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Review Article

BIOLOGICAL AND PHARMACOLOGICAL PROPERTIES OF *TERMINALIA CHEBULA* RETZ. (HARITAKI)- AN OVERVIEW

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ABSTRACT

Medicinal plants have been considered valuable and cheap source of unique phytoconstituents which are used extensively in the development of drugs against various diseases. A large proportion of the world population, especially in the developing countries relies mainly on the traditional system of medicine. The use of plants and plant products in medicines is getting popularized because the herbal medicines are cheap and have natural origin with higher safety margins and lesser or no side effects. *Terminalia chebula* Retz. (*T. chebula*) belongs to the family Combretaceae and is one of the most important medicinal plants used in medicines of ayurveda, siddha, unani and homeopathy. It is called the "King of Medicines" in Tibet and is listed first in the Ayurvedic material medica because of its extraordinary power of wound healing and a wide spectrum of medicinal properties. *T. chebula* possesses antibacterial, antifungal, antiviral, antidiabetic, antimutagenic, antioxidant, antiulcer and wound healing properties. It also prevents cardiac damage and is used for the treatment of kidney disease. It is a mild, safe and effective laxative in traditional medicine. *T. chebula* and its phytoconstituents have therapeutic effect with no toxicity. *T. chebula* is an active ingredient of the well known herbal preparation, Triphala, which is used for the treatment of enlarged liver, stomach disorders and pain in eyes. This review gives a bird's eye view on the biological and pharmacological properties of various extracts and isolated phytoconstituents of *T. chebula* to enrich our knowledge about this plant.

Keywords: *Terminalia chebula*; Haritaki; Phytoconstituents; Triphala; Chebulic acid; Anti-diabetic

INTRODUCTION

Medicinal plants are part and parcel of human society from the dawn of civilization to combat diseases and have been considered valuable and cheap source of unique phytoconstituents which are used extensively in the development of drugs against various diseases [1,2,3]. Several hundred genera of plants are used medicinally mainly as herbal preparations in the indigenous systems of medicine in different countries which have stood the test of time, and therefore, modern medicines has not been able to replace most of them. The World Health Organization reported that 80% of the world population relies chiefly on traditional medicines involving the use of plant extracts or their active constituents [4]. It has been estimated that in developed countries such as United States, plant drugs constitute as much as 25% of the total drugs, while in fast developing countries such as China and India, the contribution is as much as 80%. Thus, the economic importance of medicinal plants is much more in countries like India than in rest of the world. In the last few decades, the field of herbal medicine is getting popularized in both developed and developing countries [5]. This is because the herbal medicines are cheap, and have natural origin with higher safety margins and lesser or no side effects [6]. *Terminalia chebula* (*T. chebula*) is a flowering evergreen tree of the family Combretaceae. It has several common names such as black myrobalan, ink tree, or chebulic myrobalan (English), haritaki (Sanskrit and Bengali), harad (Hindi), harada (Marathi and Gujrati) Karkchettu (Telgu) and Kadukkaya (Tamil). In Tibet, *T. chebula* is called as the "King of Medicine" [7]. It well known as 'haritaki' since it carries away all diseases or it is sacred to God Siva (Hara). Haritaki has several interesting synonyms like 'pathya', since it removes obstructions from the pathways and channels in the body; 'abhaya', since it gives fearlessness; 'amrta', means an ambrosia; 'divya', means a divine herb; 'medhya', means a nerve tonic; 'pranada', means life saving; 'jivaniya', means a vitalizing herb; 'vayahstha', means one that promotes longevity and maintains youth; 'rasayana phala', means a rejuvenating fruit etc. In Indian mythology, this plant is supposed to be originated from the drops of ambrosa (Amrita) which fell on the earth when God Indra drunk it.

