INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA):IJPS00]
Journal Homepage: https://www.ijpsjournal.com

OPEN ACCESS

Research Article

Karkatshringi (Pistacia Integerrima) : Significant Role In Cancer Treatment

Vaidyashiromani Dheeraj Sharma*[1], Pranshu Gupta[1], Tanishka Gupta[1], Rajesh K. Mishra[2], M. K. Yadav[3], Ramakant Marde[4]

[1] *B.A.M.S. Scholar, Patanjali Bhartiya Ayurvigyan Evam Anusandhan Sansthan, Patanjali Yogpeeth Phase 1 Haridwar, Uttarakhand, India.*
[2] *Assistant Professor, Patanjali Bhartiya Ayurvigyan Evam Anusandhan Sansthan, Patanjali Yogpeeth Phase 1 Haridwar, Uttarakhand, India*
[3] *HOD Of Ras shastra Department, Patanjali Bhartiya Ayurvigyan Evam Anusandhan Sansthan, Patanjali Yogpeeth Phase 1 Haridwar, Uttarakhand, India*
[4] *HOD Of Dravyaguna Department, Patanjali Bhartiya Ayurvigyan Evam Anushandhan Sansthan, Patanjali Yogpeeth Phase 1 Haridwar, Uttarakhand, India*

ARTICLE INFO

Received: 15 Feb 2024
Accepted: 19 Feb 2024
Published: 20 Feb 2024
Keywords:
Antitumour, Anticancerous ,Cytotoxic, Michigan Cancer Foundation-7 cell line, Pistacia integerrima, Phytochemistry, Galls, Constituents, Toxicity , Karkatshringi, Physiochemical analysis, KARKA ROGA NASHINI
DOI:
10.5281/zenodo.10684897

ABSTRACT

Karkatshringi is an excellent and effective medicine of ayurvedic medical science. It is used in treatment of many diseases but it proves to be one of the best cure for cancer .Karkatshringi is also called 'Baal Bhaisajya' . According to the ayurvedic scriptures, it works specifically on glands and their secretions . It plays a significant role in balancing the aggrevated doshas in the body and maintains the health. Karkatshringi is used in preventing the growth of tumours. Due to the dominance of tikta rasa, it exhibits anti-viral and anti-fungal properties. Karkatshringi is the only medicine of ayurveda science which we can use uninterruptedly in cancer treatment. According to ayurveda science, karkatshringi also exhibits the qualities similar to its nomenclature such as in sanskrit language, cancer or arbuda is called as Karka Roga and being karka the first name of karkatshringi , it is also known as "KARKA ROGA NASHINI". It implies that the medicine which suppress the cancerous or tumourous cells in the body is known as KARKATSHRINGI or KARKA ROGA NASHINI . Karkatshringi has the anti-cancerous properties that prevents the growth and spread of tumours and cancer ; and took the body to its natural healthy state. Karkatshringi due to its fundamental properties works as a dextoxification agent and balances the vitiated doshas . Being kaphaghna and vatashamak , it act to be the anti- tumourous and anti-cancerous agent ; that is why

***Corresponding Author:** Vaidyashiromani Dheeraj Sharma
Address: *B.A.M.S. Scholar, Patanjali Bhartiya Ayurvigyan Evam Anusandhan Sansthan, Patanjali Yogpeeth Phase 1 Haridwar, Uttarakhand, India.*
Email : Thedheerajsharma1@gmail.com
Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

karkatshringi has a specific place in ayurveda science .

