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Review Article

Pharmacological Potential of Pistacia integerrima: A Comprehensive Review

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ABSTRACT

Pistacia integerrima plant or Karkatshringi is a useful medicinal plant of the family Anacardiaceae. Pistacia integerrima is a dioecious, unbranched, and 25-meter tall tree. It has large, pinnate compound leaves with horn-shaped galls and small, reddish flowers arranged in panicles. Its fruit is purple to blue, globular fruit. It occurs commonly in countries like Nepal, China, Afghanistan, Pakistan, India, Armenia, and the northwestern and western Himalayas. The plant is significant in traditional medicinal systems like Ayurveda, Unani, and Siddha. Pistacia integerrima is also used in several folkloric cultures of the world to cure a wide range of human diseases, such as diarrhea, dysentery, fever, skin infections, respiratory ailments, psoriasis, hepatitis, and liver disorders. One unusual property of this plant is the material of essential oil, which is rich in various prominent phytochemical constituents like alpha-pinene, camphene, di-limonene, 1:8-cineol, caprylic acid, alpha-terpineol, and aromadendrene. In addition, the plant is also rich in other prominent secondary metabolites like steroids, flavonoids, tannins, saponins, and phenols, which are associated with various pharmacological activities, including antibacterial, antioxidant, anti-inflammatory, cardio protective, anticancer, anti-diarrheal, anticonvulsant, and muscle relaxant activities. Pistacia integerrima extracts show significant antimicrobial activity against certain bacteria, such as the causative agents of prevalent infections. Its antioxidant properties owing to the presence of flavonoids and phenolic compounds, safeguard cells against oxidative stress and damage. Pistacia integerrima, an important Ayurvedic constituent, is found in Chavyanprash, Dashmularista and Shringyadi Churna. These preparations are famous for their multi-faceted health advantages and have been used in traditional medicine for.

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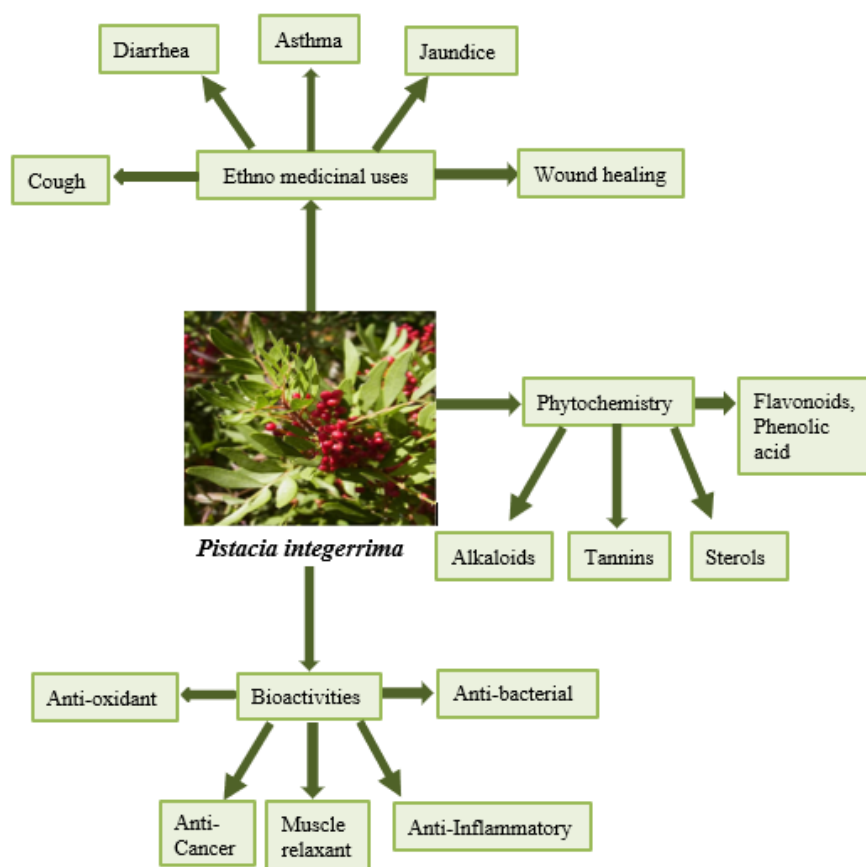
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centuries. The aim of the current objective of the study is to examine the recent pharmacological activities of *Pistacia*

integerrima with its applications in traditional medicinal traditions.

Graphical Abstract



INTRODUCTION

Pistacia integerrima also known as, Shnaie, Kangar, or Karkatshringi, is a flowering plant of the family Anacardiaceae. *Pistacia integerrima* blooms from March to May and the fruits of *Pistacia integerrima* are edible from June to October [1]. *Pistacia integerrima* is a medium-sized, broad-leaved tree that occurs in China, Pakistan, Afghanistan, Nepal, and the west and northwest Himalayas [2]. The plant occurs in the tropical region and at 900 to 1800 meters altitude [3]. *Pistacia integerrima* is a much-branched tree with big leaves. It is a member of the *Pistacia* genus, which has between 70 and 600 species. *Pistacia* is a deciduous shrub. The Persian name for *Pistacia integerrima* is “Pesteh,” and its technical name is “green almond” [4]. Tree bark