Botanical description

Taxonomy

Kingdom: Plantae

Division: Magnoliophyta

Class: Magnoliopsida

Order: Myrtales

Family: Combretaceae

Genus: ***Terminalia***

Species: ***chebula***

Habit and Habitat

T. chebula is a medium to large highly branched deciduous tree with a height up to 30 m and girth 1-1.5 m. Leaves are 10-30 cm long elliptical with an acute tip and cordate base. The vasculature of the leaves consists of 6-8 pairs of veins. Flowers are short stalked, monoecious, dull white to yellow with a strong unpleasant odour and are found in simple terminal spikes or short panicles. Fruits are 3-6 cm long and 1.3-1.5 cm broad yellowish-green ovoid drupes containing one oval seed. *T. chebula* is capable of growing in a variety of soils, clayey as well as shady. The trees may grow at places up to a height of about 2000 m from the sea level, and in areas with an annual rainfall 100-150 cm and temperature 0-17° C. *T. chebula,* though, is a native of Asia, but also found in Nepal, Sri Lanka, Myanmar, Bangladesh, Egypt, Iran and Turkey and also in Pakistan and Yunnan, Tibet, Guangdong, Guangxi province of China. In India, it grows in deciduous forests of Himachal Pradesh, Tamil Nadu, Kerala, Karnataka, Uttar Pradesh, Andhra Pradesh and West Bengal [8].

Plant Fruits

Varieties

Depending on the type of fruits, *T. chebula* (haritaki) is classified into seven types. Of these seven types, vijaya is considered to be the best.

1) Vijaya - in Vindhya - oval in shape.

2) Rohini - found everywhere, round in shape.

3) Pootana - Sindh - small and less bulky.

4) Amruta - Champaranya - bulky.

5) Abhaya - Champadesha - fruit has five lines on it (eye diseases).

6) Jeevanti - Saurashtra - yellow in colour.

7) Chetaki - found in the Himalayas - having three lines on it.

In practice, however, there are three types of haritaki viz. (1) Bala haritaki, (2) Chambhari (rangari) haritaki and (3) Survari haritaki. When the fruit of haritaki falls off from the tree, the seed gets hard called 'bala haritaki'. Sometimes, the fruits are plucked and dried while the seeds have not hardened which are also called 'bala haritaki'. Chambhari haritaki is an immature fruit of haritaki, whereas a fully mature fruit of haritaki is called 'survari haritaki'. A fruit of haritaki which doesn't float in water, which is fresh, smooth, bulky, round in shape and weighs at least 26 g is considered ideal for medicinal use. The fruit of haritaki contains five rasas namely: (1) madhur (sweet) - the fruit pulp, (2) amla (sour) - the bulky portion of the fruit, (3) tikta (bitter) – seed, (4) katu - the covering of the fruit and (5) kashaya (astringent) - the hard portion of the seed. Thus, haritaki is pancharasatmak. Ayurvedic texts emphasize daily use of haritaki for regularizing all the normal functions of the body.

Fig. 1: ***Terminalia chebula***

Phytochemical properties

T. chebula, though, contains several phytoconstituents like tannins, flavonoids, sterols, amino acids, fructose, resin, fixed oils *etc*., however, it is fairly rich in different tannins (approximately 32% tannin content). Further, tannin content of *T. chebula* largely depends on its geographic location [9]. The chief components of tannin are chebulic acid, chebulinic acid, chebulagic acid, gallic acid, corilagin and ellagic acid.

Tannins of *T. chebula* are of pyrogallol (hydrolysable) type. There are about 14 hydrolysable tannins (gallic acid, chebulic acid, punicalagin, chebulanin, corilagin, neochebulinic acid, ellagic acid, chebulegic acid, chebulinic acid, 1,2,3,4,6-penta-O-galloyl-b-D-glucose, casuarinin, 3,4,6-tri-O-galloyl-D-glucose and terchebulin) which have isolated from fruits of *T. chebula* [10]. Phytochemicals like anthraquinones, ethaedioic acid, sennoside, 4,2,4 chebulyl-d-glucopyranose, terpinenes and terpinenols have also been reported to be present [8,11]. Triterpenoids and their glycosides have been isolated from stem bark of *T. chebula* [12]. Recent studies show that *T. chebula* contains more phenolics than any other plant [13].

TRADITIONAL VALUES OF HARITAKI

Charaka Samhita and Sushrusha Samhita, though, extensively describe various medicinal plants, *T. chebula* (haritaki) enjoys the prime place among medicinal plants not only in India but also in other countries like Asia and Africa. It is extensively used in ayurveda, siddha, unani and homeopathic medicines in India. It is a top listed plant in Ayurvedic Materia medica for treatment of asthma, bleeding piles, sore throat, vomiting and gout [7]. It is used in Thai traditional medicine as a carminative, astringent and expectorant [14]. According to Vagbhata, it is the drug of choice in the therapy of 'vata-kapha' diseases. The 'Triphala', a herbal preparation of 'three fruits' from plants *Terminalia chebula*, *Terminalia bellerica*, *Emblica officinalis*, is used as laxative in chronic constipation, detoxifying agent of the colon, food digestive problems (poor digestion and assimilation) and rejuvenator of the body [15]. Certain studies have shown that 'Triphala' stimulates apetite, and is useful in treating cancer and detoxification. Triphala is considered as the most versatile of all herbal formulations and is prescribed as a cardiotonic and for candid infection [16].