INTRODUCTION

As per Ayurveda, karkatshringi is the most important medicinal plant. The galls of Pistacia integerrima are typically used in the treatment of paediatric disease. According to Acharya Charaka, the plant consists of the Hikkanigrahan and Kasaharagana, which are explained in VatajKasa and Kapha [1]

Fig.1 Karkatshringi (Pistacia integerrima)

Pistacia integerrima is a single stemmed, multibranched, and deciduous tree belonging to the family of Anacardiaceae.[2] This plant is found in native to Asia broadly circulated in West Himalaya to Kumaon, East Afghanistan, Northwest, and Pakistan.[3] Furthermore, in the Siwalik ranges/Rohilkhand,[4] zebrawood and crab' s claw are the widespread names intended for this medicinally vital plant species though it has various vernacular names in the Pakistan (thoak, khanjar, and shnai) along with India (kakarsinghi, kakroi, kakra, kakar singhi kakring, and kakkar) in Tables 1 and 2[5] The plant is well-known as kakra in Hindi, chakra, shikari, and chandraspada in Sanskrit Table 3,[6,7] worms make typically hornshaped galls on the leaves and branches. These galls consist of a pinkish, pale greenish, and brown horn shaped, curved or straight, twisted, elongated, and hollow, while young they are coriaceous, however, afterward become hard. This gall is caused through the insect Dasia aedifactor (Homoptera), (plant produce resin against insect). They create these galls beside sucking juice as of the leaves. Then, they are called karkatshringi.[8] The galls are well thought-out as store houses of secondary metabolites so have consequence in Indian established medicine system.[6] Leaves are ovate and board and are present in pairs. Flowers are red in color and small. Fruits are brown in color when mature and shiny. The rugose, horn-shaped, and hollow galls similar to excrescences are used intended for medicinal purposes and they have a bitter taste and very sharp. The galls are astringent aromatic and have elevated value in Ayurvedic medicines as a remedy intended for asthma, fever, psoriasis, pharyngitis, phthisis, dysentery, ulcers, general debility, dyspepsia, skin diseases, leprosy, anorexia, vitiated condition of tridosha, inflammation, leukorrhea, irritability of stomach, and other disorders for the respiratory tract, vomiting of children, in high cough, modern medicine for the treatment of diseases which are fever, scorpion sting, and snakebite. The bark and galls of the plant have a number of secondary metabolites containing anti-inflammatory, antimicrobial, antibacterial, and analgesic activities[9,10] and hyperuricemic effect.[11] Chemically, it has sterol,[12,13] flavonoids,[14,15] monoterpenes,[12,16-20] and dihydromalvalic acid and the leaf galls used for rejuvenator are well known along with endorsed to antioxidant pro to being there of flavonoids and phenolics.[21] Majorly, a gall includes tannins, resins, tetracyclic triterpenes, dihydromalvalic acids, camphene, amino acids, sterols, pistacienoic acid, pistancin, luteolin, and pistacinin.[22] At the

time of teething in children, it is also very helpful. It has been informed to have hyperuricemic effect disorder, analgesic anti- inflammatory activities, and depressant.[23] Pistacia integerrima has altitude between 12,000 and 8000 feet and 10–12 m in height[24] and large pinnately compound leaves, with many branches, single stem. Twenty-five cm long leaves consisting of lanceolate leaflets 2–6 pairs. Flowers are arranged in panicles band reddish in color. Globular fruits consist purple to blue in color 4–6 mm diameter.[25,26]

TABLE 1 : CLASSICAL CLASSIFICATION

Caraka	Madhur skandha, Hikkanigrahana, and Kasahara
Sushruta	Padmakadi and Kakolyadi
Vagbhata	These medicinal plants were described in Kesave Paddhati. Both caraka and Sushruta consider this plant as a poison for a vegetable origin. Acharya Sushruta kept this plant in Visa khand. Similar confusion is apparent in the context of Gunja which is categorized under Mula visa (root poison). Caraka interpreted it as amalaka and the toxic symptoms are mentioned by Acharya Sushruta. Likewise, Dalhana's comments add more confusion about its identification since Mesasringi, Ajasringi, and Uttamarni are equated to Karkatshringi because, the Asclepiadaceae family may have the same synonyms (Jivanti).[26]

