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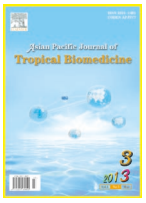

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The development of *Terminalia chebula* Retz. (Combretaceae) in clinical research

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PEER REVIEW

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Comments

This paper is a good review paper on ayuverdic and pharmacological activities of Terminalis chebula. Citations used are also a good resources for reviewing and very informative to all the ayuverdic and traditional practitioners.
(Details on Page 250)

ABSTRACT

Medicinal plants are part and parcel of human society to combat diseases from the dawn of civilization. *Terminalia chebula* Retz. (Fam. Combretaceae), is called the 'King of Medicine' in Tibet and is always listed at the top of the list of 'Ayurvedic Materia Medica' because of its extraordinary power of healing. The whole plant possesses high medicinal value and traditionally used for the treatment of various ailments for human beings. Some of the folklore people used this plant in the treatment of asthma, sore throat, vomiting, hiccough, diarrhea, dysentery, bleeding piles, ulcers, gout, heart and bladder diseases. The plant has been demonstrated to possess multiple pharmacological and medicinal activities, such as antioxidant, antimicrobial, antidiabetic, hepatoprotective, anti-inflammatory, antimutagenic, antiproliferative, radioprotective, cardioprotective, antiarthritic, anticaries, gastrointestinal motility and wound healing activity. But no systematic updated information on the therapeutic effectiveness of *Terminalia chebula*, a popular herbal remedy in India and South-East Asia has so far been reported. This review highlights an updated information particularly on the phytochemistry and various pharmacological and medicinal properties of *Terminalia chebula* Retz. and some of its isolated compounds, along with their safety evaluation. This may provide incentive for proper evaluation of the plant as medicinal agent against the human diseases and also to bridge the lacunae in the existing literature and future scope which may offer immense opportunity for researchers engaged in validation of the traditional claims and development of safe and effective botanical medicine.

KEYWORDS

Terminalia chebula, Human diseases, Medicinal value, Bioactive constituents, Safety evaluation

1. Introduction

Ayurveda is a 5000 years old healing tradition rooted in ancient Indian culture. This vast body of healing knowledge -sometimes referred to as "Mother of all healing"- has recently come to the attention of Western medical researchers on seeking novel therapeutic compounds due to concerns over more invasive, expensive and potentially toxic main stream practices. According to World Health Organization, about 80% of world population rely chiefly on plant based traditional medicine for their primary healthcare need[1]. Traditional healing system around the world that utilizes herbal remedies are an important resource for the discovery of modern drugs[2]. While screening a number of medicinal plants, scientist discovered one of the most revered medicinal plant *i.e. Terminalia chebula* (*T. chebula*) Retz. (Combretaceae), which exhibited a number of medicinal activities due to the presence of a large number of different types of phytoconstituents. The fruit of the tree possesses diverse health benefits and has been used as traditional medicine for household remedy against various human ailments since antiquity[3-5]. *T. chebula* has been extensively used in Ayurveda, Unani and Homoeopathic medicine and has become a cynosure of modern medicine.

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The observed health benefits may be credited to the presence of the various phytochemicals like polyphenols, terpenes, anthocyanins, flavonoids, alkaloids and glycosides. The purpose of this review is to gather together the available published information on pharmacological and phytochemical analysis of the extracts and some of the isolated compounds of this plant as well as their toxic effects in a bid to highlighting the importance of this untapped resource in the fight against the human diseases.

2. *T. chebula* Retz.

2.1. Botanical description

The tree is tall about 50-80 feet in height. It has round crown and spreading branches. The bark is dark brown with some longitudinal cracks. Leaves are ovate and elliptical, with two large glands at the top of the petiole. The flowers are monoecious, dull white to yellow, with a strong unpleasant odour, borne in terminal spikes or short panicles. The flowers appear May-June, the fruits July-December. The fruit or drupe is about 1-2 inches in size. It has five lines or five ribs on the outer skin. Fruit is green when unripe and yellowish grey when ripe. Fruits were collected from January to April, fruit formation started from November to January[6].