releases a fragrant fluid when pierced. Leaves bear galls, not formed by the natural growth of the tree. These growths occur because of an “insect known as an aphid (*Dasia asdifactor*), which belongs to the family Pemphigus. The aphid resides inside the tree and suck the sap from the tree. The galls are horn-shaped, hard, and hollow on the inside [5]. The galls are cylindrical and tapering at both ends. The outer surface of the galls is grayish-brown while that of the inner surface is reddish-brown. The galls are also found to have secondary metabolites, including steroids, flavonoids, tannins, saponins, and phenols [6]. It is applied to different Ayurvedic disease and medicine treatments [7]. *Pistacia integerrima* bark is boiled in water to prepare an extract that is used in jaundice and hepatitis in some regions. Stem resin is applied on

wounds to heal them. Fruits of the plant are edible and utilized to cure liver ailments as well. Apart from its medical purposes, the stem and branch of *Pistacia integerrima* are utilized as fuel wood, construction wood, and decoration wood. The leaves are fed to cattle as fodder [8]. Monoterpenes, triterpenoids, sterols, dihydromalvalic acid and flavonoids are chemical constituents present in *Pistacia integerrima* [9]. *Pistacia integerrima* contains a high percentage of alpha-pinene (25%), camphene (27%), dilimonene (4% to 5%), 1:8-cineol (10%), caprylic Acid (15%), alpha-terpineol (20%) and Aromadendrene (4% to 5%) [10].

2. Taxonomical Position: The plant's classification is as follows [11].

Kingdom	Plantae
Phylum	Tracheophytes
Division	Angiosperm
Subdivision	Eudicots
Class	Rosides
Order	Sapindales
Family	Anacardiaceae
Scientific name	<i>Pistacia integerrima</i>

3. Morphology

Pistacia integerrima species can grow to a height of roughly 40 meters. It has leaves that are a narrow oval shape, about 25 centimeters long and 1 to 3 inches wide, with two to six tiny leaflets on each leaf. Typically, this tree's bark is light brown or gray. The male and female blooms of this tree are on different trees, and the blossoms are small and reddish. The yellow or brownish blooms are about 0.2 cm wide [12]. When the fruits are fully grown, they are round, shiny, and have a purplish-blue color, measuring about 5 to 6 mm in diameter. There are also galls on the leaves of the tree, which are caused by an insect called *Aphis* (*Dasia asdifactor*). This bug consumes the sap of the tree and resides inside it. It produces hollow, horn-like structures that are reddish-brown on the inside and

grayish brown on the surface. The length of these galls ranges from 2.5 to 30 cm [13].



Fig.1 Fruit of *Pistacia integerrima*



Fig.2 Galls of *Pistacia integerrima*

4. Geographical distribution

Chinese native and occurs in the eastern part of the Indian Himalayan Region, between the Indus and Kumaon. It is found in the sub-alpine belts in the Himalayas at altitudes of 900 to 1800 meters and also cultivated in the plains. Except in the western and northwestern Himalayas, it occurs in numerous other nations outside of India, i.e., Nepal, Afghanistan, Pakistan, and Armenia. It has a widespread geographical distribution in all these countries, which can be defined as how suitably it accommodates variable conditions of an area. *Pistacia integerrima* is a species that holds major significance in its distribution areas as it enriches cultivation procedures and enriches biodiversity. It grows equally in low and high altitudinal areas of

its territory, which manifests its ecological value at both of these levels and the need for conservation to protect its habitats and be able to survive in these varied environments [14].

5. Phytochemistry

Alkaloids, flavonoids, tannins, saponins, and sterols are some of the secondary metabolites present in *Pistacia integerrima*. The phytochemicals possess significant importance in protecting the plant and are responsible for its curative powers, offering a variety of health benefits [15]. The analysis of *Pistacia integerrima*

reveals the presence of phenolic chemicals, tannins, steroids, flavonoids, and saponins [16]. *Pistacia integerrima* has a number of chemical compounds, especially in its galls. It is tannin-dominant (60%) with less volatile oil content (1.2%). It also possesses tetracyclic triterpenes, resin, pistacienoic acid A and B, essential oils, camphene, caprylic acids, cineol, α -pinene, etc. *Pistacia integerrima* galls possess pistagremic acid, a natural terpenes β -secretase inhibitor [17].

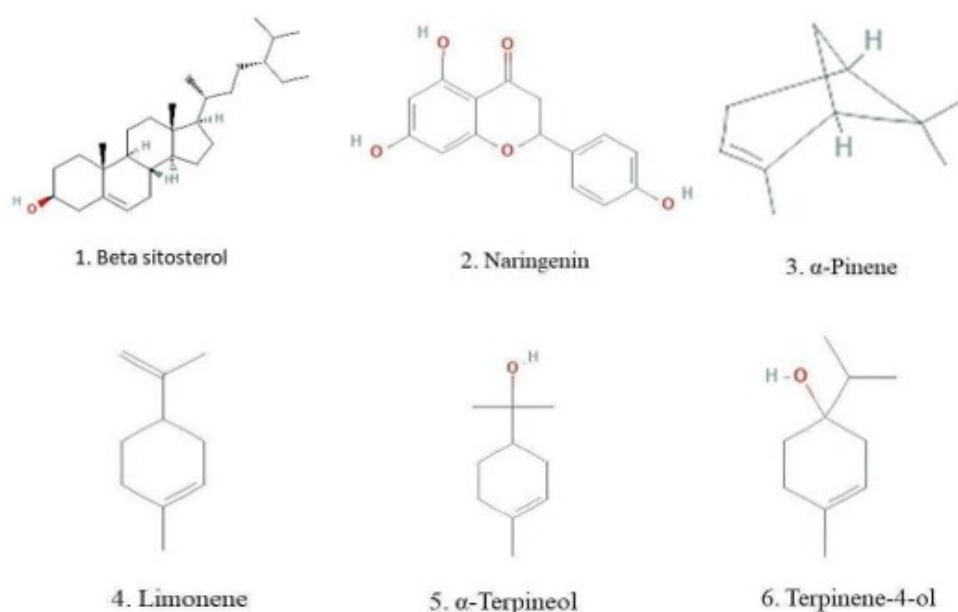


Fig.3 Chemical Structures of some Phytochemical Constituents of *Pistacia integerrima*

