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Khirni [*Manilkara hexandra* (Roxb.)]-A Review of its Uses in Unani Medicine, Phytochemistry and Pharmacology

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ABSTRACT

Khirni is fruit of *Manilkara hexandra* (Roxb.) Dubard and belongs to the Sapotaceae family. Khirni tree is a commercially and medicinally important tropical tree. The fruit has been source of livelihood and nutritional support for local tribal population in India who have been using it for medicinal benefits also. It has been used in Unani medicine for various conditions like general debility, respiratory diseases, ulcers *etc.* since ages. The aim of this review is to highlight the medicinal properties of Khirni as mentioned in Unani Medicine and also to explore its other ethnomedical uses, phytochemistry and pharmacological studies. For this purpose, Pubmed, Elseveir, Scopus, SID and Google scholar were searched for the key terms "*Manilkara hexandra*" and "Khirni" up to 30th September 2023 and also Unani classical books were studied. The work on the review article was carried out at Central Council for Research in Unani Medicine, Ministry of Ayush, Govt. of India, New Delhi. Khirni has various pharmacological properties including antioxidant, anti-ulcer, antiviral, antibacterial and hypolipidimic properties and also has several ethnomedical uses. In Unani medicine, Khirni is used as atonic for vital organs like brain, heart and liver. This fruit is a valuable source of compounds with health-promoting properties and can be used as good sources of antioxidants in our diet.

Key words: Khirni, *Manilkara hexandra*, Pharmacology, Phytochemistry, Phytotherapy, Unani medicine.

Unani Medicine is not only the original science of medicine but also a rich store house of principles and philosophies of medicine. It is a form of traditional medicine practice which originated in Greece. It is based on the principles advocated by the ancient Greek practitioner Hippocrates (460-370 BC) and Roman physician Galen (129-200 AD) (WHO Benchmarks for the Training of Unani Medicine, 2022). After the Greek and Roman periods, it was adopted in the Arab lands leading to its greater growth. In the medieval period, Unani medicine went beyond the Arab region, covering Persia, Spain, Northern Africa, Turkey, Central Asia, Indian Subcontinent and China. It was nurtured by the best of intellects of these nations and regions who contributed in its development through their valuable observations and interventions. Unani Medicine was introduced in India during the eighth century AD and soon got rooted in the country as an indigenous system of medicine due to its wide acceptance among the masses and patronage of governments of the time. During its history of over 1200 years in India, Unani Medicine made major advancements and emerged as one of the effective and commonly used systems of medicine. It is now widely practised and researched as a fully fledged system of medicine with a large network of education, clinical practice, research and training (CCRUM-Unani Medicine-The Science of Health and Healing-An Overview, 2020).

Unani medicine is strongly founded on its philosophical principles and long history of use. It uses clinical observations to maintain health and prevent and treat diseases safely, effectively and economically. Unani medicine provides dietary, lifestyle and pharmacological interventions to maintain health and prevent diseases. It treats diseases by modifying external and internal essential and non-essential factors known as *Asbab Sitta Zaruriyya wa ghayr Zaruriyya* (Six essentials of health as well as non-essentials) with various modes of *ilaj hil ghiza* (diet therapy), *ilaj bil tadabir* (regimenal therapy), *ilaj bil dawa* (pharmacotherapy) and *ilaj bil yad* (surgery) (WHO Benchmarks for the Practice of Unani Medicine, 2022).

India boasts one of the world's most diverse and rich medicinal plant heritages. Approximately 8,000 species of medicinal plants can be found in India, constituting around 50% of all higher flowering plant species. Estimates suggest that 14-28% of higher plant species are used for medicinal purposes, while 15% of all angiosperms have been chemically investigated. Notably, 74% of pharmaceutically active plant-derived components were discovered by studying the ethno-medicinal uses of these plants (Humaira *et al*., 2020).