2.2. Special identity

Taxonomic description of *T. chebula* Retz. include Kingdom: Plantae-Plants; Subkingdom: Tracheobionta-Vascular plants; Superdivision: Spermatophyta-seed plants; Division: Magnoliophyta- flowering plants; Class: Magnoliopsida-dicotyledons; Subclass: Rosidae; Order: Myrtales; Family: Combretaceae-Indian almond family; Genus: Terminalia L-tropical almond; Species: *T. chebula* (Gaertn) Retz.-myrobalan.

Varnacular names of *T. chebula* Retz. include Assamese: shilikha; Bengali: haritaki; English: Chebulic myrobalan; Gujrati: hardi, harde; Hindi: hara; Kannada: alale; Konkani : ordo, hardi; Malayalam : katukka; Manipuri: Manali; Marathi: hirda; Oriya: karadha; Persian: halela; Sanskrit: haritaki; Sindhi: har; Tamil: Kata-K-Kay, Kadukkai; Telegu: Karaka; Urdu: Haejarad.

T. chebula is found in the Sub Himalayan tracks from Ravi eastwards to West Bengal and Assam, ascending upto the altitude of 1 500 m in the Himalayas. This tree is wild in forests of Northern India, central provinces and Bengal, common in Madras, Mysore and in the southern part of the Bombay presidency[7].

Classification according to size of the *T. chebula* fruit: Survari harade-which is large, dense, and heavy about 2 inches long, yellowish brown; Rangari harade-these is smaller, less wrinkled and less furrowed than the Survari harade, in length about an inch; the epidermis is yellow; Bala harade-is smaller than the above two varieties, whose colour is deep brown to black; highly wrinkled, dark or brown epidermis; Java harade-these is the smallest of all, other characters are similar to those of Bala harade.

Classification according to the shape of the fruit: Vijaya-having alabu shape, used in all diseases, habitat in Vindahya mountain; Rohini-round in shape, used in vrana, habitat in Zansi and other parts of Madhya Pradesh; Pootana-size is small, mesocarp is less, seed is bigger, externally used, habitat Sindha; Amrita-Mesocarp is more used for shodhanakarma, hibitat Madhya Pradesh and Champaranya; Abhya- fruit having 5 ribs, used in eye diseases, habitate Champaranya, Himalaya; Jeevantee-fruit is golden yellow, used in all diseases, habitate Himalaya; Chetaki-ruit having three ribs, used as purgative.

Classification according to the growth of the fruit: Zira -when the size is that of cumin seed; Javi-when the size is that of barley corn; Zangi-when the size is of a raisin; Chini-when the fruit is greenish yellow and somewhat hard; Asfer-when it is very nearly mature; Kabul-when it is fully matured[8].

3. Ethnobotanical uses

The fruit is mild laxative, stomachic, tonic, alterative, antispasmodic. It is useful in opthalmia, hemorrhoids, dental caries, bleeding gums, ulcered oral cavity. Its paste with water is found to be anti-inflammatory, analgesic and having purifying and healing capacity for wounds. Its decoction is used as gargle in oral ulcers, sore throat. Its powder is a good astringent dentifrice in loose gums, bleeding and ulceration in gums. It is good to increase appetite, digestive aid, liver stimulant, stomachic, gastrointestinal prokinetic agent, and mild laxative. The powder of *T. chebula* fruits has been used in chronic diarrhea. It is used in nervous weakness, nervous irritability. It promotes the receiving power of five senses. It is adjuvant in hemorrhages due to its astringent nature and good for chronic cough, chorizo, sore throat as well as asthma. Also it is useful in renal calculi, dysurea, retention of urine and skin disorders with discharges like allergies, urticaria and other erythematous disorders[4,9].

4. Diseases that have beneficial effects

Digestive diseases, urinary diseases, diabetes, skin diseases, heart diseases, irregular fevers, constipation, ulcers, vomiting, colic pain, haemorrhoids.