The leaves and bark of *Pistacia integerrima* are tannin-rich. Seeds have a number of compounds, such as amino acids, triterpenoids, proteins, sterols, and dihydromalvic acid [4]. Flavonoids, catechins, triterpenoids, and carotenoids are found in leaves of *Pistacia integerrima*. *Pistacia integerrima* essential oil that has been purified by gas chromatography and mass spectrometry contains a predominating concentration of 1-terpinene-4-ol (28.82%), p-methen-8-ol (43.38%), n-octyl acetate (19.91%) and beta-Farnesene (7.88%). The monoterpenes make up 91% of the

oil, namely α -pinene, β -pinene, limonene, cineol, and sabinene [18]. Monoterpenes like α -pinene, β -pinene, limonene, cineol, and sabinene establish 91% of the oil. The levorotation character of *Pistacia integerrima* oil indicates the presence of hydrocarbons. It also contains positive phenolic compounds like *Pistacia* phenyl ether and Pistiphloro-glucynyl ester [19].

6. Pharmacological activity of *Pistacia integerrima* plant

6.1 Anti-bacterial Activity

The antibacterial potential of *Pistacia integerrima* was tested against bacteria such as *Escherichia coli*, *Enterococcus faecalis*, and *Vibrio cholera* [20]. Gall extracts of the plant *Pistacia integerrima* have higher antibacterial activity than other plant parts. Flavonoids, phenolic acids, terpenoids, and tannins are bioactive molecules in *Pistacia integerrima* that cause disruption of the bacterial cell walls. This destruction leads to cell lysis,

eventually leading to cell death. The underlying mechanisms through which such compounds inflict their antibacterial effect are important to the realization of their possible clinical uses in the fight against bacterial infection. The compound's capacity for disruption of the integrity of the bacterial cell structures makes it significant for medicinal chemistry as well as pharmacology [21].

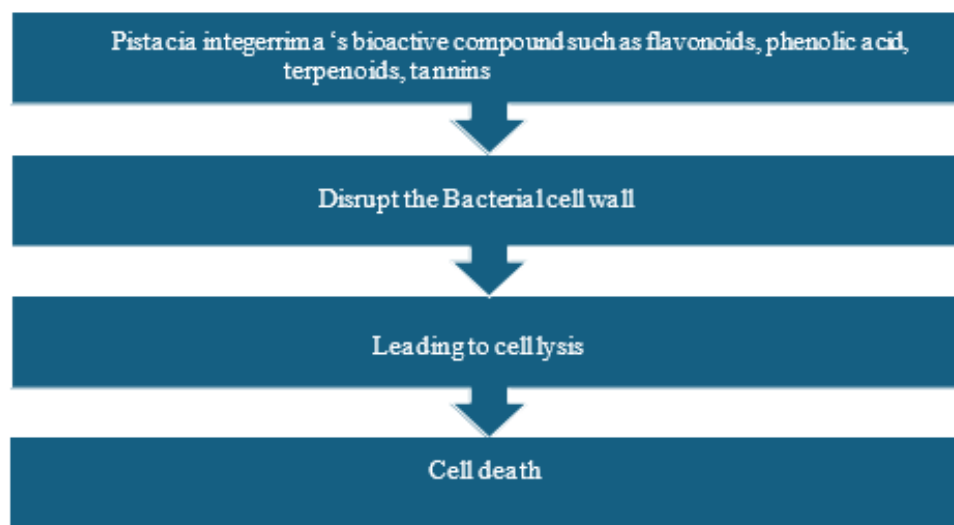


Fig.4 Moa of Anti - bacterial Activity

6.2 Muscle relaxant Activity

Pistagremic acid (PA) was found to be a potent muscle relaxant activity in a dose-dependent manner. Pistagremic acid is active by virtue of its binding to the gamma subunit of the GABA receptor, causing a conformational change of the receptor. This increases the receptor activity, and more channels open more frequently. As a result, there is enhanced chloride ion conductance, with more chloride ions entering in the neuron. This entry is responsible for causing hyperpolarization, a reduction in the excitability of the neuron as well

as suppression of the formation of action potentials. The cumulative effect of the processes is the induction of sedative and anxiolytic actions. By suppressing the levels of anxiety and stress, Pistagremic acid induces relaxation and sedation. This process holds promise for potential therapeutic use in the management of anxiety disorders as well as overall mental health, the significance of knowing how specific compounds interact with neurotransmitter systems to generate intended physiological effects [22].