The fruits of haritaki are used both externally as well as internally for medicinal purposes. Externally, the paste of fruits effectively reduces the swelling, hastens the healing and cleanses the wounds and ulcers. In erysipelas and other skin disorders, haritaki prevents accumulation of pus in skin diseases. The oil of haritaki is extremely helpful in healing of wounds especially in burns. The paste of fruit is also applied in conjunctivitis for relief due to its anti-inflammatory property. The gargles with its decoction give excellent results in stomatitis and problems of the throat. Triphala can be used externally for hair wash, for brushing the teeth in pyorrhea or bleeding gums, and its decoction for washing the chronic, non-healing wounds and ulcers. A fine powder of haritaki is used as a tooth powder to strengthen the gums. Aqueous extract *of T. chebula*, which is used as a mouth rinse, is an anticaries agent [17].

Internally, hartaki is used to cure a vast variety of diseases. Haritaki is recommended with rock salt in 'kapha' diseases, with sugar in 'pitta' diseases and with the ghee in 'vata' diseases. Haritaki acts as a rejuvenator when taken with various supportive dravyas in different seasons. There is a specific reference of the 'anupana' (a substance that serves as a medium for the herbs to be taken with) with which haritaki should be combined, with reference to the season. In varsa ritu (July- August), it should be taken with rock salt, in sarad ritu (September-October) with sugar, in hemanta ritu (November-December) with sunthi, in sisira ritu (January-February) with pippali, in vasanta ritu (March-April) with honey and in grisma ritu (May-June) with jaggery. According to Vagbhata, when haritaki powder fried in ghee is regularly consumed with sufficient ghee in food, it promotes longevity and boosts energy. Common gastrointestinal ailments, tumours, ascites, piles, enlargement of liver and spleen, worms, colitis can be treated well with haritaki. The bark of haritaki, if eaten after chewing, improves digestion. 'Bala haritaki' is useful in haemorrhoids and in clearing the bowels. The mixture of Triphala powder and haridra is a well known adjunct in diabetes. Bronchospasm is mitigated effectively with the combination of haritaki and bibhitaka powders with honey. In abdominal pain due to flatulence, it is given with jiggery and ghee. The most popular combination of haritaki, musta, sunthi and jaggery is an effective panacea for diarrhoea, dysentery, flatulence *etc*. 'Haritaki siddha ghrta' is beneficial in chronic fever. The decoction of haritaki or triphala is given along with honey in hepatitis. Haritaki powder with honey and ghee is also effective remedy for anemia. In obesity, its decoction with honey reduces the excessive body fats. Regular use of haritaki improves memory due to beneficial effects on the nerves of brain. It is also valuable in dysuria and urinary stones [18].

Precautions: Haritaki should be carefully used by lean individuals, in severe weakness, fast, mental depression, pitta conditions and in pregnancy.

Safety evaluation: The ethyl acetate-soluble portion of *T. chebula* ethanolic extract containing 29.4% chebulic acid was tested for *in vitro* mutagenicity assay, and in a single- and 14-day

repeated dose oral toxicity study to find out the safety in use of the plant extract. In the bacterial mutation assay, up to 5000 µg/ml concentration of the ethyl acetate-soluble portion, the numbers of colonies did not increase whether with or without metabolic activation. In the oral toxicity study, the single oral dose of the extract at 2000mg/kg body weight did not produce mortality or abnormal lesions in the internal organs of rats. The results of a 14-day orally repeated dose showed that *T. chebula* extract had no adverse effects at 2000 mg/kg body weight in rats [19].

Popular ayurvedic preparations: Triphala curna, Abhayamodaka, Abhayarista, Pathyadi curna/vatl/kvatha, Vyaghn haritaki, Gandharva haritaki *etc*.