5. Phytoconstituents of *T. chebula* Retz.

The fruits of *T. chebula* is rich in tannins (about 32%-34%)

and its content varies with geographical distribution[10,11]. The tannins of *T. chebula* are of pyrogallol (hydrolysable) type. A group of researchers found 14 components of hydrolysable tannins (gallic acid, chebulagic acid, punicalagin, chebulanin, corilagin, neochebulinic acid, ellagic acid, chebulinic acid, 1,2,3,4,6-penta-O-galloyl-β-D-glucose, 1,6-di-o-galloyl-D-glucose, casuarinin, 3,4,6-tri-o-glloyl-D-glucose, terchebulin) from *T. chebula* fruits[12]. Other constituents include phenolics such as chebulinic acid, ellagic acid and anthraquinones. Some of the other minor constituents were polyphenols such as corilagin, galloyl glucose, punicalagin, terflavin A, maslinic acid[13]. Besides, fructose, amino acids, succinic acid, betasitosterol, resin and purgative principle of anthraquinone are also present[14,15]. Flavonol, glycosides, triterpenoids, coumarin conjugated with gallic acids called chebulin as well as other phenolic compounds were also isolated[13,16-18]. Twelve fatty acids were isolated from *T. chebula* of which palmitic acid, linoleic acid and oleic acid were main constituents[19]. Triterpenoid glycosides such as chebulosides I and II, arjunin, arjunglucoside, 2α-hydroxyursolic acid and 2α-hydroxymicromiric acid also have been reported[20]. The leaves were found to contain polyphenols such as punicalin, punicalagin, terflavins B, C, and D[12,21,22]. The plant is found to contain phloroglucimol and pyrogallol, along with phenolic acids such as ferulic, p-coumaric, caffeic and vanillic acids[23]. Oil extracted from kernels yielded palmitic, stearic, oleic, linoleic, behenic and arachidic acids[23].

6. Pharmacological activity

6.1. Antioxidant and free radical scavenging activity

The leaves, bark and fruit of *T. chebula* possessed high antioxidant activity and phenolics were found to be responsible for this activity[24]. Aqueous extract of *T. chebula* inhibited xanthine/xanthine oxidase activity and was also an excellent scavenger of DPPH radicals[25]. *T. chebula* in a polyherbal formulation (Aller-7/ NR-A2) inhibited free radical induced hemolysis and also significantly inhibited nitric oxide release from lipopolysaccharide stimulated murine macrophages[26]. Six extracts and four compounds of *T. chebula* fruit exhibited antioxidant activity at different magnitudes of potency[27]. Strong antioxidant activity of aqueous extract of *T. chebula* was observed by studying the inhibition of radiation induced lipid peroxidation in rat liver microsomes at different doses[28], and methanolic extract was also found to inhibit lipid peroxide formation and to scavenge hydroxyl and superoxide radicals *in vitro*[29]. Acetone extract has stronger antioxidant activity than alpha-tocopherol and HPLC analysis with diode array detection indicated the presence of hydroxybenzoic acid derivatives, hydroxycinnamic acid derivatives, flavonol aglycones and their glycosides, as main phenolic compounds[30].

6.2. Anticarcinogenic activity

A group of researchers have reported the inhibitory action on cancer cell growth by the phenolics of *T. chebula* Retz fruit and found that chebulinic acid, tannic acid and ellagic acid were the most growth inhibitory phenolics of *T. chebula*[31]. Ethanol extract of *T. chebula* fruit inhibited cell proliferation and induced cell death in a dose dependent manner in several malignant cell lines including human (MCF-7) and mouse (S115) breast cancer cell line, human osteosarcoma cell line (HOS-1), human prostate cancer cell (PC-3) and a non-tumorigenic immortalized human prostate cell line (PNT1A)[32]. Besides, acetone extract of bark and fruit powder of *T. chebula* harbors constituents with promising anticarcinogenic activity[32]. Some pharmacological activities of *T. chebula* Retz. are shown in Table 1 and some isolated compounds from *T. chebula* Retz. with their bioactivities are shown in Table 2.

Table 1
Various pharmacological activities of *T. chebula* Retz.