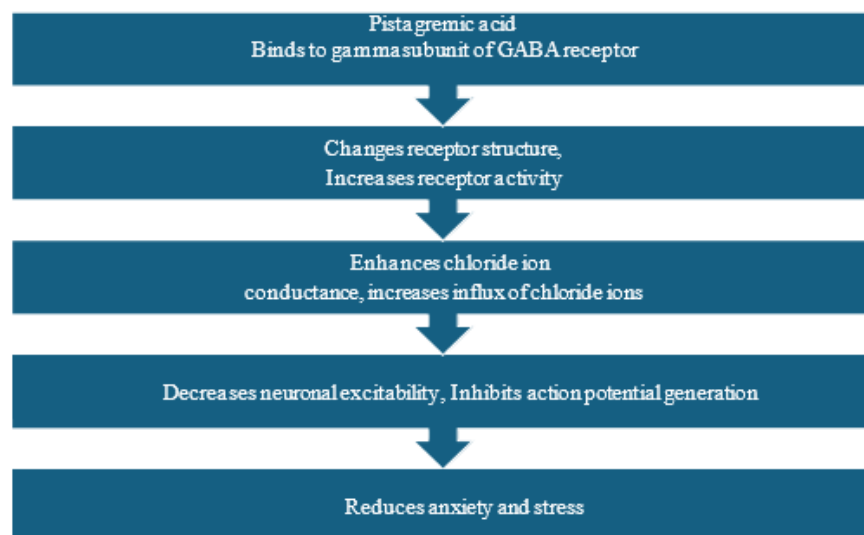


Fig.5 Moa of muscle relaxant Activity

6.3 Anti-oxidant Activity

The crude extracts and flavonoids obtained from *Pistacia integerrima* have strong antioxidant activity. Direct free radical scavenging is implicated when flavonoids become oxidized by free radicals, leading to the formation of more stable and less reactive radicals. The process helps in stabilizing reactive oxygen species (ROS). The hydroxyl groups (-OH) of flavonoids are crucial in neutralizing these radicals, rendering them easier

scavenging of superoxide and peroxynitrite. Such activity is hence responsible for in vitro prevention of oxidation of low-density lipoprotein (LDL), and it is an LDL particle-protective mechanism. Such protection is interesting in that it demonstrates prevention of atherosclerosis and suggests the value of flavonoids in cardiovascular disease and anti-oxidative stress-related injury [23].

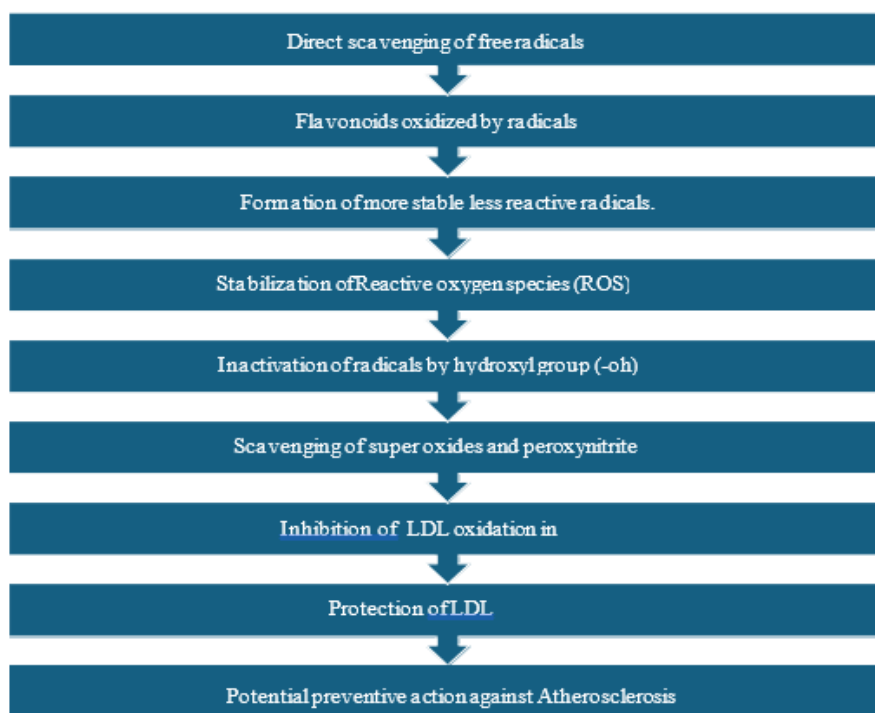


Fig.6 Moa of Anti-oxidant activity

6.4 Anti-inflammatory Activity

Flavonoids, phenolic acids, and terpenoids suppress the production of pro-inflammatory cytokines like TNF- α , IL-1 β , and IL-4, IL-5, IL-6 [25]. Through this reduction in

inflammatory substances, such compounds assist in lowering inflammation within the body. This role is crucial in ensuring overall wellness and may contribute to the prevention of other inflammatory-related diseases [24].

