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Manish Grover
Shuddhi Ayurveda, Jeena Sikho Lifecare Pvt. Ltd. Chandigarh, India

Correspondence:
Manish Grover
Shuddhi Ayurveda, Jeena Sikho Lifecare Pvt. Ltd. Chandigarh, India
Email:
shuddhi.research@jeenasikho.co.in

Pistacia integerrima (Shringi)- A Plant with Significant Pharmacological Activities

Manish Grover

ABSTRACT

Pistacia integerrima is an important medicinal plant belongs to the family *Anacardiacea.* It is commonly called as Crab's claw in English and Shani/Shringi in Hindi. It is a single-stemmed, dioecious tree widely distributed in countries like Nepal, China, Afghanistan, Pakistan, Armenia, North-west and West Himalayas. The plant has significant applications in the traditional systems of medications such as Ayurveda, Unani and Siddha. In addition, the plant is also used in many folkloric cultures around the world to treat a vast array of human ailments such as diarrhoea, dysentery, fever, vomiting, skin diseases, respiratory ailments and psoriasis appetizer, hepatitis and liver related disorders. The characteristic feature of the plant is its essential oil content comprised of many important phytochemical constituents such as alpha-pinene, camphene, di-limonene, 1:8-cineol, caprylic acid, alpha-terpineol and aromadendrene. However, the plant contains many other important secondary metabolites such as steroids, flavonoids, tannins, saponins and phenols which are associated with important pharmacological activities such as anti-bacterial, anti-oxidant, anti-inflammatory, cardio-protective, anti-cancer, anti-diarrhoeal, anticonvulsant and muscle relaxant. The aim of the present study is to summarize the recent pharmacological activities of *Pistacia integerrima* along with its utilization in traditional medication systems.

Keywords: Shringi, Rasapanchak, Pistagremic acid, Anti-bacterial, Anti-oxidant.

INTRODUCTION

Kingdom Plantae has been the most potent source of infinite valuable active ingredients of therapeutic and pharmacological significance [1, 2]. Among all the plants, medicinal plants have gained a lot of attention all over the world due their major role in the health care system as they are well recognized for maintaining physical and mental health as well as spirituality and thus, they have a major impact on the economy [3, 4]. One such important medicinal plant is *Pistacia integerrima* (figure 1). It is commonly known as Shani/Shringi in Hindi and Crab's claw in English. It belongs to the cashew family *Anacardiacea* family comprised of 500 different plant species distributed all over the tropical and warm regions of the world. The genus name *Pistacia* is originated from the Persian name 'Pesteh' which indicates the meaning of green almond. It comprises twenty different evergreen or deciduous plant species mainly shrubs and small trees with food, medicinal and ornamental significance. The species of this genus are usually dioecious except *P. atlantica* [5-7]. The genus is characterized by its high amount of terpenoids [8]. *Pistacia integerrima* is an important single-stemmed, dioecious plant of this genus evenly distributed in the Himalayan range. The plant is known for its galls as it is considered as the storehouse of secondary metabolites such as steroids, flavonoids, tannins, saponins and phenols. A phytoconstituent namely pistagremic acid (PA) present in the galls of the plant, is the known natural terpene inhibitor of β-secretase. The plant contains significant amount of essential oils such as alpha-pinene (25%), camphene (27%), di-limonene (4% − 5%), 1:8-cineol (10%), caprylic acid (15%), alpha-terpineol (20%) and aromadendrene (4% − 5%). It is extensively used as an herbal drug in the traditional medication systems like Ayurveda, Unani and Siddha and folkloric practices to treat numerous diseases like asthma, diarrhoea, dysentery, fever, vomiting, skin diseases, respiratory ailments and psoriasis appetizer, hepatitis, liver disorders, oxidative stress and counter hyperuricemia [9-15]. It is used in many important polyherbal Ayurvedic formulations such as dasamularista, chayavanaprasa, shringyadi leha and shringyadi churna. *Pistacia integerrima* has significant pharmacological activities such as anti-bacterial, anti-oxidant, anti-inflamamtory, cardiprotective, anti-cancer, anti-diarrhoeal, anticonvulsant and muscle relaxant. [16-19]. The vernacular names and taxonomic classification of *Pistacia integerrima* are given in table no. 1 and 2 respectively.