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Khirni is a fruit of *Manilkara hexandra* (Roxb.) Dubard Syn. *Mimusops hexandra* Roxb. (basionym). Khirni trees are economically multipurpose and belong to the family Sapotaceae (Singh *et al.*, 2019). *Khirni* trees are commonly distributed in tropical deciduous forests of western and central India. These are locally known as 'Khirni', 'Rayan' and 'Raina' among the tribal populations of Rajasthan, Gujarat, Madhya Pradesh and Maharashtra in India. In Bengal they are called Krikhiyur or Khirkhejur and in Karnataka they are called Bakula. These golden yellow berries are very similar in appearance to the neem fruits. These fruits are available for a very short time during the start of summer season. They are sweet in taste and the pulp is sticky and milky. Khirni trees grow in natural wild conditions and mainly propagated through seeds. It is reported that Khirni seeds are recalcitrant and have poor germination. Several studies proved that germination and seedling vigour can be improved with help of seed priming with chemicals such as GA, KNO_3 and thiourea *etc.* (Kaur Satinder *et al.*, 2020). Khirni is commercially used as a rootstock for vegetative propagation of sapota in different parts of the country as it possesses high graft compatibility and plants grafted on khirni rootstock produce fruits of excellent quality with increased production (Kaur Satinder *et al.*, 2020). The fruit is good source of iron, sugars, minerals, protein and carbohydrate *etc.* (Kanak *et al.*, 2019). In addition to the edible fruit, Khirni yields useful wood and latex which are significant source of nutritional and livelihood support for tribal population (Peter, 1999).

Khirni trees are valued in Unani medicine for their medicinal properties. These are also used as folk medicine by the tribal populations in India. Almost all parts of Khirni tree *i.e.* fruits, seeds, leaves, roots, stem bark *etc*, are used in Unani medicine. The tree is bestowed with numerous pharmacological actions medicinal benefits which have been mentioned in detail in classical Unani literature.

In spite of its high nutritional and medicinal properties, Khirni is underutilised and the species falls under the 'critically endangered' category having high risk of extinction in the wild (Keerthika *et al.*, 2015). Therefore there is a need to popularise its medicinal importance and promote its use for the benefits it offers.

A review of literature on Khirni was undertaken using the bibliographic database *viz.* Pub Med, Google Scholar, Science Direct and Scopus. The search was conducted using the terms 'Khirni', '*Manilkara hexandra* and '*Mimusops hexandra'.* All in-vitro, animal and clinical studies that evaluated medicinal properties of Khirni were included. Agriculture studies were excluded from the review. Duplication was avoided by excluding reviews of multiple copies of the same article in several databases. Books, monographs and reports on *Manilkara hexandra* were also used to compile the information. A literature survey of classical Unani texts was carried out to collect information related to temperament (mizaj), actions, therapeutic uses, Unani formulations, substitutes and correctives of Khirni.

Botanical description

It is a large evergreen slow growing tree, 50-60 ft. tall, with blackish gray and deeply furrowed bark; leaves are 7-10 cm long, dark-green, coriaceous, elliptic, obovate, oblong emarginated with grooved petioles. Flowers are bisexual, white, calyx 6-lobed, segmented, hairy, reflexed and ovate. Corolla-lobes nearly 18, in 2-series of 6 and 12; stamens 6, ovary is 12 celled, hairy and multi-locular with axile placentation. Inflorescence is solitary or in fascicles of 2-6. Fruit is berry, fleshy, 1-2 seeded shining yellow with ovoid shape. Seeds are endospermic and oily (Dwivedi and Bajpai, 1974). Its taxonomic classification is given in Table 1.

Chemical constituents

Bark of this tree is found to contain tannins, resins, wax, starch, coloring matter and mineral matter. Seeds contain a fixed amount of oil. Fruits contain sugar, caotchouc, pectin tannin and coloring matter. Distribution of chemical constituents in various parts of *Manilkara hexandra* is given in Table 2.

Mizaj (Temperament)

In Unani medicine great emphasis is laid on the temperament of the drug. It helps in rational use of the drug and indicates the potency of the drug. The temperament is defined according to the nature and extent of the deviation it produces in the state of the body *e.g.* a drug can be hot or cold and dry or wet with varying intensity of action. Unani physicians have described the *Mizaj* of Khirni as Hot in 1st degree and Moist in 2nd degree (Ashraf, YNM, Hakim 1894). It has also been described by some physicians as Cold and Moist (Khan, 2012).

