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Kakda Singhi (*Pistacia integerrima*): A Comprehensive Review of Traditional Uses, Phytochemistry, and Pharmacological Potential

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Abstract: ***Kakda Singhi (Pistacia integerrima J.L. Stewart ex Brandis) is an important medicinal plant widely used in Indian System of Medicine, particularly for the treatment of respiratory, gastrointestinal, and inflammatory disorders. Phytochemical analyses have revealed flavonoids, tannins, triterpenoids, phenolic compounds, essential oils, and various bioactive components responsible for its therapeutic properties. Experimental studies have demonstrated antioxidant, antimicrobial, anti- inflammatory, antiasthmatic, antitussive, hepatoprotective and many other important pharmacological activities. Despite encouraging preclinical evidence, well designed clinical studies and standardized formulations remain limited. Integrating traditional knowledge with modern scientific evidence may facilitate the development of evidence-based herbal formulations.***

Keywords: Kakda Singhi, flavonoids, tannins, triterpenoids, phenolic compounds, antioxidant, antimicrobial, anti-inflammatory, anti-asthmatic, antitussive.

1. Introduction

Pistacia integerrima (Anacardiaceae), commonly known as *Kakra Singhi*, is a medicinal tree native to the Himalayan regions of India, Pakistan, and Afghanistan. It is widely used in Ayurveda, Unani, and Siddha medicine. The plant is particularly valued for its horn-shaped galls, which are rich in flavonoids, tannins, phenolics, and essential oils. [1,2,3,4,5]

Traditionally, *P. integerrima* is used to treat respiratory disorders such as asthma, bronchitis, and cough, as well as digestive and liver ailments. Modern studies have demonstrated its antibacterial, antioxidant, anti-inflammatory, antidiarrheal, and anticonvulsant activities, supporting its traditional medicinal uses. [1,2,3,4,5]

2. Materials and Methods

A comprehensive literature search was carried out to obtain the relevant information on *Pistacia integerrima* (Kakda Singhi). A search of various electronic databases such as PubMed, Google Scholar, ScienceDirect and ResearchGate was performed for published articles on its traditional uses, phytochemistry, pharmacological activities and therapeutic potential. The search was performed using the keywords "*Pistacia integerrima*", "Kakda Singhi", "phytochemical constituents", "antioxidant activity", "anti-inflammatory activity", "hepatoprotective activity", "antidiabetic activity" and "pharmacological evaluation". Classical Unani literature and authentic books were also consulted to document its traditional therapeutic uses, temperament (Mizaj), therapeutic actions (Afʿāl) and indications.

The collected data were critically evaluated and compiled into various sections such as botanical description, ethnomedicinal importance, Unani pharmacological actions, phytochemical constituents and experimentally proven pharmacological activities. Studies that reported in vitro, in vivo, and clinical evidence were included, and duplicate and irrelevant articles were excluded. The available data were analyzed to provide a comprehensive overview of the traditional importance and current scientific evidence for the medicinal potential of *Pistacia integerrima*.

Botanical description:

Pistacia chinensis subsp. *integerrima* is a medium-sized deciduous tree of the family **Anacardiaceae**, reaching a height of 18–25 m. It is typically single-stemmed, with a deep root system and a broad, spreading crown. The species is dioecious, with male and female flowers borne on separate plants.

The leaves are large, pinnately compound, and up to 25 cm long, comprising 2–6 pairs of lanceolate leaflets with smooth margins. A distinctive feature of the plant is the presence of horn-shaped galls on the leaves and petioles. These hollow, rugose structures are formed by insects of the genus *Pemphigus* and are important reservoirs of bioactive secondary metabolites.

The tree bears small reddish flowers arranged in panicles, followed by small globular fruits (4–6 mm in diameter) that change from green to purple or bluish when mature. Its characteristic branching pattern, pinnate leaves, and gall formation aid in easy identification.