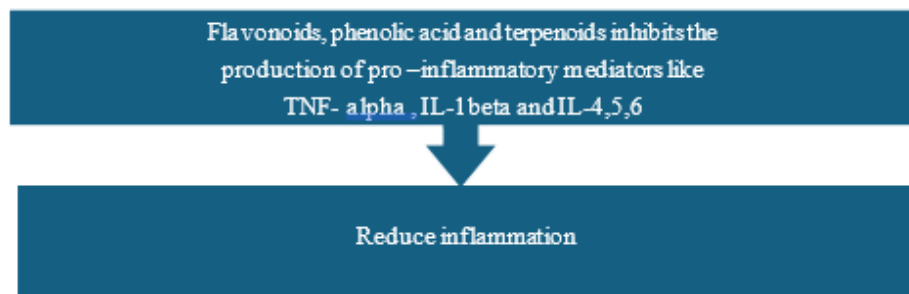


Fig.7 Moa of Anti- inflammatory activity

6.5 Anti-cancer Activity

The PI extract significantly reduces the survival of lung cancer cells, i.e., A549 and NCI-H460. Even at non-lethal concentrations, PI inhibits the proliferation of the cancer cells to form colonies, acquire spheroid morphology, and migrate [25]. PGG (Penta-O-Galloyl- β -D-Glucose) from *Pistacia integerrima* has been found to cause autophagic cell death in lung cancer cells, i.e., A549 and NCI-H460 cell lines. The mechanism for the activation of the AMPK-ULK1 pathway, a pathway that plays a central role in cellular energy homeostasis and regulation of autophagy. Activation of this pathway results in the

modification of the ERK and STAT3 signaling pathways, thereby also triggering apoptosis. The apoptosis mechanism is triggered by the activation of the key proteins caspase-3 and PARP1, which are necessary for the enforcement of cell death. Importantly, the whole process is independent of activation of reactive oxygen species (ROS), indicating a specific pathway of cell death. With such characteristics, PGG has tremendous potential as a source of natural products to discover adjuvant therapy against lung cancer, which is an important avenue toward the improvement of treatment efficacy and patient prognosis [26].

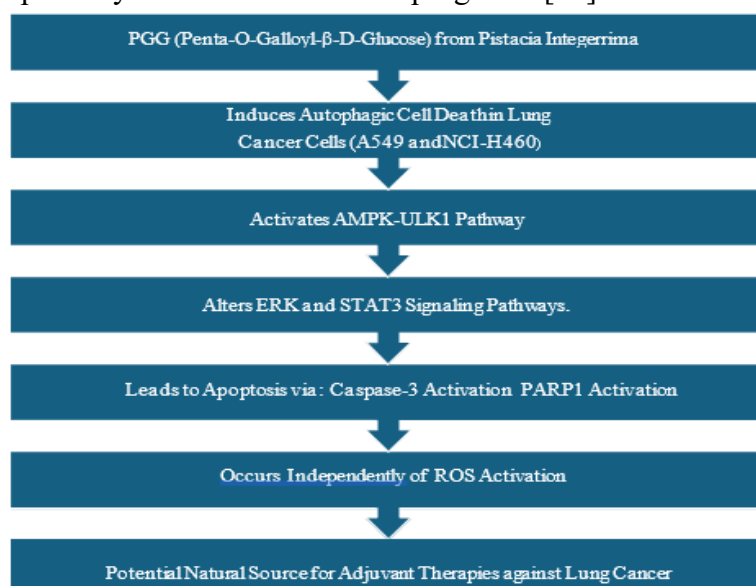


Fig.8 Moa of Anti - cancer Activity

6.6 Anti-diarrheal Activity

Flavonoids like quercetin and kaempferol, and phenolic acids like Gallic acid and ellagic acid, are important in gastrointestinal health by inhibiting the contraction of intestinal smooth muscle. It results in decreased intestinal motility, which provides additional time for electrolyte and water absorption in the intestines. Due to this process it reduces stool frequency and liquidity, causing a therapeutic effect against diarrhea diseases or

hyper bowel motion. Through intestinal contractions regulation and absorption, these drugs should keep the digestive system more regulated and the intestines' overall well-being. That they are natural in most of the fruits, vegetables, and herbs, reiterates how vital they are as dietary approaches aimed at improving gastrointestinal function and alleviation of associated diseases [27].

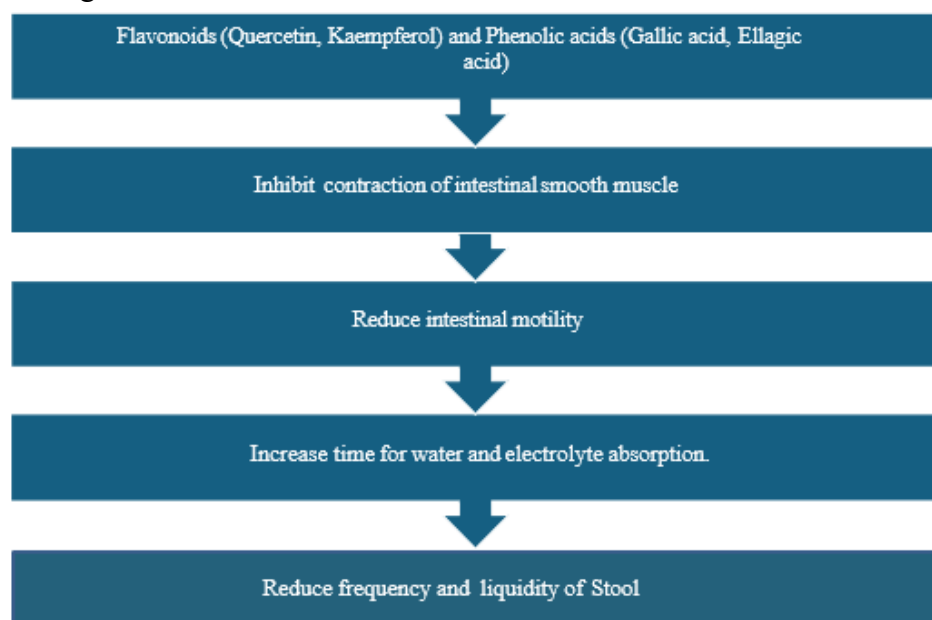


Fig.9 Moa of Anti - diarrheal Activity

6.7 Hepato-protective Activity

There was a notable decrease in the level of serum for alanine transaminase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP). These observations indicate that the fruit extract possesses protective properties for the liver, especially in instances of paracetamol-induced liver injury. This study shows the value of *Pistacia integerrima* as a natural drug that can be used to reduce the damage to the liver due to toxic compounds such as paracetamol [28].