TABLE 2 : THE OTHER NAMES OF PLANT

Sr. No.	Language	Names
1	English	Crab's claw
2	Hindi	Kakra, Kakarsingi, Kakkatasimgi, and Kakdashingi
3	Urdu	Kakra and Kakrasinghi,
4	Bengali	Kakrashingi, Kandashringi, and Kakra
5	Assam	Kakiasrngi
6	Bengali	Kakra, Kandashringi, and Kakrashingi
7	Gujarati	Kakadasingi, Kakarshingi, and Kakra
8	Punjabi	Tanbari, Kakar, Kangar Masna, Kakala,
9	Malayalam	Karkarshingi, Shne, Gurgu, Kakkeran, Tungu, Kakkrangehe, Sumak, and Drek
10	Telugu	Karkktakasingi and Karkatasringi,
11	Tamil	Kakarasimga, Kakarashingi, and Kakatakashrungi
12	Oriya	Kakkatashingi, Karkata, and Singi

TABLE 3 : AYURVEDIC PROPERTIES

Parameter	Properties
Rasa	Tikta (Pungent)
Veerya	Ushna (Hot)
Vipaka	Katu (pungent)
Effect on tridosha	Pacifies Kapha and Pitta[27]

Broad Features :

P. integerrima consists height up to 18 m and the barks are blackish or dark gray. Distinctive galls are formed on the leafy branches. Flowers are dioecious, small, unisexual, and reddish. Female flowers have long lax panicles. While male panicles short, compact, Drupe globose, rugose, wrinkled and gray while ripe. The leaves vary, pinnate, 15–23 cm long, with or without terminal leaflet, leaflets 4–5 pairs, acuminate, lanceolate, coriaceous, sub-opposite, and 7–12 cm long .

Table 4: Macroscopic importance of Pistacia integerrima

Parts	Administration mode/ form	Uses	Reference
Stem/ branches	Topical	Stem resin as wound healer	[28]
Bark	Decoction	Hepatitis and jaundice	[28]
Galls	Roasted galls with honey taken orally	Cough, asthma, and diarrhea, Hepatitis, snakebite, and scorpion sting	[10,29]
Fruits	Raw form, fresh fruits crushed in water and taken orally	Edible, jaundice, and hepatitis	[28]

Chemical Constituents :

The karkatshringi contains various chemical compounds, commonly in its galls. It contains 60% tannin and 1.2% volatile oil. It contains tetracyclic triterpenes, resin, pistacieonic acids A and B, essential oils, camphene, caprylic acids, cineol, α- pinene and others [30]. Leaves and bark are rich in tannin. Seeds contain amino acids, triterpenoids, proteins, sterols, and dihydromalvic acid [31] . The galls contain pistagremic acid, which acts as a natural terpene inhibitor of β-secretase [30,32] . The leaves contain carotenoids, triterpenoids, flavonoids, and catechins. Pistacia integerrima essential oil separated using gas chromatography and mass spectrometry contains a high concentration of 1- terpinene-4-of (28.82%), p-me then-8-ol (43.38), noctyl acetate (19.91%) and beta-Farnesene (7.88%) [33] . 91% of the oil consists of monoterpenes, including α-pinene, β-pinene, limonene, cineol, and sabinene. Oil is laevorotatory, which indicates that it incorporates hydrocarbons. It includes positive phenolic compounds, specially pistiphloroglucinyl ester and Pistacia phenyl ether [30,34,35] On the galls extract of P. integerrima, different isolation studies were conducted, which led to the purification of hydroxydecanyl arachidate, pisticialanstenoic acid, β-sitosterol, octadecan-9, and 11-diol-7-one, an[10,36] Phenolic components were characterized as 3’-(1,3-dihydroxy-5-phenoxy-1’,5’- dimethoxbenzene (pisticiphloro-glucinyl ether), 2, 4’-phenoxy-n-butyl-1’-(3- oxy5-hydroxy) benzoic acid (pistaciaphenyl ether). Ethyl gallate which was isolated from galls of P. integerrima shows good antiinflammatory diseases .

