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Mastagi (*Pistacia lentiscus* L.) an Important Drug of Unani System of Medicine: A Review

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ABSTRACT

Mastagi (*P. lentiscus*) is an important drug used in the Unani system of medicine which has various pharmacological actions and therapeutic values. Its various parts contain a variety of chemical constituents which are medicinally important such as resin, essential oil, flavonol glycosides and other chemical constituents etc. It has various kinds of pharmacological activities which have scientifically proved such as anti-arthritic, anti-bacterial, antimicrobial, antioxidant, antifungal, anticancer, hepatoprotective, hypotensive, wound healing, anti-gout activity and also used for the treatment of functional dyspepsia. It is an evergreen tree, which is cultivated in Mediterranean area, Europe, Morocco, France, Turkey, Iraq and Iran. The aim of this review article is to further highlight the discovered pharmacological effects and medicinal values of *P. lentiscus* L. as per the Unani literature as well as scientific research.

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INTRODUCTION

Unani medicine also known as tradition of Greeko-Arabic medicine which is based on the teachings of Greek physician Buqrat (Hippocrates; 460–370 BC) and Roman physician Jalinoos (Galen) and developed into an elaborate medical system by Arab and Persian physicians such as Al Razi (Rhazes), Ibn sina (Avicenna), Al Zahrawi and Ibn Nafis [1]. The Unani system of medicine is widely practice in India. This system uses all natural resources as main sources of medicine; Nabatat (Plants), Jamadat (Minerals) and Haiwanat (Animals) which are known as Mawaleed-e-Salasa (Three Sources) [2,3].

Pistacia lentiscus L. (*Anacardiaceae*) [4,5,6] it is an aromatic and medicinal plant that can reach 1-5 m in hight [7,8]. The Mastic gum is a natural resin obtained from the stem of *P. lentiscus*., an evergreen tree and producing bright red globose berries [9,10,11,12]. it is a perennial shrub, widely spread in the Mediterranean areas such as Europe, Morocco and cultivated in France, Turkey, Iraq and Iran [9,13,] and also found in North Africa [14]. It is commonly found in dry rocky areas [15] and mostly produced of Greek Island of Chios [16]. The resin part of this plant known as *Mastic* resin and plant called as mastic tree [13,17]. The resin occurs in small, hard, pear shaped, ovoid or nearly globular, sometimes elongated tears, about 2 to 8 mm in diameter; pale yellow in colour; brittle, breaking into clear glossy fracture, interior transparent, crushing to a sandy powder, taste, slightly agreeable; odour, aromatic [9]. The essential oil of *P. lentiscus* is obtained by hydro distillation of leaves, fruits or from trunk exudates called mastic gum [18]. In folk medicine, this plant is used for the treatment of many diseases[19]. This resin has been traditionally used in Sudan folk medicine to treat catarrh and as stimulant [20]. Its leaves are extensively used in folk medicine for the treatment eczema, diarrhoea, and throat infections, and as a potent antiulcer agent. The aerial parts of this species have traditionally been used in Mediterranean area as a popular cure for hypertension. vitamin E is naturally occurring in P. leaves. The pharmacological properties of this vitamin, widely used as a natural antioxidant, are well known[16]. It is an important drug of Unani system of medicine detailed descriptions about its uses is mentioned in classical literature. It is known since antiquity for its therapeutic properties documented for the first time by the ancient Greek physicians Hippocrates, Dioscorides and Galenos. Mastiha has been used by medical practitioners and botanists have used it for more than 2500 years mainly for the treatment of stomach and intestine disorders such as gastralgia, dyspepsia and peptic ulcer[21]. Various compound formulations like *Jawarish Mastagi, Jawarish Jalinoos Tiryaq-e-*

eFarooq, Qurs-e-Humma Jadeed, Qurs-e-Kharateen, Majoon Jaryan-e-Khas, Majoob-e-Azaraqi, Qurs-e-Mushil, Majoon-e-Nishara Aj wali, Majooj-e-Kalan etc., contain this drug along with other drugs used for the management of various ailments of the body [9],[22,23].

Scientific classification:[13,24]

Kingdom – Plantae*;* Division– Magnoliophyta*;* Clade – Tracheophytes*;* Clade – Eudicotus; Clade – Rosids*;* Order – Sapindales*;* Family - Anacardiaceae*;* Genus – P.*;* Species – lentiscus.