The plant is widely distributed in China, Nepal, Afghanistan, Armenia, and Pakistan, as well as in the northwestern and western Himalayan regions of India, extending from the Indus Valley to Kumaon. [1,2,3,4,5]

Vernacular name:

Sanskrit	Karkatshringi, Shringi, Vishani, Chakrangi, Karkata
Hindi	Kakra Singhi, Kakarsinghi, Kakkar, Kakroi
Urdu	Kakra, Kakar, Mastagi Desi
English	Crab's Claw, Zebrawood, Gall Tree
Tamil	Karkatasingi, Kakkata-shinigi

Taxonomy:

Kingdom: Plantae
Phylum: Streptophyta
Class: Equisetopsida
Subclass: Magnoliidae
Order: Sapindales
Family: *Anacardiaceae*
Genus: *Pistacia*
Species: *Pistacia chinensis*
Subspecies: *Pistacia chinensis* subsp. *integerrima*

Functions:
Mukharij -e- balgham (Expectorant), Dāfi'-i-Su'āl (Antitussive), Mujaffif rutubat (Desiccant), Muqawwi-e-Me'da (Stomachic), Muqawwī-i-Kabid (Hepatotonic), Muḥāfiẓ-i-Kabid (Hepatoprotective), Qabiz (Astringent), Habis ud dum (Haemostatic), Dāfi'-i-Buḥḥat al-Ṣawt(Anti-hoarseness), Māni'-i-Qay (Anti-emetic), *Dāfi'-i-Hummā* (Antipyretic)[5,6,7,8,9.]

Adverse effects: Excessive usage may cause liver damage. [5,6,7,8,9]

Corrective: Kateera (*Astragalus gummifer*), Babool(Acacia arabica). [5,6,7,8,9]

Substitute: Asl-us-soos (*Glycyrrhiza glabra*). [5,6,7,8,9]

Therapeutic dosage: 1-2 gms. [5,6,7,8,9]

Compound formulation:
Habbe zeekhun nafas, Safoof kakda singhi, Tiryaq suaal. [5,6,7,8,9]

Phytochemical:[1,2,4]

Phytochemical Class	Compounds Identified
Triterpenes	Pistacienoic acid A, Pistacienoic acid B
Flavonoids	Pistacide A, Pistacide B, Dihydrokaempferol, Naringenin
Volatile Oils (Essential Oils)	α-Phellandrene, α-Pinene, β-Pinene, β-Phellandrene, γ-Terpinene, δ^3-Carene, α-Terpineol, β-Terpineol, α-Ocimene, β-Ocimene
Fatty Acids	Caproic acid, Caprylic acid, Capric acid, Lauric acid, Myristic acid, Tridecanoic acid, Pentadecanoic acid, Palmitic acid, Palmitoleic acid, Margaric acid, Heptadecenoic acid, Oleic acid, Elaidic acid, Linoleic acid, Linolenic acid, Stearic acid, Heneicosanoic acid, Arachidic acid, Behenic acid, Tricosanoic acid, Tetracosanoic acid
Phenolic Compounds	Pistaciaphenyl ether, Pistiphloroglucinyl ester, Pisticiphloroglucinyl ether
Phytosterols	β-Sitosterol, Integriside A, Integriside B
General Polyphenols	Tannins, Phenolic acids, Polyphenolic compounds

Recent pharmacological Activities

Antiasthmatic activity:
A study by Abdysmalli et al. was conducted to assess the antiasthmatic activity of *Pistacia integerrima* galls in albino rats and guinea pigs. The aqueous extract showed a dose-dependent mast cell stabilization to 26.11% at 27 mg/kg and 56.16% at the higher dose of 54 mg/kg, while prednisolone (10mg/kg) exerted a protective effect of up to 68.01%. This extract also suppressed histamine release, suggesting the important antihistaminic activity.

In another trial, the aqueous gall extract of *Pistacia integerrima* demonstrated very strong antispasmodic actions in guinea pigs. Protection afforded by the compound against histamine-induced preconvulsive dyspnea at doses of 23.25 mg/kg was 60.55% ($p < 0.0005$) and, at a dose of 46.50 mg/kg, it was 64.19% ($p < 0.0001$) percentage inhibition which were similar to that observed with ketotifen (65.57%; $p < 0.0002$; at a dosage of~1mg/kg). In isolated tracheal tissue, the extract inhibited histamine-induced bronchospasm in a dose-dependent manner (25% inhibition at 0.1 ml, complete inhibition at 0.4 ml). [10]

A recent study in BALB/c mice demonstrated that the methanolic extract of *Pistacia integerrima* (200 mg/kg) possesses significant antiasthmatic and anti-inflammatory activity. The extract reduced the expression of inflammatory cytokines such as IL-4, IL-5, and TNF-α, while enhancing aquaporin (AQP1 and AQP5) expression, thereby decreasing pulmonary edema and improving airway inflammation.[11]