Pharmacological activities	Reference(s)
Antioxidant	24-30
Antibacterial	47-58
Antifungal	59-62
Antiviral	63-70
Antiprotozoal	71-73
Anticarcinogenic	31,32
Radioprotective	25,34
Antimutagenic	33
Chemopreventive	35
Hepatoprotective	36-38
Cardioprotective	39,40
Cytoprotective	41-44
Antidiabetic	45, 46
Renoprotective	45
Antiinflammatory	74,76
Antiarthritic	75
Adaptogenic	77
Antianaphylactic	78
Hypolipidemic	79
Hypocholesterolemic	80
Gastrointestinal motility	81
Antiulcer	82
Antispasmodic	83
Anticaries	53,84
Wound healing	85
Purgative	86
Antiallergic	76
Immunomodulatory	87

6.3. Antimutagenic, radioprotective and chemopreventive activity

Antimutagenic activity of aqueous extract and hydrolyzable tannins from *T. chebula* in *Salmonella typhimurium* has been documented[33]. Gamma radiation

Table 2
Structure and activities of some active compounds and their derivatives from *T. chebula* Retz.

Class of compounds	Compounds	Plant parts	Activities	References
Phenolic acid	Ellagic acid	Fruit	Antibacterial activity against intestinal bacteria *Clostridium perfringes, Escherichia coli*; antiproliferative activity	31,50
Phenolic acid	Chebulic acid	Fruit	Hepatoprotecttive, antioxidant and free radical scavenging activity, cytoprotective	36,41
Phenolic acid	Neochebulic acid	Fruit	Hepatoprotecttive, antioxidant and free radical scavenging activity	36
Phenolic acid	Gallic acid	Fruit	Antioxidant, antibacterial, antiviral, cytoprotective activity	41,51,63
Phenolics	2, 4-chebulyl-beta-D-glucopyranose	Fruit	Antiproliferative activity	31
Phenolic acid	Chebulinic acid	Fruit	Antiproliferative activity	31
Benzoic acid	Hydroxybenzoic acid derivatives	Fruit	Antioxidant activity	30
Cinnamic acid	Hydroxycinnamic acid derivatives	Fruit	Antioxidant activity	30
Flavonoid	Falvonol aglycones	Fruit	Antioxidant activity	30
Glycosides		Fruit	Antioxidant, antibacterial activity	30,50
Phenolic acid	Chebulagic acid	Fruit, Seed	Cytoprotective, anti-arthritic activity	41,75

induced strand breaks formation in plasmid PBR322 DNA was inhibited by aquesous extract of *T. chebula*[25]. The administration of aqueous extract of *T. chebula* prior to whole body irradiation of mice resulted in a reduction of peroxidation of membrane lipids in the mice liver as well as a decrease in radiation induced damage to DNA. It also protected the human lymphocytes from undergoing the gamma radiation-induced damage to DNA exposed *in vitro*[34]. *T. chebula* showed chemopreventive effect on nickel chloride -induced renal oxidative stress, toxicity and cell proliferation response in male Wistar rats[35].

6.4. Hepatoprotective activity

A mixture of chebulic acid (CA) and its minor isomer, neochebulic acid with a ratio of 2:1 isolated from ethanolic extract of *T. chebula* fruits showed strong hepatoprotective activity[36]. Ethanol extract *T. chebula* was found to prevent the hepatotoxiocity caused by the adminstration of rifampicin, isoniazid and pyrazinamide (combination) in sub-chronic model (12 weeks)[37]. Protective effects of an aqueous extract of *T. chebula* fruit on the tert-butyl hydroperoxide-induced oxidative injury was observed in cultured rat primary hepatocytes and rat liver have also been documented[28,29]. *T. chebula* in a herbal formulation (HP-1) showed hepatoprotective activity against carbon tetrachloride induced toxicity in rat hepatocytes[38].

6.5. Cardioprotective activity

T. chebula extract pretreatment was found to ameliorate the effect of isoproterenol on lipid peroxide formation and retained the activities of the diagnostic marker enzymes in isoproterenol induced myocardial damage in rats[39]. Its pericap has also been reported to have cardioprotective activity in isolated frog heart model[40].