Vernacular names: [4,5,9,22,25,26,27,28,29,30]

Urdu: Mastagi; Arabic: Mastakee, ilk-ur-Roomi, Mastagi; Persian: Kundur Roomi; English: Mastic; Hindi: Rumi Mastagee, Rumi Mastiki, Mastagee; Bengali: Rumi-Mastungi; Gujrati: Rumi Mastagee; Marathi: Rumaa Mastakee; Roomi: Mastakhi.

Botanical description:

P. lentiscus is shurb or tree with separate male and female plants evergreen, 1 to 5 m height, with pinnate leaves and small (4-5 mm diameter) and globose black drupes[31]. *P. lentiscus* has a strong smell, aromatic, ivory coloured resin, also known as mastic, cultivated from mastic trees. Originally liquid, it is sun dried into drops of hard, brittle, translucent resin, when chewed; the resin softens and becomes bright white and opaque gum. The resin exudes naturally from the bark but for commercial purposes, it is obtained by making small vertical incisions in it and picking off the hardened product about three weeks later. Average annual yield of resin per tree is 3.6-5.4 kg. Mastic is globular, pyriform or elongated tears, 4-8 mm. In diameter, pale yellow, clear and glassy when fresh, becoming dull and brittle on keeping; it has an aromatic odour and agreeable taste [13].

Habitat:

Mastic tree is native to the Mediterranean region (France, Spain, Portugal, Turkey) [14,32]. And also found in North Africa [14]. It grows wild in scrub and on waste ground. Besides growing wild, it is also cultivated for its resin, which is collected from incisions made in the bark in summer and autumn [32]. This resin is imported into India from Asia Minor through Persian and Afghanistan [4,29].

Description in Unani literature

Mastagi is derived from Roomi word Mastakhi. It is gum collected from a tree which is found in areas of Sham (Syria) and Room (Italy)[33,34]. According to *Ibn-e-Maswaih* it is pieces of gum like *Cicer arietinum* L. and *Lens culinaris* Medikus. in size, white and yellow in colour like *Boswellia seerata* Trian and aplanch. Its woods and leaves are soft and weak, fruits likely bitter in taste [34]. It has two varieties; one is Roomi which is white, soft, aromatic, transparent, likely sweet in taste and sticks to mouth when chewed. The fresh gum is very soft which is unable to pound. No need incisions for the collection of gum, because it gets out itself from the trunk of tree. Other type is Qibti which is blackish, bitter in taste and it is able to pound. This type is collected by the incisions process [33,34,35,36]. The Roomi type is better than the Qibti [27,36]. Mastagi is dipped in vinegar for a few days, after that removed it and dried. After this process, the Mastagi is better to perform [34,36].

Parts used:

Various parts of the plant like resins, leaves, bark, roots and essential oils are used in Indian traditional system of medicine like Ayurveda, Siddha and Unani as well as other folk system of turkey and Sudan etc. But in Unani system of medicine in India mostly used resin/gums of this plant [32,34,35, 37].

***Mizaj* (Temperament):**

All Unani drugs are divided in five degrees according to their *Mizaj*: viz., normal, first, second, third and fourth degree [38]. Temperament of Mastagi is mentioned in Unani literature har and yabis (hot and dry) in 2nd degree [9,28,30,34,35].

***Afal* (Pharmacological actions):**

Every drug has one or more pharmacological action due to presence of chemical constituents [39]. Mastagi also has some great and important pharmacological actions like:[4,5,9,29,33,34,36,37]

Muhallil-e-Auram (Anti-inflammatory), *Mushtahi-e-Ta'am* (Appetizer), *Mujaffif-e-Rutoobat* (Siccative), *Musakhkhin* (Calorific), *Mulayyin* (Softening Agent), *Qabiz* (Astrigent), *Mulattif* (Demulcent), *Jali* (Detergent), *Muqawwi-e-Aam* (General tonic), *Muqawwi-e-Meda* (Stomach Tonic), *Muqaww-e-Aza-e-Raisa* (Tonic to Vital organs), *Mufatteh-e-Sudad* (Deobstruent), *Mufarreh qalb* (Exhillarant), *Musakkin-e-Alam* (Analgesic), *Mundamil-e-Qurooh*

(Cicatrizant), *Munaffis-e-Balgham* (Expectorant), *Mudirr-e-Baul* (Diuretic), *Jazib-e-Rutoobat* (Absorbant), *Habis-e-Dam* (Heamostatic), *Habis-e-Ishal* (Anri-diarrhoeal), *Kasir-e-Riyah* (Anti Flatulant).

