IJPSR (2023), Volume 14, Issue 3 (Review Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 09 June 2022; received in revised form, 19 October 2022; accepted 20 November 2022; published 01 March 2023

KARKATSHRINGI (*PISTACIA INTEGERRIMA*): PHYTOPHARMACOLOGICAL REVIEW

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Keywords:

Pistacia integerrima, Karkatshringi, Physicochemical analysis, Pharmacological activity

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ABSTRACT: Karkatshringi ***(****Pistacia integerrima)* is an essential Ayurvedic medicinal plant belonging to the family Anacardiaceae. The plant originated in India and grows in the ranges of the north-western Himalayas. It is distributed over China, Afghanistan, Pakistan, and Nepal. The flowers of this plant is small and red, fruits are shiny and brown. Galls are hollow, horn-shaped, bitter and used for medicinal purposes. Gall powder is most commonly used in diseases such as cough, diarrhoea, fever, *etc*. also effective against staphylococci, pseudomonas and Escherichia coli bacteria. The different parts of the plant contain amino acids, sterols, alkaloids, flavonoids, tannins and saponin. In *Pistacia integerrima*, the volatile chemical constituents are extracted by hydro distillation or liquid-liquid extraction. *Pistacia integerrima*is associated with fungi which causes rust and blight diseases. Traditionally it is used for rheumatic pain, analgesic, and antipyretic effects. Karkatshringi is an important ingredient of Ayurvedic formulations like Chavyanprash, Dashmularista and Shringyadi Churna. Galls are used in the treatment of diarrhoea. Diabetic patients also use it. Essential oil of *Pistacia integerrima* was used for *in-vitro* studies like antioxidant activity, angiogenesis, and mast cell degranulation. Karkatshringi studied for its various activities such as anti-inflammatory, anti-oxidant, anti-bacterial, anti-cancer, anti-diarrhoeal, anti-convulsant, muscle relaxant, *etc*. This article includes detail information of *Pistacia integerrima* related to chemical constituents and pharmacological activities.

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]. As a moderate-sized, broadleaf tree, the karkatshringi can be found in Nepal, China, Afghanistan, Pakistan and the northwest& West Himalayas ranges [2].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.14(3).1063-70

This article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.14(3).1063-70

The plant grows between 900 and 1800 meters in height in a tropical climate [3, 4]. The *Pistacia integerrima* consists of numerous branches with large leaves. It is classified under the genus *Pistacia*. The genus *Pistacia* contains about 70 genera and, overall, six hundred species. The species of the genus *Pistacia*are called deciduous shrubs. The Persian name of *Pistacia integerrima* is Pestehmeans green almond in English [2, 5].

The bark produces scented liquid when pierced. On the leaves, there are galls. They are not a tree's growth but rather excrescences brought on by an insect called an aphis (*Dasia asdifactor*), a member of the Pemphigus genus, which lives inside the tree and feeds on its juice. These galls are horn-like, solid, and hollow inside [6]. They are typically cylindrical, tapering at both ends, outwardly greyish-brown and internally reddish-brown. The

galls are also known for storing secondary metabolites, including's steroids, flavonoids, tannins, saponins, and phenols [2, 7]. An average tree of 15-20 years old produces 0.40 kg of galls. Since, the methanolic extract of *Pistacia integerrima* was nontoxic, it is used in a variety of Ayurvedic medicines and illness therapies. In the repeated-dose toxicity look (OECD- 407) animals received each day dose of *Pistacia integerrima* extract for 28 days (4 weeks) [8]. *Pistacia integerrima* is at risk of several fungal diseases. During a normal mycological survey conducted between July 2013 and June 2014, rust and blight-causing fungi were discovered on the leaves of *P. integerrima*. Three fungus, identified as *Skierkahimalayensis, Pestalotiopsis sp*., and *Pileolaria pistaciae,* were discovered to be the perpetrators behind the rust and blight infections, according to morphological and microscopic investigations. For the first time, *Skierka himalayensis* sp. and Pestalotiopsis sp., two new species of rust fungi, are reported from India [9].

Thekarkatshringi is the main ingredient in the Bal-Guti, Brihattalishadi Churna, Karkatadi Churna, and Balachatur Bhadra. *P. integrrima*is is well known as an antidiarrheal in Indian conventional medicinal drug [10]. The galls of the plant are also beneficial in pelvic inflammatory disorders, diarrhoea, fever in children, excessive bleeding in menstruation and many more. The methanolic extract of *Pistacia integerrima* has shown anti-inflammatory activity in acute and chronic phases of inflammation [11]. Thecyclo-oxygenase (COX) pathways of arachidonic acid metabolism, which are responsible for prostaglandin synthesis, are suppressed by analgesic and anti-inflammatory medications [12].