Figure 1: *Pistacia integerrima*

Table 1. Vernacular names [20]

English	Crab's claw
Hindi	Kakdashingi, Kakarsingi, Kakra, Kakkatasingi
Urdu	Kakrasinghi, Kakra
Punjabi	Kakar, Kakarshingi, Drek, Gurgu, Kakkeran, Kakkrangehe, Kakala, Kangar Masna, Sumak, Tungu, Tanbari, Shne,
Bengali	Kakra, Kakrashingi, Kandashringi
Gujrati	Kakadasingi, Kakra, Kakarshingi
Marathi	Karkadasringi, Kakra, Kakarsingi, Kakadshingi
Tamil	Karkata, Singi, Kakkatashingi
Telgu	Kakarashingi, Kakatakashrungi, Kakarasimga
Assam	Kakiasrngi
Malayalm	Karkatasringi, Karkktakasingi
Oriya	Kakadashrungi, Kakadashringi,

Table 2: Taxonomic Classification

Taxonomic Rank	**Taxon**
Kingdom	Plantae
Phylum	Tracheophytes
Order	Sapindales
Family	Anacardiaceae
Genus	*Pistacia*
Species	*integerrima*

Botanical Description [21]

It is a single-stemmed, dioecious tree with spreading branches that belongs to the family *Anacardiaceae*. The plant is deep-rooted and can grow up to a height of 25 m. Leaves are large, pinnately compound with 25 cm length and consists of 2 to 6 pairs of lanceolate leaflets. The leaves and petioles contain galls that are horn-shaped, rugose and hollow. Flowers are small, reddish, arranged in panicles. Fruits are purple to blue, globular with diameter of 4-6 mm.

Geographical Distribution [22, 23]

The plant is a native species of China and is also distributed in the Eastern part of the Indian Himalayan Region i.e. from Indus to Kumaon. The plant can grow at an altitude of 350-400 m in the sub-alpine regions of Himalaya and also cultivated in the plain areas. The plant is distributed in countries like Nepal, China, Afghanistan, Pakistan, Armenia, North-west and West Himalayas worldwide.

Phytochemistry

The plant contains secondary metabolites such as alkaloids, flavonoids, tannins, saponins and sterols [24, 25]. Nair *et al*., studied the various samples of galls of *Pistacia integerrima* and revealed the presence of steroids, flavonoids, tannins, saponins and phenols in almost all the varieties [26]. Khobragade *et al*., reported the presence of tannins, resins, saponin, glycosides, oxalic acid, iron and sulphate in the gall powder [27]. Ahmed *et al*., identified three novel phytoconstituents from the galls of the plant along with the known compound b-sitosterol. The compounds were n-decan-30 -ol-yl-n-eicosanoate, n-octadecan9,11-diol-7-one and 3-oxo-9b-lanost-1,20(22)-dien-26-oic acid [28]. Uddin *et al*., isolated a novel triterpene compound named as pistagremic acid ((3-methyl-7-(4,4,10,13,14-pentamethyl-3-2,3,4,5,6,7,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-17-yl)-oct-3-enoic) and revealed its leishmanicidal activity [29]. Ullah *et al*., reported the presence of two novel flavonoid glycosides Pistacides A and B in the methanolic extract of the aerial parts of the plant along with four other compounds viz. 2′-hydroxyisoorientin, echioidinin 2′-O-β-D-(6″-O-acetyl) glucopyranoside, chrysoeriol, and diandraflavone A [30]. Ullah *et al*., in another study isolated two novel acylated oligosaccharides namely integrisides A and B from the sub fraction (*n*-butanol-soluble) of methanolic extract of the aerial parts [31]. Rauf *et al*., isolated two flavonoids namely naringenin and 3,5,7,4'-tetrahydroxy-flavanone from the methanolic extract of the galls and reported their *in-vitro* inhibitory activity against phosphodiesterase-1 (PDE1) [32]. Ahmed *et al*., reported three novel phenolic constituents from the galls namely 14'-phenoxytetradecany 3,5-dihydroxy benzoate (pistiphloro-glucinyl ester), 4'-phenoxy-*n*-butyl-1'-)3-oxy-5-hydroxy) benzoic acid (pistaciaphenyl ether) and 3'-(1,3-dihydroxy-5-phenoxy-1',5'-dimethoxbenzene (pisticiphloro-glucinyl ether) along with one known phytoconstituent i.e. stigmata-5-en-3beta-ol (beta-sitosterol) [33]. Rajopadhye *et al*., investigated the leaf galls for the essential oil composition and reported the presence of α-pinene, terpinene-4-ol, β-pinene, Δ3 -carene, limonene, γ-terpinene, and α-terpineol and reported their hepato-protective and anti-oxidant activities [34]. Chemical Structures of Some of the Phytochemical Constituents of *Pistacia integerrima* are given in figure 2.