6.7.1 Inhibition of ALT (Alanine Transaminase)

The phenolic acids and flavonoids of *Pistacia integerrima* have hepatoprotective activity by inhibiting the enzymatic activity of ALT. In particular, these biologically active metabolites bind to the active site of ALT and thus inhibit transamination of alanine to pyruvate. The inhibition leads to a reduction in ALT levels in the blood, which is a biomarker for decreased hepatic damage and inflammation.

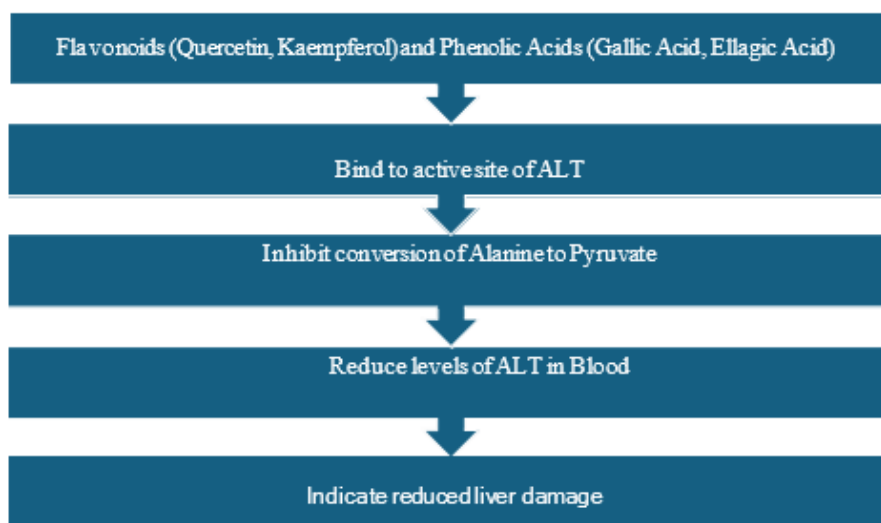


Fig.10 Moa of Hepato- protective activity

6.7.2 Inhibition of AST (Aspartate Transaminase)

By blocking the flavonoids and phenolic acids of *Pistacia integerrima* it have Hepatoprotective effects by suppressing the enzymatic action of AST. To be specific, these bioactive compounds

bind to AST's active site and thereby prevent transamination of Aspartate into oxaloacetate. This inhibition leads to lowering of AST concentration in blood, which is being used as a biomarker for decreased hepatic inflammation and damage [29].

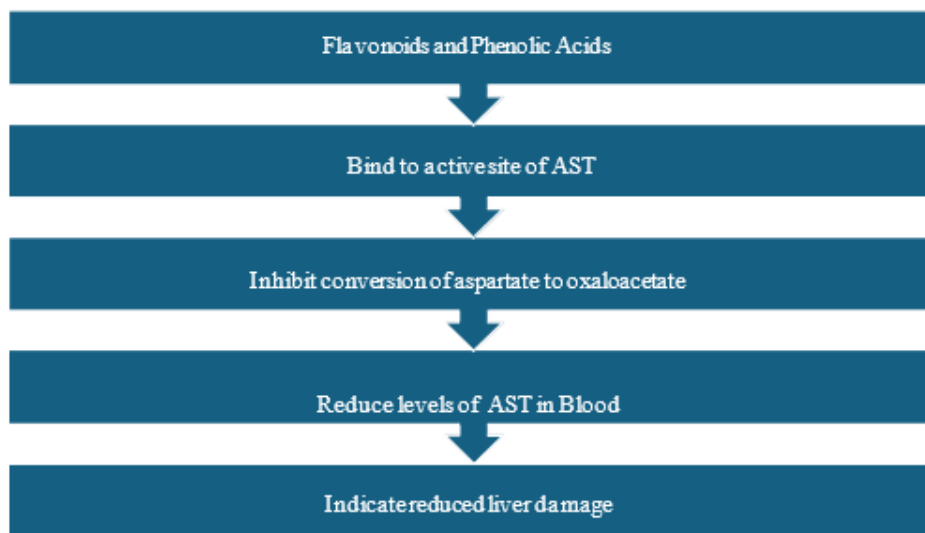


Fig.11 Moa of Hepato- protective activity

6.8 Gastro-protective Activity

Pistacia integerrima galls have a special compound known as pistagremic acid, a significant contributor to reducing gastrointestinal motility. By reducing gastrointestinal motility, pistagremic acid facilitates relief from flatulence. It does so through the blocking of muscarinic receptors that

interfere with the smooth muscle contraction in the gastrointestinal tract. Consequently, the decrease in gastrointestinal motility brings relief from flatulence, emphasizing the use of *Pistacia integerrima* galls against gastrointestinal disorders [30].