The aqueous extract of *Pistacia integerrima* is effective in the treatment of hepatic injury caused by carbon tetrachloride in rats. The *Pistacia integerrima* ethyl acetate and chloroform fractions are strong cytotoxic fractions [13]. The effect of pistagremic acid isolated from the galls of *Pistacia integerima* in acute toxicity and gastrointestinal (GIT) motility tests, showed a strong dose-dependent reduction in GIT motility with considerable safety [14]. Gold nanoparticle developed by the interaction between *P. integerrima* gall extract and hydrated hydrogen tetrachlorocuprate have antimicrobial activity against *Klebsiella pneumonia, Bacillus subtillis, Aspergillus niger* and *Staphylococcus aureus* [15]. The gold nanoparticles' UV-Vis spectra showed surface plasmon resonance at 540 nm, and SEM analysis showed that the particles were between 20 and 200 nm in size. Alcohols, amide groups, and amines contributed to the capping and reduction of gold nanoparticles, according to FTIR spectra. In a variety of NaCl and pH solutions and at high temperatures, Au-NPs demonstrated outstanding stability. As seen from their zone of inhibition and considerable attenuation, Au-NPs have high antifungal activity and antinociceptive and muscle relaxant effects. Au-NPs were tested for enzyme inhibition, antibacterial, antifungal, antinociceptive, muscle relaxant, and sedative activities [16].

Balachaturbhadra Churna has many health advantages and combines four Drugs Musta, Pippali, Ativisha, and Karkatshringi. This Churna is a very popular and beneficial compound formulation in paediatrics [17].

Bronchial Asthma is a troublesome condition that can affect the population irrespective of age, sex, economic status, etc. Shringyadi Churna contains the most potent ingredients: Karkatshringi, Pushkarmool, Shati, Musta, Pippali, Marich, Shunthi, and Sharkara are in totality responsible for its anti-asthmatic properties and adding to the potency the anupandravya are Guduchi, Vasa, etc. *Pistacia integerrima* was studied for anti-asthmatic activity also [18]. The aqueous and methanol extracts of *Pistacia integerrima* possess the potential of significant immunomodulatory and adaptogenic activity [19].

Vernacular Name [18]:

- **Latin name:** *Pistacia integerrima*
- **English name:** Crabs Claw and Zebrawood
- **Sanskrit name:** Sringi, Karkatsringi, Kulirvishanika, Ajsringi, Karkatakhya
- **Urdu name:** Kakarasingi
- **Hindi name:** Kakadasrngi
- **Panjabi name:** Kakar, Kakarsingi
- **Kannada:** Kakadshingi
- **Marathi:** Kakadshringi, Karkatshringi.

Ayurvedic properties [13]:

- **Taste:** Bitter and Astringent
- **Physical Properties:** Dry
- **Potency:** Hot
- **Metabolic Property:** (after digestion)- Pungent.

Taxonomical position [18]:

- **Kingdom:** Plantae
- **Phylum:** Tracheophytes
- **Division:** Angiosperm
- **Subdivision:** Eudicots
- **Class:** Rosides
- **Order:** Sapindales
- **Family:** Anacardiaceae
- **Scientific name:** *Pistaciaintegerrima.*

Morphological Characters: *Pistacia integerrima* is a multi-branched deciduous tree approximately 40 m in height. Each leaf is 25 cm long and 1 to 3 inches wide, with ovate-shaped lanceolate leaflets with 2 to 6 leaflets. The bark of this tree is grey or light brown. Flowers are small reddish in colour and dioecious. Flowers are 0.2 cm wide, yellow or brownish. The fruits are globular, shiny, purplish-blue and are approximately 5-6 mm in diameter when mature. Galls can be found on the leaves of a tree, which are produced by an insect called Aphis (*Dasia asdifactor*), which lives inside and absorbs the juice of the tree. This insect produces hard, horn-like structures that are hollow inside. Its exterior is greyish brown and its interior is reddish-brown. The size of the gall'sranges from 2.5 to 30 cm long [10].

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 [20]. Leaves and bark are rich in tannin. Seeds contain amino acids, triterpenoids, proteins, sterols, and dihydromalvic acid [5]. The galls contain pistagremic acid, which acts as a natural terpene inhibitor of β- secretase [7, 20]. 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), n-octyl acetate (19.91%) and beta-Farnesene (7.88%) [21]. 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 [11, 20, 22].