Actions (Afal) and uses in Unani Medicine

Unani physicians have attributed several pharmacological properties to this drug. Khirni is *Muqawwi Aza* or Tonic for the organs. *Muqawwi Aza* are those drugs that have the ability to improve and maintain the health of the human body when used regularly over a long period of time. They tone up the internal organs and improve the body functions. Khirni is also termed as *Musakkin Akhlat i.e.* it neutralizes the heat of the humours. The khirni fruits are used for *Muqawwi Baah* (aphrodiosiac) and *Mufarrih* (exhilarant)

Table 1: Taxonomic classification (www.indiabiodiversity.org).

Kingdom	Plantae
Phylum	Tracheophyta
Class	Equisetopsida C. Agardh
Order	Ericales Bercht. and J. Presl
Family	Sapotaceae
Genus	*Manilkara*
Species	*M. hexandra*

properties. (Ashraf, YNM, Hakim 1894, Kirtikar and Basu 1988, Nadkarni 1989).

Uses of khirni

Fruits

The fruits are nutritious and strengthen organs. They are helpful in relieving dizziness. (Ashraf, YNM, Hakim 1894, Ghani 1920). They also help in regaining consciousness and relieve vomiting and fever. They improve appetite. Khirni fruits are given in respiratory disorders like cough. They are aphrodisiac and increase semen. They are also used to treat intestinal worms (Ashraf, YNM, Hakim 1894, Ghani 1920, Khan 2012, Kabiruddin 1951). They are prescribed in phlegmatic diseases like hemiplegia and tremors (Ghani 1920).

Seeds

The seeds of khirni are said to improve eyesight. A fine paste of the seeds is mixed with milk and applied in the eyes to relieve itching, corneal ulcers and opacities (Hakim 1894; Khan, 2012; Kirtikar and Basu, 1988; Ghani, 1920; Kabiruddin, 1951) Seeds are also used for the treatment of *hurqatul baul* (dysuria) and ulcers of urinary tract (Khan, 2012). The seeds of khirni are used as ingredients in preparation of several classical Unani formulations which are used in sexual disorders and ophthalmic diseases. Halwa Supari Pak containing khirni seeds is a tonic for kidney and bladder, inspissant and retentive to semen and aphrodisiac. It is useful in spermatorrhoea, premature ejaculation, sexual debility and leucorrhoea (NFUM, 2008).

The ophthalmic formulations prepared from Khirni seeds are Kohal-e-Dafe-e-Shabkori and Kohal-e-Filfil which are used in the treatment of night blindness, corneal opacity, pterygium and conjunctivitis. Shiyaf-e-Dahna-e-Farang, another ophthalmic preparation is prescribed in cataract, Vascular Keratitis and pterygium (NFUM 2007).

Bark and root

Powder of bark is *Mughalliz i mani i.e.* it increases the viscosity of semen (Hakim, 1894; Kabiruddin, 1951). It is prescribed in spermatorrhoea and gonorrhea. The paste of bark as well as roots is mixed with honey and given to children to relieve diarrhea (Ghani, 1920).

Leaves

Leaves are boiled in sesame oil then a paste of the bark is made in this oil and applied on hands and feet to relieve their coldness (Ghani, 1920). A *Zimad* (paste) prepared with leaves mixed with *Curcuma amada* and dried *Zingiber officinale* cures swellings.

Exudate

The milky exudate of khirni is applied on eyes and ears to relieve their bilious swelling (Kirtikar and Basu, 1988; Nadkarni, 1989). The milky juice made into a paste with leaves of *Cassia fistula* and seeds of *Calophyllum inophyllum* is applied on the boils (Nadkarni, 1989).