***Mahall-e-Istemal* (Therapeutic Uses):**

Various scientific studies have to be done in relation of action and uses, which should depend on the nature and level of indication [40]. Mastagi has some beneficial therapeutic uses on the basis of their actions[9,27,33,34]. *Jarah wa qurooh* (Woond and Ulcers), *Zof-e-Hazam* (Indigestion), *Zof-e-Jigar* (Weakness of Liver), *Nafakh-e-Shikam* (Flatulence of stomach), *Zof-e-Badan* (Weakness of Body), *Suda-e-Barid* (Cold Headache), *Qarh-e-Am'a* (Intestinal ulcer), *Zof-e-Ishtiha* (Anorexia/Loss of appetite), *Jarb* (Wet-scabies), *Sailan-e-Dam-e-Rahem* (Uterine bleeding), *Razz (Contusion), Zarba wa Saqta* (Strain and Sparain), *Ehtibas-e-Baul* (Anuria/Retention of urine), *Nafs-ud-Dam* (Heamoptesis).

Actions with other drugs: [33,34,35]

- It expectorate the phlegm with Ghariqoon (*Agaricus campestris* L.).
- It eliminate the bile with Ailwa (*Alove barbadensis* Mill.).
- It increased memory and brainpower with Kundur (*Boswellia serrata* Roxb.).
- It is stopped bleeding with Kohraba (*Vateria indica* L.).

***Badal* (substitute):**

Substitution of drugs (Abdaal-e-Advia) is an important principal of USM. If the specific drug which required for the treatment is not available, Unani scholars suggested using their substitute in place of the required drug [2], and that substitute drug similar to required drug in physical properties, temperament and actions [41]. The *Mastagi* is not available and cannot be ensured everywhere in any time therefore the Unani physician have suggested some substitutes namely *Ood* (*Aquilaria agallocha* Roxb.), Izkhar (*Andropogon schoenanthus* L.) for tonic of stomach and liver, Gul-e-Surk (*Rosa damascena* Mill.) for bladder, gum acacia (*Acacia Arabica* Willd.) and sugar for Lung [33,34].

***Mazarrat* (Adverse effect)**:

The Mastic is harmful for the Bladder and Lungs [33,34,35].

***Musleh* (Corrective):**

The Musleh (Correctives) used to improve the potency and efficacy and minimize the undesirable effects [2]. The Musleh for *Mastagi* are Kateera (*Cochlospermum gossypium* DC), Samagh-e-Arabi (Gum of *Acacia arabica* Willd.) Vinegar, Kishniz (*Coriandrum sativum* L.) and sugar [33,34,35].

***Miqdar-e-Khurak* (Dose):**

It is used in the dose of 2-7 gm [9,34,35].

Chemical constituents:

P. lentiscus contains resin, volatile oil, a bicyclic terpenoid and fatty acids [9]. Resin contains 1,8-cineole, isoterpinolene, alpha-cubebene, 5-isopropenyl -3,8-dimethyl-1,2,4,5,6,7,8,8a alpha-octahydroazulene, alpha ylangene, alpha-copaene, beta-bourbonene, 8,8-dimethyl-9-methylene-1,5-cycloundecadiene, valencene, germacrene D, beta-caryophyllene, alpha-longipinene, gamma-gurijunene, alpha-amorphene, alpha-humulene, isocaryophyllene, beta-cubebene, beta-patchoulene, (-)-alpha-muurolene, gamma-muurolene, guaiene, beta-selinene, gamma-elemene, cyclostivene, 17-(acetyloxy)kauran -19-al, pyrethrin 1, (-)-spathulenol, ledol, megastigmatriene, allethrin, beta-cubene, cubenol, bicyclo[5,2,0]nonane,4 ethenyl-4,8,8-trimethyl-2- methylene, bicycle[3.1.0]hexane,6-isopropyl, 16-kaurene, 2/-dodecyl-1,1/,3/,1"-tercyclopentane [20].

Pharmacological studies

Antiatherogenic Activity:

Dedoussis *et al.* (2004) reported that this study investigated the molecular mechanisms through which total polar extract of the resin inhibits oxidized low-density lipoprotein (oxLDL) cytotoxic effect on peripheral blood mononuclear cell (PBMC). Cells exposed to oxLDL underwent apoptosis and necrosis, dependent on the duration of exposure. When culturing cells with oxLDL and the polar extract concurrently inhibition of both the phenomena was observed. oxLDL decreased GSH levels and up regulated CD36 expression.