Pharmacological Action:

Karkatashringi galls are used in traditional medicines in India for the treatment of asthma, chronic bronchitis, phthisis, diarrhoea, fever, and other reported activities such as antispasmodic, carminative, antiamoebic and anthelmintic. It is used for its phytotoxic, antibacterial, anti-cancer, anti-inflammatory, antiasthmatic, anti-diarrheal, anticonvulsant, antioxidant, etc Activities [37] .

Chemotherapeutic Activity:

Pistacia integerrima galls have anticancer properties. The crude extract of Pistacia integerrima has cytotoxic activity against the human bosom growth cell line Michigan Cancer Foundation-7. The crude extract of this plant's stem is effective against antitumor activity. The methanol extract of pistacia integerrima acts against the MCF-7 human breast cancer cell line. Gold particles are reduced and stabilized by Soursop and exhibited greater inhibition against breast cancer cells. The cell was maintained in Dulbecco Modified Eagle Medium (DMEM) supported with fetal bovine serum (FBS), penicillin, streptomycin, and L-glutamine at the

temperature of 370C, humidity of 95%, and under 5% CO2. The pistacia integerrima galls extract in a different solvents like hexane, chloroform, and ethyl acetate fractions are used against human cervical cancer (HeLa) and baby hamster kidney (BHK–21) cell lines. Pistacia integerrima methanol extract inhibits the growth of the MCF-7 human breast cancer cell line. Soursop reduces and stabilizes gold particles, resulting in greater inhibition of breast cancer cells. The cell was grown in Dulbecco Modified Eagle Medium (DMEM) supplemented with foetal bovine serum (FBS), penicillin, streptomycin, and L- glutamine at 370°C, 95% humidity, and 5% CO2

Anticancer Activity:

As per the studies , the extract of Pistacia integerrima (PI), preferentially reduces the viability of lung cancer cells A549 and NCI-H460. At nonlethal quantities, PI reduced the ability of lung cancer cells to form colonies, spheroid forms, and spread throughout the body. The extract was characterized using UPLC/QToF-MS and then confirmed the results using UHPLC to pinpoint the phytomolecule that gives PI its anti-lung cancer effects. UPLC/QToF-MS was used to determine the gallotannin penta-O-galloyl-D-glucose (PGG), among others. PGG shows promise as a chemopreventive agent for a variety of cancers. PGG has been shown to slow the progression of lung cancer, although its exact mode of action is yet unknown. Even without intracellular ROS activation, bioactivity-guided column fractionations allowed for identifying PGG as the primary phytochemical that controlled PI-mediated AMPKULK1-dependent autophagy and death. In addition, the study showed that PI and PGG activated ERK and inhibited STAT3 to cause apoptosis via the caspase-3 and PARP 1 pathways. Overall, the results shows that PGG, a plant extract found in the PI extract, significantly inhibits lung cancer progression by changing the ERK/AMPKULK1/STAT3 signalling axes [38] The crude methanol extract of Pistacia integerrima showed moderate cytotoxic, good antitumour and weak antifungal activities, whereas fractions exhibited varying cytotoxic activity against human breast cancer MCF-7 cell line. The crude extract exhibited tumour inhibition on potato discs in a dose-dependent manner. The minimum inhibition (8.1%) with average number of tumours 3.4 was observed at a concentration of 10 ppm. At 100 ppm, 40% tumour inhibition was observed with average number of tumours 2.2 whereas 86.4% inhibition was calculated at 1000 ppm, where average number of tumours was 0.5 per disc (fig. 2). The theoretically calculated IC50 was ~125 ppm. The tumorigenesis occurs in the living systems both in animal and plants[39]. The tumour inhibition on potato discs through methanol extract envisages the potential of P. integerrima against cancer cell lines.