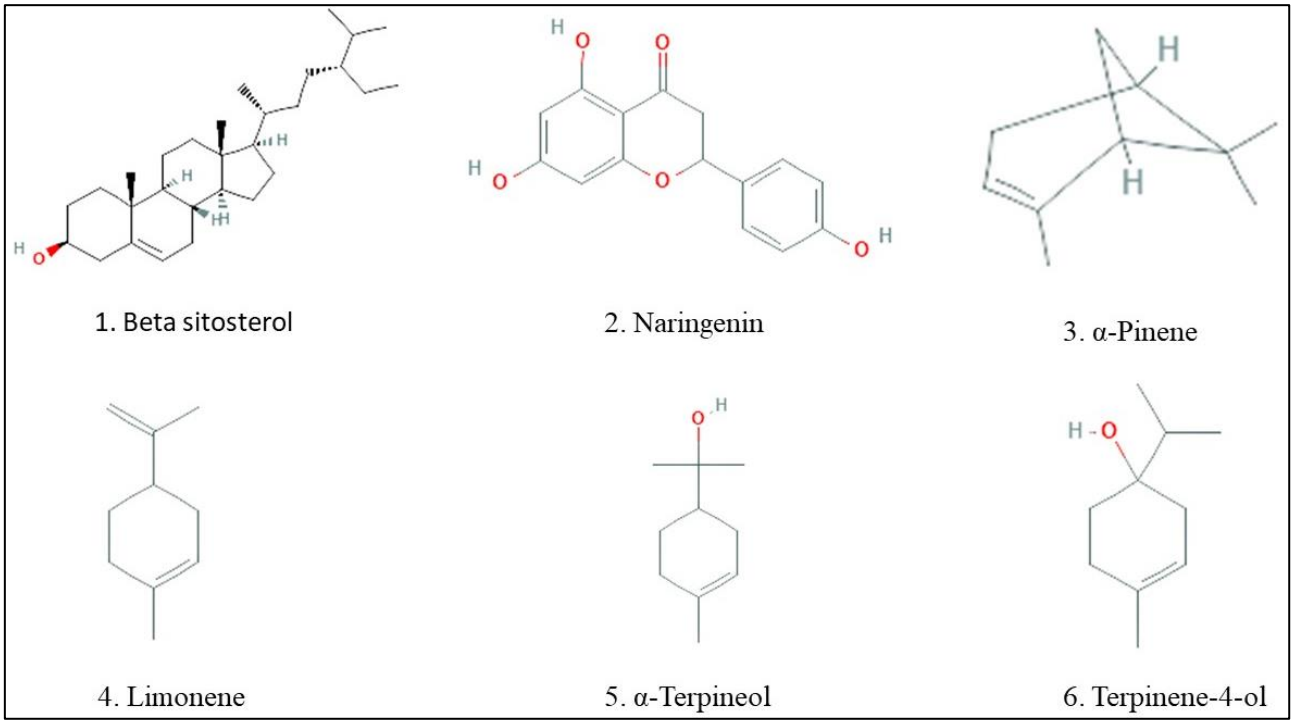

Figure 2: Chemical Structures of Some of the Phytochemical Constituents of *Pistacia integerrima*

Traditional and Modern View

Ayurvedic View

Ayurveda simply means the "science of life". It works on balancing the three body components/doshas of the body i.e. *Kapha* (water and earth), *Pitta* (fire) and *Vata* (space and air) [35-37]. *Pistacia integerrima* is an important plant with significant importance in *Pistacia integerrima* Ayurveda. It is commonly known as Karkatshringi in Sanskrit. The plant is associated with aromatic, astringent and high medicinal properties as per Ayurvedic medication system. It balances *Kapha* and *Vata* doshas of the body and used to treat diseases like kshayahara (chronic respiratory disorders), jwarahara (fever), shwasa (asthma, bronchitis), kasa (cough), hikka (hiccup), and vamana (vomiting), aruchi (anorexia), trut (excessive thirst), atisara (diarrhea) and asrapitta (bleeding disorders) [38, 39]. Rasapanchak (properties) of *Pistacia integerrima* is given in table number 3.