Ethnobotanical uses: *Pistacia integerrima* is a plant that has historically been used in a variety of treatments and is thought to have the ability to heal common illnesses like coughs, appetite loss, dyspeptic vomiting, phthisis, asthma and dysentery. *Pistacia integerrima* galls have a fragrant bitter taste and are used as a tonic and expectorant. In northern Pakistan, roasted galls are taken with honey to treat cough, asthma, and diarrhoea. Additionally, Pakistan uses galls to treat hepatitis and other liver diseases. Galls are frequently used in conjunction with other medications to treat snakebite and scorpion stings. In some parts of Pakistan, the extract from the boiled bark of *Pistacia integerrima* is used to treat hepatitis and jaundice. Stem resin is used in wound healing. Also used in nose bleeding, vomiting, diarrhoea, and loss of appetite. Fruits can be eaten and utilised to treat liver problems. *Pistacia integerrima* stems and branches are utilised for construction and aesthetic purposes in addition to traditional therapeutic purposes. *Pistacia integerrima* leaves are utilised as livestock feed. The generation of coal and fuel benefits from the roots. The stems are additionally employed in the management of back pain [23].

Medicinal Property: In Ayurveda, for medicinal purposes, the powder of galls is used alone or with other herbs. *Pistacia integerrima* galls powder is marketed as Shringyadi Churna for use in the treatment of asthma. The Chyawanprash containing *Pistacia integerrima*g alls powder is used for digestive, bronchodilator and antitussive activity. It has been used for the treatment of different conditions such as diarrhoea, cough, asthma, fever and as blood purifier, remedies for vomiting, expectorant. Antibacterial, antioxidant and cytotoxicity of different parts of this plant is due to

its chemical compounds mainly terpenoids, saponin, phenols and sterols which are released by the plants as secondary metabolites. *Pistacia integerrima* galls have CNS depressant activity. Karkatshringi is spermatogenic and given for improving vigour and vitality. For this purpose, the paste of karkatshringi is given with milk [24, 25].

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, anti-asthmatic, anti-diarrheal, anticonvulsant, antioxidant, *etc* Activities [10].

Antibacterial Activity: Gall extracts of *Pistacia integerrima* has more antibacterial activity than other parts of the plant. The karkatshringi had inhibitory action against *E. coli* bacteria and *Vibrio cholera* [2]. The antibacterial activity was done by agar diffusion method. The culture is taken in the form of triplicates at an incubation temperature is 37^0 C for 24 to 72 hrs. After the incubation period, the diameter of the zone of the inhibition of microbial growth was measuredon the plate in millimeters (mm) [25]. Au-NPs were checked for antibacterial activity against *Klebsiella pneumonia, Bacillus subtillis* and *staphylococcus aureus* as well as forantifungal activity using the agar well diffusion method [16]. Theethanolic gall extract in 200µL concentration formed a maximum zone of inhibition of 25mm against *Bacillus subtilis* and Proteus Vulgaris. *Bacillus subtilis* is a Gram-positive spore formed by bacteria that is caused by food spoilage, its spores are difficult to kill but *P. integerrima* completely inhibits bacterial growth. The crude extract of *Pistacia integerrima* shows more effectiveness against antibacterial strains, including 69.6% inhibition of *S. Setubal* and 65.5% inhibition of *Pseudomonas pickettii* [25].

Phytotoxic Activity: Phytotoxic activity can be used to develop herbicides. Allelochemicals are produced when dead organs decompose in the environment or when plant tissue is extracted. These allelochemicalsact as secondary metabolites in the plants which are known to have allelopathic effects on other plants. This chemical inhibits the growth of weeds without any effects on the main crop. The phytotoxic activity is shown by ethyl acetate with 90% growth inhibition, chloroform with 70% growth inhibition, and methanol with 60% growth inhibition at the concentration of 500ppm.[4]

Anticancer Activity: As per the research by Acharya Balkrishna *et. al.*, 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 AMPK-ULK1-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/AMPK-ULK1/STAT3 signalling axes [26].

Anti-asthmatic Activity: *Pistacia integerrima* shows anti-asthmatic activity, inhibition of histamine release, and 5-lipoxygenase activity. Bronchial asthma is due to the contraction of smooth muscle in response to multiple stimuli resulting in the release of chemical mediators like ACh and citric acid. *Pistacia integerrima* acts as an expectorant and helps in the clearance of mucus from airways, lungs, bronchi, and trachea. It is also used quite well in whooping cough in children. It also manages the hiccough.