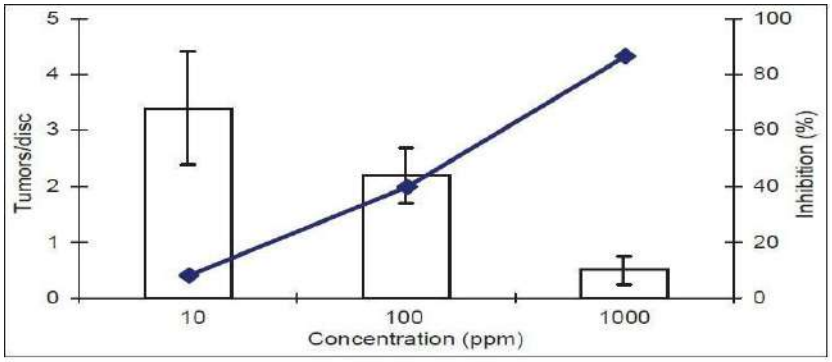

Fig. 2: Antitumour activity of *Pistacia integerrima*.
Antitumour activity of *Pistacia integerrima* against potato disc assay. The error bars represents standard deviation (▭) Numbers of tumors/ disc, (—●—) % Inhibition

Anticancer potential was further confirmed by subjecting the crude extract of P. integerrima against MCF-7 cell line. The crude extract of P. integerrima showed moderate cytotoxicity in a dose-dependent manner up to 100 µg/ml concentration with a maximum inhibition of 55.4±2% at this concentration (fig. 3). At much higher concentrations (100 to 500 µg/ml), cytotoxicity of P. integerrima crude extract against MCF-7 cell line was static. The dose-dependent activity of extracts has also been reported in Sandoricum koetjape (Meliaceae)[40], Tinospora cordifolia (Menispermaceae)[41] and Aspidosperma tomentosum (Apocynaceae)[42]. The theoretically calculated IC50 value was ~90.9 µg/ml.

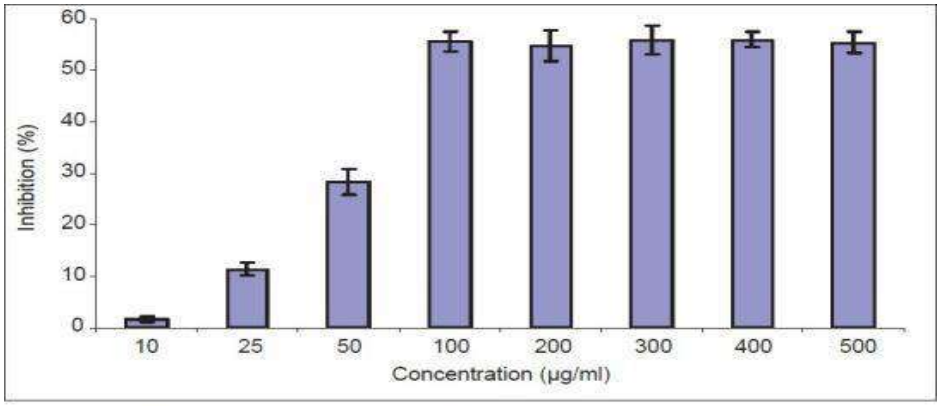

Fig. 3: Cytotoxic activity of crude *Pistacia integerrima*.
Cytotoxic activity of crude *Pistacia integerrima* methanol extract against MCF-7 human breast cancer cell line. The error bars represents standard deviation

The crude extract was fractionated, and the fractions at a concentration of 200 µg/ml were also tested against MCF-7 cell line. The highest inhibition (100%) was calculated in ethyl acetate fraction followed by chloroform fraction (97.4±1.5%). The other three fractions showed moderate activity. Hexane fraction demonstrated 58.2±2% activity whereas methanol and aqueous fraction showed almost equal activities 57.6 and 58.1%, respectively (fig. 4). Similar results were also found in studies on bioactivities of Nephelium longan where all fractions proved active, whereas maximum cytotoxic activity was shown by ethyl acetate and chloroform fractions[43]. The ethyl acetate fraction of Bacopa monnieri extract was also found more potent among other tested extracts[44]. These results also proved that the fractions of P. integerrima are remarkably more active compared to its crude extract. Similarly fractions of Vitex negundo (Lamiaceae) were also found more cytotoxic in comparison with crude extract of that plant[45].