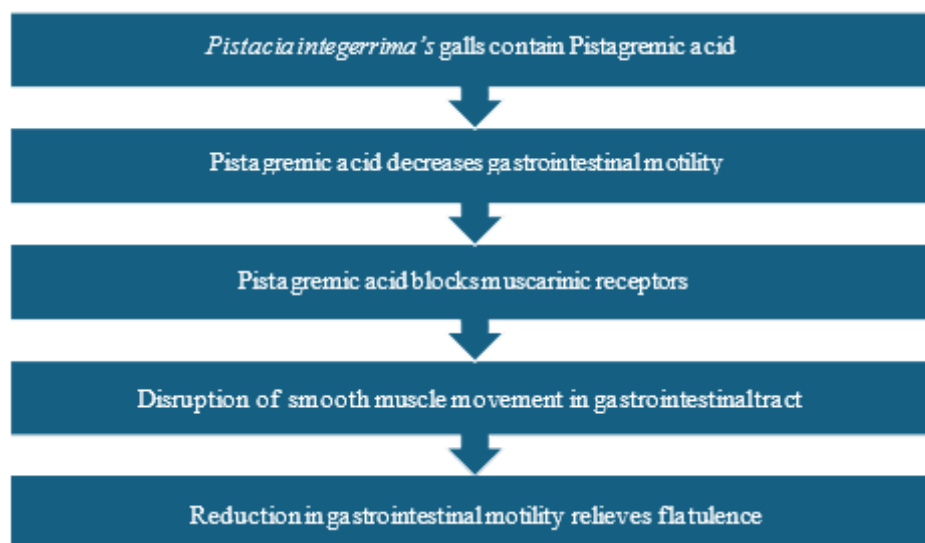


Fig.12 Moa of Gastro protective activity

6.9 Anti-hyperglycemia Activity

Pistacia integerrima Stewart is also used traditionally in the management of many diseases like diabetes. They extracted Flavonoids and pistagremic acid from *Pistacia integerrima* dried galls. Molecular docking simulations showed flavonoids and pistagremic acid possess great potential for inhibiting α -glucosidase and α -Amylase, an enzyme that regulates diabetes [31]. Experimental tests concluded that flavonoids and pistagremic acid actually have great α -glucosidase, α -Amylase inhibitory activity, validating the initial computer results.

6.9.1 Inhibition of α -Glucosidase

Flavonoids were discovered to possess anti-hyperglycemic action through inhibition of α -glucosidase. The enzyme inhibition decreases the degradation of carbohydrates into simple sugar, thus decreasing the rate of absorption of carbohydrates. As a result, postprandial blood glucose levels are reduced, leading to lower peak blood glucose levels and enhanced glucose tolerance. This effect demonstrates the capability of these bioactive substances in the management of hyperglycemia and increasing insulin sensitivity [32].

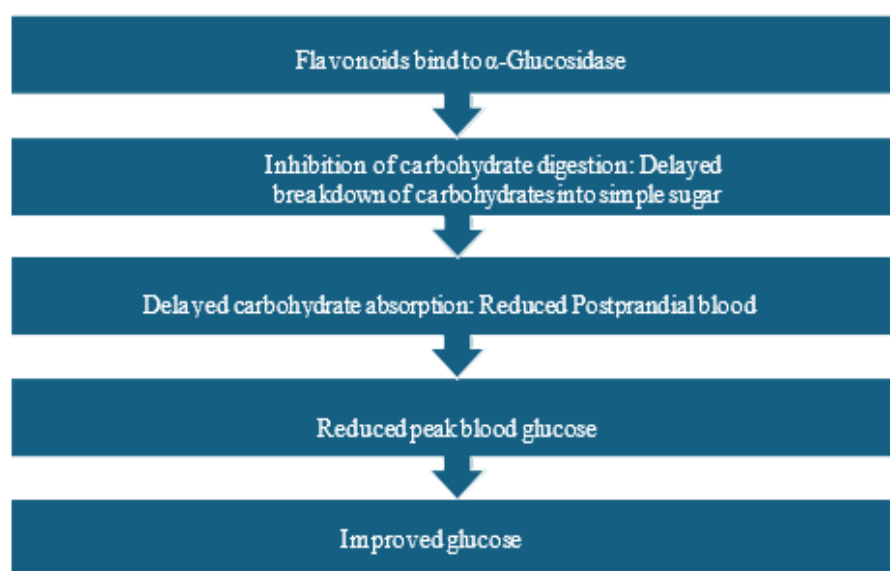


Fig.13 Moa of Anti-hyperglycemia activity

6.9.2 Inhibition of α -Amylase

Pistagremic acid bind to α -amylase, a hydrolyzing enzyme of the starch into simple sugars. This binding prevents α -amylase activity, thus reducing the breakdown of starch into simple sugars. As a

result, carbohydrate assimilation is reduced, which brings about reduced blood glucose. Accordingly, the glycemic index is lowered, insulin sensitivity is enhanced, ultimately leading to effective blood sugar control [33].