Muzir (adverse effects) and muslih (correctives)

Some adverse effects of the khirni have been mentioned in classical Unani literature. Khirni fruits takes a long time to digest and cause flatulence (Hakim, 1894). If they are consumed in large quantity they cause abdominal colic (Ashraf YNM). These adverse effects can be corrected by using correctives or *Muslih* drugs like *Gulqand* (a preparation made from rose petals and sugar) and *Sikanjabeen* (a preparation made with honey and vinegar) (Ashraf YNM Hakim, 1894).

Table 2: Phytoconstituents of *Manilkara hexandra*.

Part of Plant	Constituents
Leaves	Cinnamic acid ester of α-and β-amyrins, taraxerol, hentriacontane, α-spinasterol, quercitol, Sterols, tannins and volatile oil, Terpenic hydrocarbon, Taraxerol, Hentriacontane, Triterpene ketone, 4-methyl benzaldehyde, p-coumaric acid, 3,4-dihydroxy benzaldehyde
Fruits	Proteins, lipids, carbohydrates, fatty acid esters of common triterpene alcohols, α-amyrin acetates, ursolic acid, β-amyrin acetate, gallic acid, kaempferol, quercetin, tetra-hydroxy alcohol, monohydroxy monocarboxylic acid
Flowers	D-Quercitol, ethyl nicotinate
Seeds	Bidesmosidic saponins, gallic acid, myrecetin, quercetin, unsaponifiable lipid constituents, sterol, quercitol, arabinose, rhamnose, glucose, vanillic acid, dihydroquercetin, xylose
Stem bark	Triterpenoid saponin, 1β 2α, 3β, 19α-tetrahydroxyursolic acid 28-O-β-D-glucopyranoside, β-sitosterol, 7,9-di-tert-butyl-1oxaspiro [4.5] deca-6,9-diene-2,8-dione, Taraxerol, α-amyrin cinnamate, α-spinasterol, triterpenoid acid, taraxeryl acetate, flavan-3-ol, Trigonelline, Rutin
Roots	Cinnamic acid ester of α-and β-amyrin cinnamates, taraxerol, hentriacontane, α-spinasterol and quercitol. Taraxerol, β-D-glucoside of β sitosterol

Source: (Misra and Mitra 1968, Madhak *et al.* 2013, Daripkar and Jadhav 2010, Misra *et al.* 1974, Eskander *et al.* 2013, Saeed *et al* 1991, Srivastava and Singh 1994, Gopalkrishnan *et al.* 2014, Monisha and Vimala 2018, Irudaya and Vimala 2019, Moustafa *et al.* 2016, Annamalai *et al.* 2018)

Ethnomedical uses

Khirni is used for its medical benefits by tribal populations in various parts of India. In Jalgaon district of North Maharashtra, khirni fruits are used to relieve digestive disorders. Mashed fruits of khirni are taken to cure arthritis, jaundice and worm infestation and to purify blood by local population of Nawargaon village and Bhadrawati tehsil of Chandrapur District, Maharashtra. Tribal people of Rayalaseema region of Andhra Pradesh use khirni leaf extract for treatment of asthma .The latex of Khirni is applied on teeth and gums for toothaches. In Paderu division of Eastern Ghats of Andhra Pradesh root extract of khirni is used for relief from headache. A decoction of the stem bark is used to cure dysentery and diarrhea by Koyas tribes in Khammam district of Andhra Pradesh. The stem barks infusion is widely used in Konda Dora Tribes in Vishakhapatnam district of Andhra Pradesh as galactagogue. A decoction of bark and mashed fruits are used in sacred groves in Pudukottai district Tamil Nadu for fever and hallucinations (Mishra and Pareek 2014). Madhya Pradesh has a number of tribal dominated districts. The main tribes in the region include Baiga, Gond, Bhil and Bharia. These tribes utilise their vast knowledge of healing properties of the plant species available near their surroundings for treatment of various ailments. (Bisen *et al.*, 2021) The stem bark of Khirni tree is boiled with water is used for bathing to cure body ache by Bhil tribe of Jhabua district, Madhya Pradesh. Extract of stem bark is taken as tonic by Bharia and Gond Tribes of Tamiya and Petalkot of Madhya Pradesh (Mishra and Pareek, 2014).

