryadrenal axis, through a discerning increase in brain-derived neurotrophic factor in the frontal cortex and the hippocampus of the rats. A direct effect of curcumin in decreasing the amyloid pathology of Alzheimer's disease (AD) has been shown by an experimental model of AD. (Xia et.al., 2007; Xu et.al., 2006; Ringman et.al., 2005; Thiyagarajan, and Sharma, 2004)

Anti-cancer activity

- Numerous animal studies involving rats and mice, as well as *in-vitro* studies utilizing human cell lines have been done on turmeric that influence carcinogenesis. Several *in-vitro* studies have reported that curcumin is able to control carcinogenesis at three stages: angiogenesis, tumour promotion, and tumour growth. Curcumin exerts inhibition of cell proliferation and tumour

growth, noted by two studies on colon and prostate cancer. The activity of several common mutagens and carcinogens are also suppressed by turmeric and curcumin. The anti-carcinogenic effects have been related to direct anti-oxidant and free-radical scavenging effects, as well as their ability to indirectly increase glutathione levels, thereby aiding in hepatic detoxification of mutagens and carcinogens, and inhibiting nitrosamine formation. Curcumin has also showed to inhibit the mutagenic induction effect of UV rays. (Chanda S & Ramachandra, 2019)

- It was observed, in a study, on Swiss mice that dietary turmeric could be well used as a chemo-preventive agent in benzo-(alpha)- pyrene-induced stomach tumours. A notable symptomatic relief in patients with external cancerous lesions was reported when an ethanolic extract of turmeric, as well as an ointment containing curcumin was applied. Turmeric demonstrated neutralization of carcinogenic free radicals due to its anti-oxidants property. (Chanda S & Ramachandra, 2019)

- Many reports showed that turmeric inhibited tumour necrosis factor (TNF)-α- and acted as an antitumor agent to be helpful in inducing apoptosis or programmed cell death (PCD) in human myeloid leukaemia cells (HL—60). It was found that the Curcumin-I, II, and III from turmeric have the properties of cytotoxicity, anti-oxidant and anti-inflammatory. Extensive research reveals that these compounds possess strong inherent property against leukaemia and colon, central nervous system (CNS), melanoma, renal, and breast cancer cell lines. (Chanda S & Ramachandra, 2019)

Additional activities

- The Root (Rhizome) of *Curcuma longa* has also been reported to possess anti-microbial, hepato-protective, anti-diabetic, anti-coagulant, anti-mutagenic, gastro-intestinal protective, anti-inflammatory, cardio-protective and anti-fungal activities. (Chanda S & Ramachandra, 2019; Ashraf and Sultan, 2017)

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