P. lentiscus extract restored GSH levels and down regulated CD36 expression, even at the mRNA level [42].

Antibacterial Activity:

Mezni *et al.* (2012) performed a study on oil extracted from mature fruits of *P. lentiscus*. Extraction was done by two methods: Traditional method practiced by women in forest areas and pressing method. Gas chromatography-mass spectrometry analysis showed that Oleic acid was the main fatty acid with more than 56%, followed by palmitic with 27%. Antibacterial activity was tested against *Escherichia coli, Salmonella typhimurium* and *Clostridium perfringens*. The results showed a significant bactericidal effect in the case of *C. perfringens*. The effect was not significant in the case of *E. coli* and *S. typhimurium*.[8].

In another *in vitro* study *P. lentiscus* L. extracts were tested on bacteria (*Sarcina lutea, Staphylococcus aureus* and *Escherichia coli*) and fungi (*Candida albicans, Candida parapsilosis, Torulopsis glabrata* and *Cryptococcus neoformans*). Plant extractions, decoctions showed the best antibacterial activity, but the activity against fungal cells appears to be much more interesting [43]. Antibacterial activity of mastic gum, a resin obtained from the *P. lentiscus* tree, against clinical isolates of *Helicobacter pylori*. The minimal bactericidal concentrations (MBCs) were obtained by a microdilution assay. Mastic gum killed 50% of the strains tested at a concentration of 125 mg/ml and 90% at a concentration of 500 mg/*ml*. The influence of sub-MBCs of mastic gum on the morphologies of *H. Pylori* was evaluated by transmission electron microscopy. The *lentiscus* resin induced blebbing, morphological abnormalities and cellular fragmentation in *H. pylori* cells. [11] Aqueous and flavonoid-enriched extract as well as essential oil obtained from leaves of *P. lentiscus* were assessed for antibacterial activity against six bacterial strains. Significant effect was observed against Salmonella typhimurium, whereas lower activity was observed against Staphylococcus aureus, Pseudomonas aeruginosa, and Salmonella enteritidis. essential oil showed significant inhibitory effects against Salmonella typhimurium, Salmonella enteritidis and Staphylococcus aureus [19].

Antimutagenic Activity:

Hayder *et al.* (2005) investigated that the antimutagenic activity of the different extracts against Aflatoxin B1 (AFB1) and sodium azide was demonstrated with the Salmonella typhymurium assay. The number of revertants per plate decreased significantly when the

plant extracts were added to the assay system using Salmonella typhimurium TA100, TA98 and TA1535[19].

Antioxidant Activity:

Some of the herbal therapies are used to treat liver disease, jaundice or diabetes, conditions in which oxidative stress is prominent. In this study selected eight plants used to treat these two conditions and assessed their antioxidant potential by measuring their ability to suppress the extent of iron-induced lipid peroxidation in rat liver homogenates and their potential toxicity by evaluating their effects on mitochondrial respiration and cell membrane integrity in cultured PC12 and HepG2 cells. Result showed that all the extracts can suppress iron-induced lipid peroxidation and are not toxic. Those extracts prepared from *Teucrium polium* and *P. lentiscus* were the most effective in suppressing iron-induced lipid peroxidation [44].

In another study antioxidant properties of galloyl quinic derivatives isolated from *P. lentiscus*, L. leaves have been investigated by means of Electron Paramagnetic Resonance spectroscopy (EPR) and UV-Vis spectrophotometry. Antioxidant properties have been 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, have been estimated against 1,1 diphenyl-2-picrylhydrazyl (DPPH) radical, superoxide radical, and hydroxyl (OH) radical. On the whole, the scavenger activity increase 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[45].

Antiproliferative Activity:

Present study demonstrate that a 50% ethanol extract of the plant-derived product, Chios mastic gum, contains compounds which inhibit proliferation and induce death of HCT116 human colon cancer cells in vitro. Chios mastic gum 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 Chios mastic gum is not inhibited in HCT116 cell clones expressing high levels of the anti-apoptotic protein, Bcl-2, or dominant-negative FADD, thereby indicating that

Chios mastic gum induces cell death via a yet-to-be identified pathway, unrelated to the death receptor- and mitochondrion dependent pathways. The findings presented here suggest that Chios mastic gum (a) induces an anoikis form of cell death in HCT116 colon cancer cells that includes events associated with caspase-dependent pathways and (b) might be developed into a chemotherapeutic agent for the treatment of human colon and other cancers.[46].