Table 3: Rasapanchak (properties) of *Pistacia integerrima* [40]

Sanskrit/English	Sanskrit/English
Virya/Potency	Ushna/Hot
Vipak/Metabolic Property	Katu/Pungent
Guna/Physical Property	Laghu/Light, Ruksha/Dry
Rasa/Taste	Katu/Pungent, Tikat/Bitter

Actions and Properties of *Pistacia integerrima* [41]

Sansthanik Karam Wahay: It has blood purifying and anti-inflammatory properties. Its decoction is helpful against bleeding gums whereas churna is used against abrasions and wounds.

Abhyantar Paachan Sansthaan: It acts as an appetizer, anti-flatulence and enhances digestion.

Paachan Sansthan: It is helpful in weak digestion, thirst, anorexia, diarrhoea and dysentery. It is beneficial to combat the complications of teeth eruption in children.

Swasan Sansthan: It has mucolytic properties and is used in throat infections, hiccups and cough.

Prajanan Sansthan: It reduces the uterine swelling as well as acts as uterine tonic, useful in leucorrhoea and other vaginal discharges.

Taapkram: It acts as an anti-pyretic.

Saatmikaran: It improves strength.

Ayurvedic Formulation [42]

It is used in polyherbal Ayurvedic formulations like dasamularista, chayavanaprasa, shringyadi leha and shringyadi curna which are used against swasa (asthma), yakshma (tuberculosis), ajeerna (indigestion), hridyaroga (heart disease), jwara (fever) and yakrit roga (liver disorder).

Folk View

Some plants are used in many folk medication practices which represent their rich ethnobotanical value [43]. *Pistacia integerrima* is an important medicinal plant with significant utilization in folkloric practices to treat many diseases. For instance, galls are used in many areas of Pakistan to treat cough, asthma, diarrhoea liver disorders and anti-venom against snake bites and scorpion sting whereas the bark is used against jaundice and hepatitis [44]. The tribal communities of Lesser Himalayas-Pakistan, orally use leaf galls powder to treat cough and asthma [45]. In Shawar valley, Pakistan, people use the plant as a tonic, antiseptic, bark powder as a wound healer and fruit extract to treat jaundice [46]. In some regions of Pakistan, the branches and stem of the plant are used as an ornamental wood, fuel wood and for construction purposes while the leaves are used as a fodder for cattle [47, 48]. In Kaghan Valley, Pakistan, people use galls as a tonic and

expectorant [49]. In North India, galls are used to treat inflammatory conditions, diabetes, liver infection, pain and fever [50]. The gall and leaves of the plant are used to treat cough, asthma, common fever, jaundice, diarrhoea and snake bites in many regions [51]. The local vaidyas (Hakims) used galls for the treatment of pulmonary infections, vomiting and diarrhoea [52]. The plant is also used to restrict haemorrhage from gums, to suppress bleeding from nose and to treat ear infections in children [53, 54]. As per Hamdard laboratories (WAQF), Pakistan, a traditional dosage form "habb-e-suranjan' is used as an antipyretic and analgesic agent which is also used to treat rheumatic pain [55]. In Northwest Himalayas, people use galls to treat coughs, asthma, diarrhoea, dysentery, fever, vomiting, appetite loss, nose bleeding, snake bites and scorpion stings [56].

Modern View

In the modern scenario plant-based products (medicines, cosmetics and food supplements) have gained attention due to their beneficial impacts on consumer health without causing any ill effects. But at the same time these products are facing a major risk to their quality due to the implication of factors like adulteration, contamination and fillers which alter the chain formulations of the products [57, 58]. The primary reasons behind adulteration are overexploitation, deforestation and high cost of the genuine plant [59]. However, these hurdles in the quality of herbal products can be successfully overcome by proper standardization and quality analysis techniques [60]. There are several methods of detecting adulterants for instance, chemotaxonomy, chromatography, and microscopy are some conventional methods which were used in previous era but due to their complex chemistry, unavailability of unique compounds, environmental influence, plant age, and geographical variations these techniques were replaced by a modern advanced molecular-based technique named as DNA barcoding which has a potential to detect adulterants and contaminants in the herbal products [61, 62].

Recent Therapeutic and Pharmacological Activities of *Pistacia Integerrima*

Pistacia integerrima has been extensively explored by many researchers for its extraordinary pharmacological and therapeutic activities. Some of the recent studies on the plant from a pharmacological viewpoint are discussed below:

Anti-bacterial

Sonawane *et al*., studied the anti-bacterial activity of Balchaturbhadra Yoga, a polyherbal formulation made up of Pippali, Karkatshringi, Musta, and Ativisha against *Escherichia coli, Enterococcus faecalis* and *Vibrio cholera*. The results indicated that the alcoholic and aqueous extract of Karkatshringi had inhibitory actions against *Escherichia coli* and *Vibrio cholera* whereas *E. faecalis* was inhibited by the aqueous extract only [63]. Thakur *et al*., suggested the anti-bacterial potential of *Pistacia integerrima* against *Escherichia coli, Salmonella Gallinarum* and *Salmonella Typhimurium* [64].