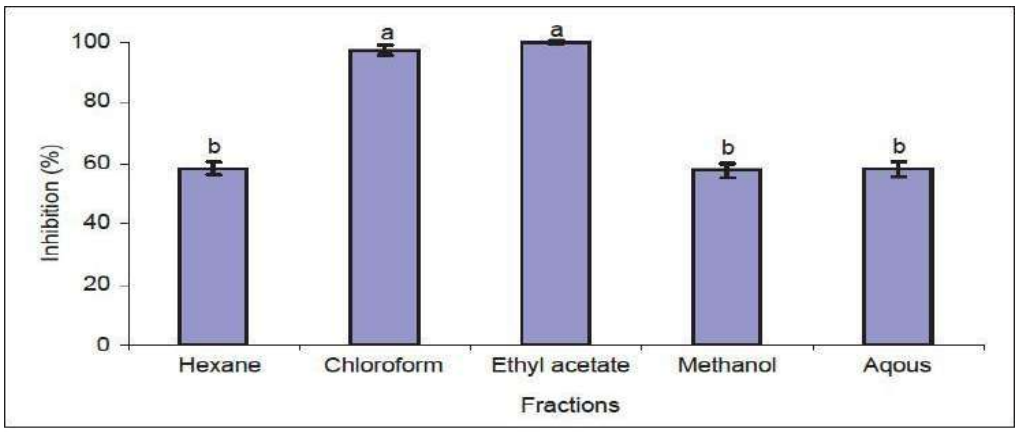

Fig. 4: Cytotoxic activity of fractions of *Pistacia integerrima* methanol extract.

Cytotoxic activity of fractions of *Pistacia integerrima* methanol extract against MCF-7 human breast cancer cell line. The error bars represents standard deviation. The alphabets on the bars present statistical difference in values obtained after least significant difference at $P<0.0$

The usefulness of Karkatshringi in Ayurvedic Formulation :

Karkatshringi is one of the key components of various types of Ayurvedic formulations like Shringiadi Chura, Karkatadichurna, Brihat Talisadechurna, Kumari Asava, Kumari Kalp, 19 Devadar vayadi kwath churna, shatavaryadighrit, chayanprash-awaleha, Dashmularista, Kantakaryavaleha, Siva gutika and khadiradigutika, which are used in various therapeutic purposes. Karkatshringi with kanchnaar shows effective anticancerous properties .

CONCLUSION :

In view of its wide range of phytochemical constituents along with bioactivities supported from its traditional uses; P. integerrima is a good for candidate of new drug synthesis. Pistacia integerrima is most commonly used for the treatment of cold, cough, fever, vomiting, and diarrhoea. The use of isolated crude essential oil for anticancerous, antioxidant and antibacterial for various types of bacterial infection. It should be properly identified and used for medicinal purposes. Methanolic extract of pistacia integerrima galls studied anticancerous , antiinflammatory activity in the in-vivo animal model. These drugs are useful in speeding up the cough suppressant, mucolytic, and expectorant. Pistacia integerrima essential oil component alpha-pinene, beta-pinene which helps to its anticonvulsant property. The present review offers a scientific basis for the traditional uses of the various extracts of P. integerrima. Recent research on this species shows that the bark of the plant shows promising anticancerous ,antibacterial as well as antiasthmatic activity. The main aim of this article is to enlighten the anti cancerous properties of Karkatshringi (Karka Roga Nashini)

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HOW TO CITE: Vaidyashiromani Dheeraj Sharma, Pranshu Gupta, Tanishka Gupta, Rajesh K. Mishra, M. K. Yadav, Ramakant Marde, Karkatshringi (Pistacia Integerrima) : Significant Role In Cancer Treatment, Int. J. of Pharm. Sci., 2024, Vol 2, Issue 2, 535-544. https://doi.org/10.5281/zenodo.10684897