Hepatoprotective Effect

The boiled and non-boiled aqueous extracts of *P. lentiscus*, *Phillyrea latifolia*, and *Nicotiana glauca* were evaluated using carbon tetrachloride (CCl4) intoxicated rats. Extracts were administrated orally at a dose of 4 ml/kg body weight, containing various amounts of solid matter. Only total serum bilirubin level was reduced by treatment with non-boiled aqueous extract of *N. glauca* leaves, while the boiled and non-boiled aqueous extracts of the *N. glauca* flowers were noneffective. Bilirubin level and the activity of alkaline phosphatase (ALP) were both reduced upon treatment with boiled aqueous extract of *P.*. *latifolia* without reducing the activity of alanine aminotransferase (ALT) and aspartate aminotransferase (AST). Both the aqueous extract of *P. lentiscus* showed marked antihepatotoxic activity against CCl4 by reducing the activity of the three enzymes and the level of bilirubin. The effect of the non-boiled aqueous extract was more pronounced than that of the boiled extract. [47].

Gastric and duodenal anti-ulcer activity:

The effect of mastic obtained from the stem of the tree ***P. lentiscus*** has been studied on experimentally induced gastric and duodenal ulcers in rats. Mastic at an oral dose of 500 mg/kg produced a significant reduction in the intensity of gastric mucosal damage induced by pyloric ligation, aspirin, phenylbutazone, reserpine and restraint + cold stress. It produced a significant decrease of free acidity in 6-h pylorus-ligated rats and a marked cytoprotective effect against 50% ethanol in rats which could be reversed by prior treatment with indomethacin. The protective effect was not seen when it was given I.P. in phenylbutazone and restraint + cold stress models. The reduction in the intensity of ulceration in cysteamine-induced duodenal ulcers was not found to be statistically significant in mastic-pretreated rats. The results imply that mild antisecretory and a localized adaptive cytoprotectant action may be responsible for its anti-ulcer activity [48].

Hypotensive activity

It was shown that lyophilized aqueous extract *P. lentiscus* caused a dose-dependent decreased of the systemic arterial blood pressure in normotensive urethane anaesthetized wistar rats[49].

Antiarthritic and Antigout Activity:

The total phenolic contents of the leaves and bark of *F. angustifolia* and the leaves and seeds of *P. lentiscus* were estimated. *P. lentiscus* aqueous fractions from hexane and chloroform extractions and *F. angustifolia* aqueous fraction from ethyl acetate extraction inhibited XO activity by 72.74±2.63% (50% inhibitory concentration [IC50] = 27.52 µg/mL), 68.97±3.89% (IC50 42.46 µg/mL) and 53.92±3.17% (IC50 58.84 µg/mL), respectively, at 100 µg/mL, compared to that of reference drug, allopurinol (98.18% [IC50 6.34 µg/mL]. Moreover, at a concentration of 50 µg/mL, both *P. Lentiscus* extracts showed inhibition rates higher than 50%. *F. angustifolia* leaf extracts showed only mild inhibition. Lineweaver-Burk analysis showed that the inhibitory activity exerted by F. angustifolia bark aqueous extract and *P. lentiscus* aqueous extracts is of mixed type, whereas the leaf extracts from *F. angustifolia* inhibited XO noncompetitively. Positive correlations were established between XO inhibition and total phenols (r=0.89) and flavonoids (r=0.93) for *P. lentiscus* and with total phenols (r=0.72) and tannins (r=0.54) for *F. angustifolia*. [50]

Wound Healing Activity:

Boulebda *et al.*,(2009) evaluate the effect of *P. lentiscus* fruits fatty oil on cutaneous wound healing in rat, and compared this effect to that of saponifiable and unsaponifiable oily fractions. Full-thickness excision wounds were made on the back of anesthetised rats. The fruit′s oil and the two fractions were assessed together with a conventional drug, i.e. Madecassol®. Preparations were topically applied on the area of excised wounded once a day and assessed for a period of 26 days. During this period, wound area was measured and photographically documented. Wound contraction was significantly ($P< 0.05$) enhanced in the presence of *P. lentiscus* oil, unsaponifiable oily fraction and Madecassol ® treatments compared to the control, untreated animals. Furthermore, wound healing potentially effect was more pronounced in case of the oily unsaponifiable fraction-treated group compared to the others groups[51].

Anticancer 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 [46].

CONCLUSION:

P. lentiscus is having important medicinal properties and it is used as a single drug or in combination with other drugs. It is also important ingredients of various compound formulations used in Unani system of medicine to treat the various types of diseases. The different parts of the mastic plant showed various pharmacological activities like antiatherogenic, anti-bacterial, antimicrobial, antioxidant, antihypertensive, anticancer, antiarthritic and antigout, wound healing and antiulcer activity. This review comprehensively highlighted the pharmacological and phytochemical details of *P. lentiscus* and it may provide a way for further analysis and research.

Figure: Mastic Gum

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