Muscle relaxant

Rauf *et al.,* studied the muscle relaxant activity of *Pistacia integerrima* in BALB/c mice models by using various tests. The study revealed that pistagremic acid (PA) in a dose-dependent manner exhibited remarkable muscle relaxant activity. The pretreatment of the models with pistagremic acid in the inclined plane test caused effective results. In traction and chimney tests, PA produced effective outcomes [65]. Shirole *et al*., carried out an *in-vitro* study on rabbit jejunum spontaneous contractions, guinea pig ileum to investigate the relaxant and spasmolytic activities of *Pistacia integerrima* essential oils extracted from the galls. The impact of essential oil was observed against K^+ induced contraction where the oil caused 28% relaxation of basal tone in rabbit jejunum. In contrast, a strong inhibition was exhibited by the oil in Ca^{2+} induced contraction of isolated guinea pig ileum in Ca^{2+} free medium. A reversal of a KCl-induced tonic contraction was also observed in Ca^{2+} free medium [66].

Anti-Oxidant

Bawazeer at al., suggested that crude extract and isolated flavonoids (1 & 2) of *Pistacia integerrima* are associated with significant anti-oxidant activities. The study revealed that the ethyl acetate, n-hexane, chloroform and methanol fraction as well as isolated compounds 1 and 2 exhibited potent radical scavenging activities by using 2, 2-diphenyl-1-picrylhydrazyl (DPPH) assay. Among all the fractions and compounds, ethyl acetate and isolated compound 1 were the most effective antioxidants with percent inhibition of 82.53% and 94.51% at 100 (µg/ml) concentration [67]. As per Zahoor *et al*., ethyl acetate fraction of the plant has potent radical scavenging activity. The fraction exhibited significant anti-oxidant activity in ABTS (2,2'-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid) and DPPH assays [68]. Eshwarappa *et al*., studied the anti-oxidant activity of aqueous and ethanol extract of leaf galls using diphenylpicrylhydrazyl (DPPH), hydroxyl scavenging and ferric reducing power (FRAP) assays. The study revealed that high total phenolic and flavonoid content in the ethanol extract was associated with potent anti-oxidant activity compared to the aqueous extract [69].

Anti-inflammatory

Rauf *et al*., suggested the anti-inflammatory potential of *Pistacia integerrima* against carrageenan induced paw edema in mice models. It was revealed from the study that the compounds isolated from the chloroform fraction of the galls i.e. flavonoids (1-4) exhibited potent anti-inflammatory actions during various assessment times (1-5h). Their impact was significantly noticed in the 3rd hour of treatment which remained up to the 5th hour [70]. Rana *et al*., studied the anti-inflammatory and immunomodulatory activity of *P. integerrima* in ovalbumin-induced allergic asthma mouse models. The study revealed that the methanol extract of the plant (PI) and methylprednisolone (MP) at the dosages of 200 mg/kg and 15 mg/kg body weight respectively caused an alleviation in the delayed type hypersensitivity. The treatment of the subjects with PI and MP caused a significant reduction in the mRNA expression levels of TNF-*α*, IL-4, and IL-5 along with an increase in Aquaporin 1 (AQP1) and Aquaporin 5 **(**AQP5) expression levels be the reason behind the amelioration of airway inflammation [71]. Thakur *et al*., carried out an *in-vivo* study on on carragenen induced paw edema in rat models to evaluate the anti-inflammatory actions of galls extract of *Pistacia integerrima.* A remarkable impact on paw edema was observed upon treatment with the gall extracts at the dosage of 100, 200 mg/kg body weight [72].