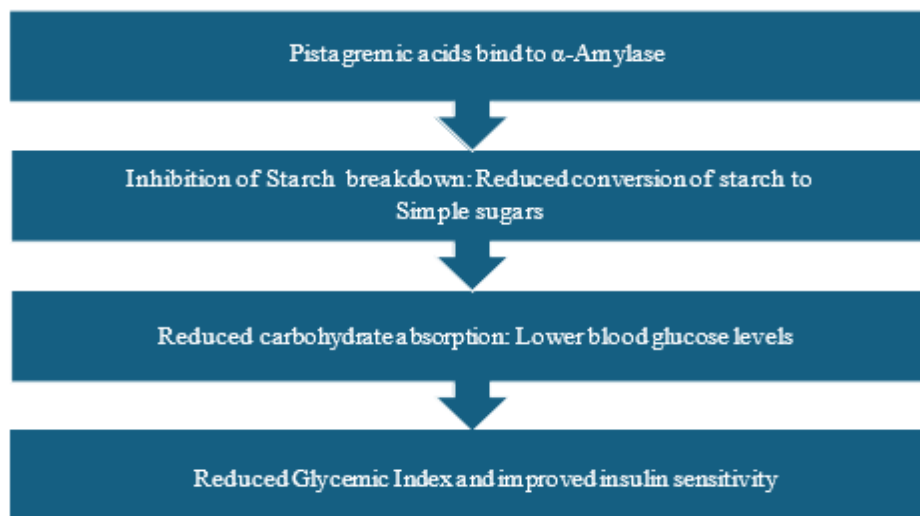


Fig.14 Moa of Anti-hyperglycemia activity

6.10 Anti-convulsant Activity

Pistacia integerrima possesses anticonvulsant activity since it is able to block sodium channels. The active constituents of the oil of *Pistacia integerrima*, like α -pinene and β -pinene, and 4-carvomenthol, are the compounds that cause this anticonvulsant activity. To assess the

anticonvulsant activity, researchers conduct initial tests referred to as PTZ and MES. These tests assist in identifying whether the drugs are also effective in treating tonic-clonic seizures and generalized absence seizures in human beings [34].

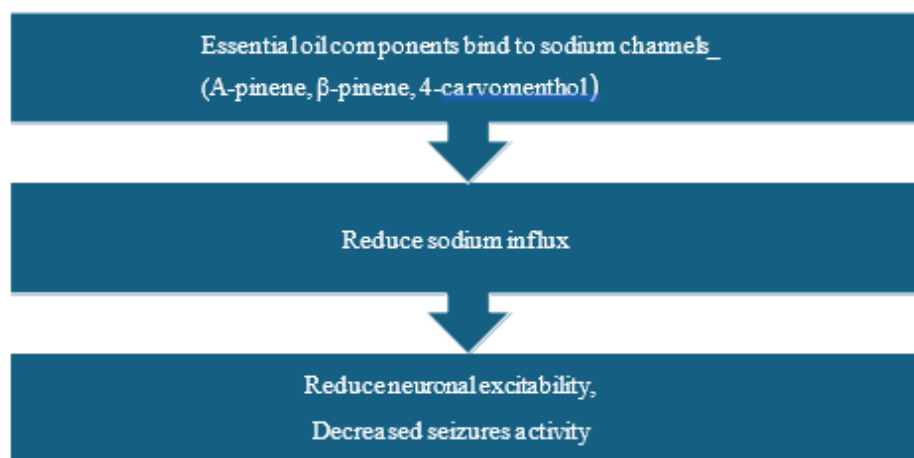


Fig.15 Moa of Anti-Convulsant activity

CONCLUSION

The article concludes by highlighting the significance of *Pistacia integerrima* as a valuable medicinal plant and its diverse roles in traditional

and modern medicine. *Pistacia integerrima* is also known as Karkatshringi. *Pistacia integerrima* is recognized for its rich array of bioactive compounds. It is a significant part of the

Anacardiaceae family. *Pistacia integerrima* is not just another tree but a source of various essential oils and also Phytochemicals that possess potential therapeutic applications. The major point argued is the plant's function in conventional health care. The fact that it has had a long history of use in such systems as Ayurveda, Unani, and Siddha implies the high cultural value of *Pistacia integerrima*. It has traditionally been used to treat various diseases, from gastrointestinal diseases to liver diseases. The review lists its uses in some Ayurvedic formulations, highlighting its historical significance as a stimulant for health and well-being in those medicinal traditions. The conclusion deals with the specific phytochemical constituents which are mainly found in *Pistacia integerrima*, such as, phenolic acid, flavonoids and essential oils like alpha pinene and beta pinene. These components have potent antioxidant and anti-inflammatory properties, which are used in managing conditions such as seizures and other health disorders. The plant's extracts can significantly inhibit enzymes related to liver damage, thereby showcasing its hepatoprotective effects. In addition, the conclusion highlights the importance of ongoing scientific investigation to confirm traditional uses and to possibly advance the therapeutic potential of *Pistacia integerrima*. It appeals for additional pharmacological studies to establish through which mechanisms its components have their therapeutic actions, leading the way to the use of the plant's properties in modern medicine. *Pistacia integerrima* as a potential candidate for future pharmacological studies, with the emphasis on its potential not only in conventional medicine but also in the discovery of new medicines. *Pistacia integerrima* is sold in several marketed drug formulations such as Karkatadi Churna, Brihat Palisade, Chawanprash, Shiva Gutika, and Devadavayadi Churna. The very high Phytochemistry, along with its cultural value in most societies, emphasizes the need to preserve

this species and continue researching its numerous health benefits, thereby increasing its potential as a health promotion and wellness resource for the world.

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Competing interests

No Competing interests

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