Anticancer activity:
Recent studies have shown that **3-oxo-6β-hydroxy-β-amyrin**, a triterpenoid isolated from *Pistacia integerrima*, exhibits significant anticancer potential. The compound inhibits P-glycoprotein-mediated multidrug resistance, suppresses tumor-promoting activity and early tumor antigen expression, and demonstrates strong binding affinity toward cancer-related target proteins in molecular docking studies, indicating its promise as a potential anticancer agent.[12]

Antidiarrheal activity:
Recent pharmacological studies have demonstrated that *Pistacia integerrima* possesses significant antidiarrheal activity in castor oil-induced diarrheal models in mice. Among the tested fractions, the ethyl acetate fraction exhibited the strongest effect, followed by the chloroform fraction. Isolated flavonoids, particularly compounds 1 and 4, showed marked protection against diarrhea, suggesting that the plant's antidiarrheal activity is largely attributed to its bioactive flavonoid constituents.[13]

Janbaz et al. that the methanolic extract of *Pistacia integerrima* exhibits significant antidiarrheal activity in castor oil-induced diarrhea models. The extract provided 40% protection at 700 mg/kg and 60% protection at 900 mg/kg. Its antidiarrheal effect is attributed to dual inhibition of calcium channels and muscarinic receptors, supporting its traditional use in gastrointestinal disorders.[14]

Antimicrobial activity:
Rauf et al. demonstrated that the methanolic extracts from the galls of *Pistacia integerrima* exhibited effective growth inhibition against several gram positive bacteria especially *Staphylococcus aureus*, *Enterococcus faecalis*, and *Bacillus subtilis*, with inhibition zones measuring 6mm,6mm,and 8mm, respectively at a very minimum concentration of 20 µl. Also the extract showed strong antibacterial activity at the same concentration.[15]

Analgesic activity:
The antinociceptive (pain-relieving) activity of Pistacia integerrima was assessed using an in vivo study in mice. The gall extract showed dose-dependent effect and significant protection against chemically induced pain. The extract at 200 mg/kg dose produced about 56.12% inhibition of pain in BALB/c mice. But it was comparatively less effective against thermally induced pain, showing about 40.45% protection at the same dose. These results indicate that the plant extract has significant analgesic activity especially against chemically induced pain stimuli.[16]

Another study on analgesic activity of *Pistacia integerrima* extract against acetic acid-induced writhing in BALB-c mice was conducted. The methanolic bark extract significantly inhibited the writhing response induced by acetic acid by 35.30 and 38.89% at 50 and 100 mg kg−1, respectively.[17]

Antifungal Activity:
Pistacia integerrima has shown significant antifungal activity against some fungal species. Aqil and Ahmad found that the ethanolic extract from the plant stem had potent inhibitory effects on fungal growth. It was especially effective against Candida albicans, Alternaria alternata, Aspergillus niger, Rhizoctonia bataticola and Fusarium chlamydosporum with zones of inhibition ranging from 31–35 mm, 21–25 mm, 16–20 mm, 11–15 mm and 11–15 mm respectively. The antifungal activity of the bark extracts was comparatively low. The bark extract in ethyl acetate 10 mg/ml exhibited a 14 mm inhibition zone against Candida albicans. The bark extract in hexane showed a 10 mm inhibition zone against Aspergillus niger.[18]

Antioxidant Activity:
The antioxidant activity of *Pistacia integerrima* was evaluated using the DPPH free radical scavenging assay. The crude extract, solvent fractions, and two isolated flavonoids—naringenin (compound 1) and 3,5,7,4′-tetrahydroxyflavanone (compound 2)—exhibited significant antioxidant activity. Among the fractions, the chloroform fraction showed the highest scavenging activity, while naringenin demonstrated the greatest antioxidant potential among the isolated compounds (94.51% inhibition at 100 µg/mL). These findings suggest that the flavonoid constituents contribute substantially to the antioxidant properties of *P. integerrima*.[19]

Anti-inflammatory:
The anti-inflammatory activity of *Pistacia integerrima* was evaluated using a carrageenan-induced paw edema model in mice. The findings indicated that flavonoid compounds isolated from the chloroform fraction of the plant galls, demonstrated significant anti-inflammatory effects at different time intervals ranging from 1 to 5 hours. The maximum reduction in inflammation was observed around the third hour after administration, and this effect was sustained up to the fifth hour.[20]