6.6. Cytoprotective activity

Gallic acid (GA) and CA were isolated from the extract of the herbal medicine Kashi (myrobalan, the fruit of *T. chebula*) as active principal that blocked the cytotoxic T-lyphocyte-mediated cytotoxicity. Granule exocytosis in response to anti-CD3 stimulation was also blocked by GA and CA at the equivalent concentrations[41]. The ethanolic extract of *T. chebula* fruit exhibited a notable cytoprotective effect on the HEK-N/F cells. In addition its extract exhibited significant cytoprotective effect against UV-induced oxidative damage. These observations were attributed to the inhibitory effect of the *T. chebula* extract on the age dependent shortening of the telomere length as shown by the Southern Blots of the terminal restriction fragments of DNA extracted from sub-culture passages[42]. It exhibited the development of duodenal ulcers and appeared to exert a cytoprotective effect on the gastric mucosa *in vitvo*[43]. Cytoprotective effect on oxidative stress and inhibitory effect on cellular aging of its fruits have also been documented[44].

6.7. Antidiabetic and renoprotective activity

T. chebula fruit and seeds exhibited dose dependent reduction in blood glucose of streptozotocin induced diabetic rats both in short term and long term study and also had renoprotective activity[45,46].

6.8. Antibacterial activity

T. chebula exhibited antibacterial activity against a number of both Gram-positive and Gram-negative human pathogenic bacteria[47-49]. Ethanedioic acid and ellagic acid isolated from butanol fraction of *T. chebula* fruit extract had strong antibacterial activity against intestinal bacteria, *Clostridium perfingens* and *Escherichia coli*[50]. It is effective in inhibiting the urease activity of *Helicobactor pyroli*,

an ubiquitous bacterium implicated in the development of gastritis, ulcers and stomach cancers[49]. GA and its ethyl ester isolated from ethanolic extract of *T. chebula* showed antimicrobial activity against methicillin-resistant *Staphylococcus aureus(S. aureus)*[51]. Ripe seeds of *T. chebula* also exhibited strong antibacterial activity against *S. aureus*[52]. The aqueous extract of *T. chebula* strongly inhibited the growth of *Streptococcus mutans*, salivary bacteria[53]. Diffusate of *T. chebula* showed an inhibitory effect against strain X-100 of the bacterium *Xanthomonas campestris* pv. citri indicating its usefulness for the management of citrus canker disease[54]. It has also growth inhibitory action against *Salmonella typhi*[55], *Klebsiella*[56], *Shigella*[47] and intestinal bacteria[50]. Ethanol extract of *T. chebula* fruit showed strong antibacterial activity against multidrug-resistant uropathogenic *Escherichia coli* and phenolics were found to be responsible for this antibacterial activity[57,58].

6.9. Antifungal activity

An aqueous extract of *T. chebula* exhibited antifungal activity against a number of dermatophytes and yeasts[59,60]. It is effective against the pathogenic yeast *Candida albicans* and dermatophytes *Epidermophyton, Floccosum, Microsporum gypseum* and *Trichophyton rubrum*[59]. Its inhibitory effect on three dermatophytes (*Trichophyton* spp.) and three yeasts (*Candida* spp.) has also been documented[61]. An aqueous extract of galls of *T. chebula* showed inhibitory effects on three dermatophytes (*Trichophyton* spp.) and three yeasts (*Candida* spp.)[59]. *In vitro* anticandidal activity of methanol extract of *T. chebula* was observed against clotrimazole resistant *Candida albicans*[62]. Seed extract exhibited antifungal activity against *Trichophyton glabrata*[59].

6.10. Antiviral activity

T. chebula fruits afforded four immunodeficiency virus type 1 (HIV-1) integrase inhibitors, GA (I) and three galloyl glucoses (II-IV). Their galloyl moiety plays a major role for inhibition against the 3′-processing of HIV-1 integrase of the compounds[63]. *T. chebula* has also retroviral reverse transcriptase inhibitory activity[64]. It protects epithelial cells against influenza A virus, supporting its traditional use for aiding in recovery from acute respiratory infections[65]. The methanol and aqueous extracts of *T. chebula* showed a significant inhibitory activity with $IC_{50} \leqslant 5$ μg/mL on human immunodeficiency virus-1 reverse transcriptase[66]. It also demonstrated the therapeutic activity against herpes simplex virus both *in vitro* and *in vitvo* tests[67]. These finding prompted a team of Japanese researchers to investigate *T. chebulas*′s effect on human cytomagalovirus (CMV). They found that *T. chebula* was effective in inhibiting the replication of human cytomagalovirus *in vitro* and in an AIDS model with immunosuppressed mice and concluded that it may be beneficial for the prevention of CMV diseases and immonocompronised patients[68]. It is also helpful in sexually transmitted diseases and AIDS[69]. Tannins from *T. chebula* are effective against potato virus x[70].