In Unani system of medicine, karkatshringi is used in combination as well as single formulation. Unani physicians have been treating asthma disease for

thousands of years. It is known to help in cough and asthma and it gives strength to mucus membrane [27]. The essential oil of *Pistacia integerrima* (EOPI) contains tetracyclic triterpenoids and can be effective in an animal model in bronchial asthma for acute and chronic inflammatory conditions. *In-vivo* study of the essential oil of *Pistacia integerrima* on rats shows improvement of LPS-induced lung inflammation (neutrophilia), containing inhibition of protein level. While *Pistacia integerrima* essential oil inhibits 5-lipoxygenase, L-type voltage-gated Ca channel, and DPPH oxidation in an *in-vitro* research on guinea *pig ileum*. The aqueous extract of *Pistaciaintegerrima* exhibits antiasthmatic activity by stabilizing the mesenteric mast cell membrane. *In-vitro* study of *Pistacia integerrima* in aqueous extract acts as bronchoconstrictor by inducing histamine in the guinea pigs [28].

Anti-diarrheal Activity: *P. integerrima* galls extracts showed marked antidiarrheal activity against castor-oil-induced diarrhoea. The isolated flavonoid from *Pistacia integerrima* galls has strong protection against diarrhoea. Karkatshringi helps to manage diarrhoea and stops the infection-causing bacteria in the large intestine. The *Pistacia integerrima* galls extract and isolated compound acts as antidiarrheals by inhibiting mu and delta-opioid receptors [29].

Hepatoprotective Activity: Uttari *et al.* studied the antioxidant and hepatoprotective activity of isolated compounds from *Pistacia integerrima*. Liver disorders are mainly due to Free radicals. *P. integerrima* had revealed presence of phenolics and flavonoids. The compounds isolated from the ethyl acetate fraction of methanol extract of *Pistacia integerrima* were subjected to determination of antioxidant activity by DPPH free radical activity, reducing power assay, scavenging of hydroxyl radicals *etc*. Antioxiants have good hepatoprotective activity; therefore, the isolated compounds were subjected to *in-vitro* hepatoprotective studies using paracetamol-induced hepatotoxicity in primary rat hepatocytes. By evaluating the change in hepatocyte viability as well as other factors including glutamic transaminase, glutamic pyruvic transaminase and total protein, *in-vitro* hepatoprotective efficacy was evaluated. The fractions restored the changed parameters in the chosen *in-vitro* model, demonstrating a strong protective impact. The fractions isolated from the ethyl acetate fraction of methanol extract of *Pistacia integerrima* showed presence of phenolics and flavonoids which are potent antioxidants. The hepatoprotective activity of the plant may be through its antioxidant potential [30].

Anti-inflammatory Activity: The gall's chloroform fraction contains Flavonoids, which show anti-inflammatory activity during assessment time. The anti-inflammatory potential of *Pistacia integerrima* against carrageenan-induced paw edema. The methanolic extract of *Pistacia integerrima* galls determines the anti-inflammatory activity on the animal model by the *in-vivo* method [34]. It possesses anti-inflammatory activity in acute and chronic phases of inflammation. The galls extracts had significant protection against thermal-induced algesiain a dose-dependent way [31].

Anticonvulsant Activity: *Pistacia integerrima* has anticonvulsant activity due to its ability to block sodium channels. The essential oil component in *Pistacia integerrima* (α-pinene, β-pinene and 4-carvomenthol) is responsible for its anticonvulsant activity. PTZ and MES are the preliminary tests used to determine the anticonvulsant activity. These tests are used to determine whether drugs are effective against tonic-clonic seizure and human generalized absence [32].

Action on the Gastrointestinal Tract: *Pistacia integerrima* has carminative and astringent properties, it helps to reduce flatulence in the gastrointestinal tract [23]. The effect of pistagremic acid isolated from Pistacia integerrima's galls is a strong reduction in gastrointestinal motility. Pistagremic acid caused a dose-dependent reduction in the strong anti-GIT motility effect. It has been obtained that the obstruction of muscarinic receptors in gastrointestinal motility has unsettled effects on the GIT smooth muscle motility [14].

Anti-oxidant Activity: *Pistacia integerrima* galls were rich in phenol and flavonoid content and possessed high anti-oxidant activity. Ethanolic extract was considerably more effective for extracting radical scavenger molecules.