Pharmacological studies

A summary of the pharmacological studies on *M. hexandra* is outlined below:

Antiviral activity

A molecular docking study was performed to evaluate the inhibitory effect of flavonoids isolated from khirni against SARS-CoV-2 main protease enzymes. The results proved that rutin which is a citrus flavonoid glycoside exhibits the strongest inhibition effect to the SARS-CoV-2 protease enzyme. Consequently, it can contribute to developing an effective antiviral drug lead against the SARS-CoV-2 pandemic (Abd El-Mordy *et al*., 2020).

Antiulcer activity

Manilkara hexandra is reported to exert preventive effect in several experimental ulcer models. A study demonstrated the gastric ulcer healing activity of methanolic stem bark extract of *Khirni* against acetic acid (AA)-induced gastric ulcer in male rats. In a subsequent set of experiment, trigonelline, a potent Nrf2 antagonist, significantly abrogated the gastric ulcer healing activity of *Manilkara hexandra* in AA challenged animals (Garabadu *et al.,* 2021). Effects of the flavonoid rich fraction of the stem bark of Khirni, demonstrated protective effect on ethanol, ethanol-indomethacin and pylorus ligated gastric ulcers in experimental animals (Shah *et al.,* 2004). Another study reported antiulcer effects of acetone extract and its different fractions (diethyl ether, ethyl acetate and aqueous fractions) from stem bark of *Khirni.* Oral administration of ethyl acetate extract inhibited formation of gastric lesions induced by aspirin in a dose dependent manner. The antiulcer activity shown by this extract in experimental gastro-duodenal ulcer could be attributed to decrease in gastric acid secretory activity along with strengthening of mucosal defensive mechanisms (Modi *et al*., 2012).

Antioxidant activity

A study carried out by Nimbekar *et al*. (2010) had demonstrated a dose dependent increase in nitric oxide, superoxide and DPPH free radical scavenging potentials of the methanolic extract of bark of *M. hexandra*. In vitro free radical scavenging and reducing potentials of the leaf extract fractions of *M. hexandra* were explored in a study and the methanolic extract fraction of the leaf was found to be the most potent extract fraction and contained the highest quantities of antioxidants which positively correlated with the presence of relatively higher quantities of total phenolic contents (Dutta and Ray, 2015). Parikh and Patel (2017) estimated the total antioxidant capacity of fruit and seed of *M. hexandra* by six different assays. The fruit of Rayan proved to be a better source of antioxidants as measured by 1,1-diphenyl-2-picrylhydrazyl (DPPH) free radical scavenging, ferric ion reducing antioxidant power (FRAP), hydroxyl radical scavenging (HRS), Reducing Power Assay (RPA) and ABTS (2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid)) except nitric oxide radical scavenging activity (NORSA) in comparison with that of seed. The study explained that *M. hexandra* is a relatively good source of antioxidants such as phenols and flavonoids for diet. The *in vitro* antioxidant potential of the methanolic leaf and bark extracts of *Khirni* were tested through DPPH free radical scavenging, FRAP, HRS and TAC assays. The leaf methanolic extract of *khirni* was found to possess more *in vitro* antioxidant potential and total phenolics content than its bark methanolic extract (Dutta and Ray, 2020).

Hypoglycaemic activity

The effects of the methanolic extracts *M. hexandra* on blood glucose levels were assessed in normoglycemic and alloxan induced diabetic rats. The results showed that *M. hexandra* reduced glucose levels significantly (Nimbekar *et al*., 2012). The effects of leaf aqueous extract of *M. hexandra* was found to reduce serum glucose significantly in Rohu (*Labeo rohita*) fingerlings. The study also revealed a decline in activities of the metabolic enzymes which may be associated with the non-availability of glucose owing to reduced activity of the digestive amylase in the treated groups (Dutta *et al.*, 2021).