6.11. Antiprotozoal activity

A combination of *T. chebula* and four other botanicals (*Boerhavia diffusa*, *Berberis aristata*, *Tinospora cordifolia*, and *Zingiber officinale*) had a maximum cure rate of 73% in experimental amoebic liver abscess in hamsters[71] and 89% in experimental caecal amoebiasis in rats showing its antiamoebic activity against *Entamoeba histolytica*[72]. The acetone extract of *T. chebula* seeds showed anti plasmodial activity against *Plasmodium falciparum*[73].

6.12. Anti-inflammatory and anti-arthritic activity

Aqueous extract of dried fruit of *T. chebula* showed anti-inflammatory by inhibiting inducible nitric oxide synthesis[74]. Chebulagic acid from immature seeds of *T. chebula* significantly suppressed the onset and progression of collagen induced arthritis in mice[75]. *T. chebula* in a polyherbal formulation (Aller-7) exhibited a dose dependent anti-inflammatory effect against Freund′s adjuvant induced arthritis in rats[76].

6.13. Adaptogenic and antianaphylactic activities

T. chebula fruit was one of the six Ayurvedic herbs administered to animals to test their adaptogenic potential. All six traditional rasayana plants were able to aid the animals against a variety of different stressors working in different ways[77]. Besides, animal studies show that when extract of *T. chebula* was administered following induction of anaphylactic shock, the serum histamine levels were reduced, indicating its strong antianaphylactic action[78]. Water soluble fraction of *T. chebula* had a significant increasing effect on anti-dinitrophenyl IgE-induced tumor necrosis factor-alpha production from rat peritoneal mast cells indicating its strong antianaphylactic action[78].

6.14. Hypolipidemic and hypocholesterolemic acivity

Hypolipidemic activity of *T. chebula* extract against experimentally induced athersclerosis have been documented[79]. It also possessed hypocholesterelomic activity against cholesterol-induced hypercholesterolemia and atherosclerosis in rabbits[80].

6.15. Gastrointestinal motility improving and anti-ulcerogenic activity

Although its traditional use as laxative is well established,

T. chebula fruit has been shown to increase gastric emptying time[81]. This action appeared to be balanced with a protective effect on the gastrointestinal mucosa, with the improvement in the secretory status of Brunner's gland involved in the protection against duodenal ulcer[82].

6.16. Antispasmodic activity

One of the numerous studies of *T. chebula* demonstrated its 'anti-vata' or 'anti-spasmodic' properties by the reduction of abnormal blood pressure as well as intestinal spasms. This confirm its traditional usefulness for spastic colon and other intestinal disorders[83].

6.17. Anticaries activity

The aqueous extract of *T. chebula* strongly inhibited the growth, sucrose induced adherence and glucan induced aggregation of *Streptococcus mutans*. Mouth rinsing with a 10% solution of the extract inhibited the salivary bacterial count and glycolysis of salivary bacteria for upto 90 min post rinsing[53, 84].

6.18. Wound healing activity

Topical administration of an alcoholic extract of *T. chebula* leaves on the healing of rat dermal wounds showed that *T. chebula* treated wounds healed faster as indicated by improved rates of contraction and decreased period of epithelialization[85].

6.19. Purgative property

Purgative action of an oil fraction from *T. chebula* has been documented[86].

6.20. Immunomodulatory activity

Aqueous extract of *T. chebula* produced an increase in humoral antibody titer and delayed type hypersensitivity in mice[87]. Crude extract of *T. chebula* stimulated cell-mediated immune response in experimental amoebic liver abscess in golden hamsters[71].