There was a strong association between the higher antioxidant activities with that of higher total phenolic and flavonoid content in the ethanolic leaf gall extracts of *P. integerrima*. Hence, the folklore use of *P. integerrima* leaf gall extracts as a natural antioxidant was confirmed and justifies the ethnobotanical approach in the search for novel bioactive compounds. So, the more utility of *P. integerrima* leaf gall extracts for medicinal health, functional food and nutraceuticals applications due to their antioxidant properties [33].

Other Activities: *Pistacia integerrima* galls are quite good in the problem of edema. It helps to reduce fluid accumulation in the tissues. In contrast, these galls are also helped to provide relief from a problem like swelling in the legs, arms, hands, ankles, and feet which are associated with edema. *Pistaciaintegerrima* galls are useful in the gum diseases like pyorrhea and gingivitis. Decoction of galls is useful in the elimination of pus from gums also, it's anti-inflammatory activity to relieve pain [23].

Pistacia integerrima helps to control bleeding gums due to its astringent and healing properties. *Pistacia integerrima*is beneficial to supporting the health of the female reproductive system. It helps to eliminate debris and impurities after menstruation. According to Ayurveda, *Pistacia integerrima*is has valuable insymptoms of menstruation like pain or cramps. *Pistacia integerrima*helps these illness due to its Ushna and Vata-balancing properties [23].

Utility of Karkatshringi in Ayurvedic Formulation: Karkatshringi is one of the major ingredients 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. According to Acharya Charaka- important yoga in that karkatshringi is used.

Chitrakadi Leha: It is used to treat Kasa (Cough), Hridya rog (Cardiac disease), Shvasa (Asthma), and Gulma (Abdominal tumour, Distension). The karkatshringi is used in combination with other drugs like Tulsi, Pippalimool, Ganjpipal, Giloy, and Munakka.

DuhsparshadiLeha: This medicationis used to heal VatikaKasa. This medication is used together with karkatshringi- Nagarmotha, Pippali, Bharangi, and Kachoora.

Pathadi Yoga: It is used to treatkaphajaKasa. The other drug used for preparing this medication isSunthi, Shati, Pippali, Hingu, and Patha.

Leham Yoga: Also, it is used as kaphajaKasa. Other drugs combined with karkatshringi like Devdaru, Pippali, Nagara, and Rasna.

DuralabhadiLeha: It is used in vatajakasa. The karkatshringi combined with other drugs like Duralbha, Shringver, and Kachoor.

DashmooladiYevagu: It is used in the treatment of heart diseases, Kasa, parshavshoola (pain in the side of the chest), and hikka. Other drugs used in its preparation- are Dashmool, Kachoor, Rasna, Pippalimoola, and Amla.

NidigdhikaYusha: It is used for treating the patient Shvasa (Asthma) and tikka (hiccups). Other drugs used for its preparation like Duralbh, Gokshur, Guduchi, and Kultha.

Common Ayurvedic Formulation available in the market of Karkatshringi with their indications are Lala Dawasaz Herbal Hair Oil, Dusparshadi Yog (herbal compound) used in tropical pulmonary Eosinophilia, Astangavaleha [34, 35] Karkatshringi Churan or Powder gives antipyretic properties, Bharat Karkatshringi Tablets, Yuvika Kakra Singhi.

CONCLUSION: *Pistacia integerrima* is most commonly used for the treatment of cold, cough, fever, vomiting and diarrhoea. The essential oil of *Pistacia integerrima* used as antioxidant and antibacterial for various types of bacterial infection. *Pistacia integerrima* contains essential oil component alpha-pinene, beta-pinene which helps to its anticonvulsant property.

Methanolic extract of *Pistacia integerrima* galls hasanti-inflammatory activitystudied in the *in-vivo* animal model. Karkatshringi is used in various marketed formulations like KarkatadiChurna,

Brihat Palisade, Chawanprash, Shiva Gutika, and DevadavayadiChurna. The present article, therefore, offers a scientific basis for the phytochemistry, traditional, pharmacological uses of the various extracts of *Pistaciaintegerrima.*

ACKNOWLEDGEMENT: Authors are grateful to Marathwada Mitra Mandal's College of Pharmacy, Thergaon, Pune - 411033, for providing the necessary facility to carry out the study.

CONFLICTS OF INTEREST: NIL

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How to cite this article:
Kadam PV, Yadav KN, Karanje AS, Mukadam RJ, Giram DK and Patil MJ: Karkatshringi (*Pistacia integerrima*): phytopharmacological review. Int J Pharm Sci & Res 2023; 14(3): 1063-70. doi: 10.13040/IJPSR.0975-8232.14(3).1063-70.