Anti-cancer

Rauf *et al*., isolated 3-oxo-6-β-hydroxy-β-amyrin (1) from the chloroform fraction of the plant and studied its impact on reversal of MDR (multidrug resistance) mediated by P-gp (P-glycoprotein) by using rhodamine123 exclusion on multidrug-resistant human ABCB1 gene transfected mouse T-lymphoma cell line. The compound caused

reduction in the applied anti-tumor promotion experiment. A reduction of early tumor antigen expression was also observed which was similar to the positive control curcumin. Furthermore, the compound exhibited remarkable docking results through Autodock Vina 1 and i-GEMDOCK v 2.1 tools. Overall the study concluded the anti-cancer activity of the compound [73]. Rauf *et al*., in another study subjected naringenin (1) and dihydrokaempferol (2) along with crude extract of the plant for their impact on reversion of multidrug resistance (MDR) mediated by P-glycoprotein (P-gp) by using rhodamine123 exclusion on human mdr1 gene transfected mouse gene transfected L5178 and L5178Y mouse T-cell lymphoma cells in an *in-vitro* test and revealed the remarkable MDR reversing activity in particular doses whereas the results of *in-silico* test revealed that both the subjected compounds and rhodamine123 had a common binding site. It was indicated from the computational investigation that the interaction of the compounds with the hydrophobic pocket of P-gp might be linked to the inhibitory activity [74].

Anti-diarrheal

Alhumaydhi *et al.,* studied the anti-diarrheal activity of *Pistacia integerrima* extracts/fractions and four isolated flavonoid compounds in mice models induced with diarrhoea using castor oil. The study revealed that the extracts and the fractions at particular doses caused a remarkable attenuation in diarrhoea. Ethylacetate extract was found to be the most significant anti-diarrheal agent followed by chloroform. Whereas in the case of isolated compounds, 1 and 4 compounds were the most effective against diarrhoea [75].

Hepato-protective

Ilahi *et al*., evaluated the fruit methanol extract of *Pistacia integerrima* for its hepato-protective activity against paracetamol (PCM) intoxicated male rabbit models. The oral administration of the extract at the doses of 200 mg and 400 mg/kg body weight for 16 days caused a remarkable decrease in the serum alanine transaminase (ALT) aspartate aminotransferase (AST) alkaline phosphatase (ALP) levels [76].

Gastro-protective

Rauf *et al*., carried out an *in-vivo* study to investigate the gastro-protective activities of pistagremic acid extracted from the galls of *Pistacia integerrima* in mice models. The pretreatment of the models with the extract at the dosage of 500 mg/kg p.o. whereas, in charcoal meal GI transit test, the compound significantly reduced the GIT motility as well as increased the intestinal transit time. These results were comparable to atropine [77].

Anti-hyperglycaemic

Vashist *et al*., carried out an *in-vivo* study on alloxan induced hyperglycaemic rat models to check the anti-hyperglycaemic activity of ethanolic extract of *Pistacia integerrima* leaves. The study revealed that the extract at the dosage of 200mg/kg remarkably lowered down the hyperglycaemia and lipidemic actions [78].

Cardio-protective

Ishtiaq *et al*., investigated the effect of *Pistacia integerrima* against Bisphenol A (BPA) induced oxidative stress in Sprague Dawley rat models. The administration of 200 mg/kg body weight of *P. integerrima* reversed all the actions of BPA in terms of p53, p53-upregulated modulator of apoptosis (PUMA) and dynamin-related protein (Drp1), ubiquitin-conjugating enzyme (Ubc13) expression and cellular architecture along with effective impact on liver markers level [79].

Anticonvulsant

Jian *et al*., studied the anticonvulsant activity of gall extracts of *Pistacia integerrima* against acute epilepsy induced by pentylenetetrazole (PTZ) in zebrafish and mice models and maximal electroshock (MES) rat models. In zebrafish models, the petroleum ether extract caused a dose-dependent delay in the onset of various seizure parameters at the dosage of 50mg/kg, 100mg/kg, and 200 mg/kg body weight whereas in the mice models, dose-dependent delay was observed in 50 mg/kg and 100 mg/kg doses. A delay in the duration of hind limb extension was observed in (MES) rat models on treatment with the extract at the dosage of 50 mg/kg, 100mg/kg, and 150 mg/kg boy weight. This study suggested the use of plant as an anticonvulsant agent [80].

CONCLUSION

Pistacia integerrima is a wonder tree belong to the family *Anacardiacea.* The plant is well recognized for its medicinal properties in the traditional medication systems as it is used in the treatment of human ailments like diarrhoea, dysentery, fever, vomiting, skin diseases and respiratory disorders. Its essential oils are used in many therapeutic applications such as anti-bacterial, anti-oxidant, anti-inflammatory, cardio-protective, anti-cancer, anti-diarrhoeal, anticonvulsant and muscle relaxant and many more. Various exploratory studies have proved its pharmacological significance. From the present review, it can be concluded that it is a wonder tree and can be successfully used in the drug development.

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Conflict of Interest

None.

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