Flavonoids isolated from the chloroform fraction of *Pistacia integerrima* gall extract demonstrated significant in vivo anti-inflammatory activity in a carrageenan-induced paw edema model using BALB/c male mice. The peak anti-inflammatory effect was observed approximately 3 hours after administration and was maintained up to the fifth hour. Among the tested compounds, dihydrokaempferol showed the highest level of protection, producing 65.10% inhibition at a dose of 10 mg/kg, while naringenin exhibited 63.69% inhibition at the same dose.[21]

Hepatoprotective Activity:
The hepatoprotective potential of *Pistacia integerrima* has been demonstrated in both carbon tetrachloride (CCl_4)- and paracetamol-induced liver injury models. In a CCl_4-induced hepatotoxicity study, a polyherbal formulation containing *P. integerrima* (400 mg/kg) along with *Galium aparine* and *Berberis lyceum* significantly restored altered liver enzyme levels (AST, ALT, and ALP), with greater protection observed when the formulation was administered after toxin exposure.¹⁸ Similarly, the methanolic fruit extract of *P. integerrima* (200 and 400 mg/kg) significantly reduced serum ALT, AST, and ALP levels in paracetamol-induced hepatotoxic rabbits, confirming its hepatoprotective efficacy.[22]

Nephroprotective Activity:
The methanolic fruit extract of *P. integerrima* demonstrated nephroprotective activity in paracetamol-induced nephrotoxic rabbits. Treatment with 200 and 400 mg/kg of the extract significantly improved renal function by reducing serum creatinine and urea levels, enhancing urine output and renal clearance, and restoring normal renal histoarchitecture, indicating its protective effect against drug-induced kidney injury.[23]

Antidiabetic Activity:
Pistagremic acid, a bioactive constituent isolated from the methanolic gall extract of *P. integerrima*, exhibited significant

in vitro α-glucosidase inhibitory activity against both rat intestinal and *Saccharomyces cerevisiae* enzymes, with IC_{50} values of 62.47 µM and 89.12 µM, respectively. By inhibiting α-glucosidase, the compound may reduce intestinal glucose absorption, indicating promising antidiabetic potential comparable to α-glucosidase inhibitors such as acarbose.[24]

Anticonvulsant Activity:

The anticonvulsant activity of *P. integerrima* was evaluated using petroleum ether and methanolic extracts in zebrafish and Wistar rat models. The petroleum ether extract produced dose-dependent protection against pentylenetetrazol-induced seizures in zebrafish and significantly delayed seizure onset while reducing maximal electroshock-induced hind limb extension in rats. In contrast, the methanolic extract showed minimal anticonvulsant activity, suggesting that the active anticonvulsant constituents are predominantly present in the non-polar fraction.[25]

Toxicological Profile

Toxicological profile of Pistacia integerrima has been studied in acute and sub-acute animal studies. The acute oral toxicity study was performed according to OECD Guideline 425 and single oral dose of 2000 mg/kg of methanolic extract was administered and it did not cause mortality, behavioral abnormality or signs of toxicity during 14 days observation in Wistar rats. In the 28 day repeated dose toxicity study (OECD Guideline 407), the oral administration of the extract at doses of 250, 500 and 1000 mg/kg/day did not cause any significant changes in the body weight, hematological or biochemical parameters, or histopathological architecture of major organs, which suggests a favorable safety profile with a no-observed-adverse-effect level (NOAEL) within the tested dose range.[26] A detailed review also reported that animal studies indicate the methanolic extract is safe at therapeutic doses, although doses around 1,500 mg/kg may be the limit of toxicity. However, long-term toxicity studies and properly designed clinical safety assessments are still needed before it could be therapeutically used in a broad range.[1]

3. Conclusion

Kakda Singhi (Pistacia integerrima J. L. Stewart ex Brandis) is a popular Unani medicinal drug traditionally used for the management of respiratory, gastrointestinal and inflammatory disorders. Its classical Unani actions, especially as an expectorant, antitussive, lung tonic and anti-inflammatory agent are substantiated by modern pharmacological studies revealing antioxidant, antimicrobial, bronchodilatory, hepatoprotective and immunomodulatory activities. The presence of bioactive phytoconstituents further supports its therapeutic potential. However, more well-designed clinical studies and standardization of formulations are required to confirm its safety, efficacy and quality. The application of traditional Unani knowledge with modern scientific research will promote the evidence-based use of Kakda Singhi in modern health facilities.

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