6.21. Anti-allergic activity

Aller-7, a polyherbal formulation of seven medicinal plants including *T. chebula* exhibited potent *in vitro* antiallergic activity in isolated guineapig ileum substrate[76].

7. Clinical studies

Oral rinsing with extract of *T. chebula* was found to significantly reduce both total bacterial counts and streptococcal counts in saliva samples. The protective effect lasted for about 3 h after rinsing, demonstrating a potential role of *T. chebula* in the prevention of dental caries[53].

A short term clinical trials have been carried out on patients with simple constipation. *T. chebula* increases the stools and has got property of evacuating the bowel completely[88].

Besides, some Ayurvedic drugs, consisting of *T. chebula* as one of the constituents have been subjected to clinical trials regarding their effects on constipation, mental and physical disability, allergic rhinitis and mental stress. In all the cases *T. chebula* containing drugs showed good effects in the treated groups when compared to their normal control patients[89,90].

8. Safety evaluation

From the literature it has been noted that *T. chebula* exhibited significant hepatoprotective[36-38], cardioprotective[39,40], antimutagenic/anticarcinogenic[31-33], cytoprotective[41-44], antioxidant[24-30] and adaptogenic[77,78] effects. Aqueous, ethanol, and ethyl acetate extracts of *T. chebula* fruits also demonstrated no cellular toxicity on sheep erythrocytes as well as acute oral toxic effects on rats at recommended and higher doses[48,91,92]. Besides, hydroalcoholic extract of *T. chebula* fruits demonstrated cytochrome P-450 inhibition potential in rats[93]. *T. chebula* by itself had no genotoxic effect both in VITOTOX test and Ames assay[94]. Rather, *T. chebula* fruit could reduce the lead and aluminium induced genotoxicity[95,96]. The hydrolysable tannins obtained from *T. chebula* fruits also showed antimutagenic activity against direct acting mutagens like sodium azide and 4-nitro-O-phenylene diamine. These findings indicated that it is a safe substance to be used as drug ordinarily.

9. Conclusions and recommendations

T. chebula is one of the most versatile plants having a wide spectrum of pharmacological and medicinal activities. This versatile medicinal plant is the unique source of various types of compounds having diverse chemical structure. Though it has a number of pharmacological activities due to the presence of various types of bioactive compounds, very little work has been done on the plausible medicinal applications of this plant against the diseases particularly on multidrug resistant bacterial pathogens. Hence extensive investigation is needed to exploit their therapeutic ability to combat diseases including drug resistant infections. As the global scenario is now changing towards the use of nontoxic plant products having traditional medicinal use,

a drug development programme should be undertaken to develop modern drugs with the compounds isolated from *T. chebula* effective against different types of diseases and also to overcome the problem of drug resistance after extensive investigation of its bioactivity, mechanism of action, pharmacotherapeutics, toxicity and after proper standardization and clinical trials.

Conflict of interest statement

We declare that we have no conflict of interest.

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Comments

Background

This is a review paper on the benefits of *T. chebula* as an alternative medicine for many diseases. The pharmacological effects exhibited by this plant have been elaborated in depth with citations from studies that have been conducted using this Ayurvedic plant.

Research frontiers

There is no lab experiment being done in this manuscript since it is a review paper. However, the author cited latest and recent publications on works done in this particular field, in which bring the readers to the recent analytical approach for pharmacological potential of this plant.

Related reports

The author cited different papers in his manuscript to support the therapeutic potential of *T. chebula* in traditional medicine. Past studies mostly presented the pharmacological activities of this plant done *in vitro* and *in vivo*.

Innovations and breakthroughs

This review paper is one of its own in which it summarizes any research that have been conducted on *T. chebula* specifically in medicinal field. It is a good source of literature survey for researchers who intended to do studies in this particular field, and using this plant.

Applications

This paper could be applied by most Ayurvedic practitioners in their medication activities to treat patients with different types of diseases.

Peer review

This paper is a good review paper on Ayurvedic and pharmacological activities of *T. chebula*. Citations used are also a good resources for reviewing and very informative to all the Ayurvedic and traditional practitioners.

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