Antibacterial/Antimicrobial activity

Antimicrobial potential of *Khirni* leaf extracts (petroleum ether, acetone and methanol) was investigated against 9

Gram-positive bacteria, 14 Gram-negative bacteria, 7 yeast and 4 moulds by agar disc diffusion method. Maximum antibacterial activity was shown by methanol extract. The antimicrobial activity was found to be concentration dependent. All the three extracts showed better activity against bacterial than fungal strains (Sumitra and Jigna, 2010). Extracts of *M. hexandra* seeds were screened for their antibacterial activity against *Streptococcus mutans* and were found to inhibit both the test strains of *S. mutans* used in this study with minimum inhibitory concentration (MIC) ranging from 600-800 µg/mL and minimum bactericidal concentration (MBC) of 600-900 µg/mL (Patel *et al*., 2015). The methanol root extracts of *M. hexandra* demonstrated potent antibacterial activity against *Staphylococcus aureus, Micrococcus leutius, Salmonella paratyphi*, *Serratia marcescens* and *Klebsiella pneumonia* (Bharvad *et al*., 2011).

Immunostimulant activity

Crude polysaccharides extracted from *M. hexandra* bark and their immunomodulatory property was assessed using four methods, *viz* Humoral immune response, Cellular immune response, White blood cell count and Phagocytic index. The results showed that the polysaccharides significantly stimulated the immune system function (Gomathi *et al*., 2012).

Anti-fertility activity

Antifertility activity of Khirni seeds was studied on male albino rats. The aqueous powdered drug proved to be an effective antifertility drug by significant decrease in sperm count, biochemical assays and histopathological investigations (Gopalkrishnan *et al*., 2016).

Anti-arthritic activity

In vivo anti-arthritic activity of hydro alcoholic extract of seeds of *M. hexandra* were evaluated against formaldehyde and Complete Freund's adjuvant induced arthritis. A dominant protective effect of the extract was observed against arthritis in animal models (Deepa *et al*., 2019). Earlier the *in-vitro* antiarthritic activity of methanolic and hydroalcoholic leaf extracts of *M. hexandra* were evaluated by protein denaturation method and proteinase inhibition method. A dose dependent increase in the antiarthritic activity of the extracts was observed (Pingili *et al.,* 2012).

Khirni is commercially important but underutilized medicinal tree. It is a source of livelihood support by local tribal population. It has been traditionally used in Unani medicine for its medicinal benefits. The fruits are used as tonics for strengthening organs and for treatment of respiratory diseases. The seeds are used for improving eyesight and treatment of corneal ulcers and opacities. Fruits and bark are aphrodisiac and increase semen. The phytochemical studies conducted on this plant indicate presence of various important compounds such as sterols, triterpene alcohols, tannins, saponins, unsaponifialble lipids, terpenoids *etc*.in different parts of the plant. Various pharmacologic properties of khirni have been evaluated during *in vitro* and animal studies such as antiviral, antibacterial, anti-oxidant, antiulcer, antihypoglycaemic and immunostimulant *etc.* It's worth noting that these pharmacological studies align with some of the traditional uses of khirni, validating the plant's potential as a source of therapeutic compounds. Still many of its uses in Unani medicine are yet to be validated by experimental and clinical research. Thus further research can be focussed on these aspects of Khirni.

Bons and Rehal (2019) had carried out a study on physical attributes and processing suitability of sapota cultivars and also explored the possibility of using them for preparation of jam along with analysis of its acceptability. It would be worthwhile to conduct such studies on Khirni in order to develop some low cost technologies to process these fruits into value added products and reduce post harvest losses. This would promote its cultivation and help farmers in getting good returns for their produce.

CONCLUSION

Khirni, deeply rooted in traditional medicine, not only serves as a nutritional fruit but also offers a spectrum of medicinal properties. The synergy between traditional knowledge and modern pharmacological studies provides a comprehensive understanding of the diverse benefits of khirni, making it a promising candidate for further exploration in the field of natural medicine.

Conflict of interest

It is hereby informed that the authors have no conflict of interest in the publication of this article in "Asian Journal of Dairy and Food Research".

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