PHARMACOLOGICAL PROPERTIES

Antibacterial activity

Two antibacterial compounds, gallic acid and ethyl ester against methicillin-resistant *Staphylococcus,* have been isolated from ethyl alcohol extract of fruits of *T. chebula* [20]. Various extracts of *T. chebula* exhibit antibacterial activity against a number of bacterial species [21]. *T. chebula* is well effective against *Helicobacter pyroli*, a bacterium responsible for gastritis, ulcer and stomach cancers. The ether, alcoholic and aqueous extracts of *T. chebula* were tested against *Helicobactor pylori*, but aqueous extract of the plant, at a concentration of 1-2.5 mg/ml, inhibited urease activity of *H. pylori* [22]. Several biologically active components were isolated from butanol fraction of fruit extract of *T. chebula* and tested against six intestinal bacteria. Ethanedioic acid showed strong and moderate inhibitory activity against *Clostridium perfringens* and *Escherichia coli*, respectively, with no adverse effects on the growth of the four tested lactic acid-producing bacteria. Ellagic acid exerted a potent inhibitory effect against *C. perfringens* and *E. coli,* but little or no inhibition was observed for behenic acid, β-caryophyllene, eugenol, isoquercitrin, oleic acid, α-phellandrene, β-sitosterol, stearic acid, α-terpinene, terpinen-4-ol, terpinolene, or triacontanoic acid [23]. The ethanolic extract of *T. chebula* fruit was found effective against both gram-positive and gram-negative bacteria such as *Salmonella typhi* SSFP 4S, *Staphylococcus epidermidis* MTCC 3615, *Staphylococcus aureus* ATCC 25923, *Bacillus subtilis* MTCC 441 and *Pseudomonas aeruginosa* ATCC 27853 suggesting its broad spectrum antimicrobial activity [24].

Antifungal activity

Aqueous extract of *T. chebula* has been reported to show antifungal activity against a number of dermatophytes (*e.g. Epidermophyton*, *Floccosum*, *Microsporum gypseum* and *Tricophyton rubrum*) and yeasts (*e.g. Candida albicans*) [25,26,27]. Aqueous, alcoholic and ethyl acetate extracts of leaves of *T. chebula* were also tested against five pathogenic fungi (*Aspergillus flavus*, *A. niger*, *Alternaria brassicicola*, *A. alternata* and *Helminthosporium tetramera*) using paper disc method and were found effective compared to that of the reference standard Carbendazim [28].

Antiamoebic and immunomodulatory activities

The antiamoebic effect of a crude drug formulation of *T. chebula* was investigated in experimental caecal amoebiasis in rats with a curative rate of 89% at 500 mg/kg body weight due varying degrees of inhibition of enzyme activities such as DNase, RNase, aldolase, alkaline phosphatase, acid phosphatase, α-amylase and protease in axenically cultured amoebae [29]. In another study, *T. chebula* was evaluated in experimental amoebic liver abscess in golden hamsters and in immunomodulation studies. The formulation had a maximum cure rate of 73% at 800 mg/kg body weight in hepatic amoebiasis. In immunomodulation studies, humoral immunity was enhanced where T-cell counts remained unaffected in the animals, but cell-mediated immune response was stimulated [30].

Antiplasmodial activity

The water extract of *T. chebula* showed antiplasmodial activity *in vitro* by its ability to inhibit the uptake of [^{3}H] hypoxanthine into the *Plasmodium falciparum* K1 multidrug-resistant strain and *in vivo* [31].

Acetone seed extract of *T. chebula* was also found to have good antiplasmodial activity in a study [32].

Molluscicidal activity

The molluscicidal activity of ethanolic extract of *T. chebula* fruit powder was studied against the vector snail *Lymnaea acuminata* and was found time and concentration dependent. Column, thin layer and high performance liquid chromatography analyses demonstrated that the active molluscicidal component in *T. chebula* was tannic acid. Hence, *T. chebula* could be a potent source of molluscicides against the snail *L. acuminata* [33].

Anthemintic activity

The ovicidal and larvicidal activities of ethyl acetate, acetone, and methanol extracts of dried leaves and seeds of *T. chebula* were tested *in vitro* on *Haemonchus contortus* based on egg hatch and larval development assays at 50, 25, 12.5, 6.25 and 3.13mg/ml. The extracts of leaves and seeds of *T. chebula* showed complete inhibition at 50mg/ml [34].

Antiviral activity

The extract of fruits of *T. chebula* showed inhibitory effects on human immunodeficiency virus-1 reverse transcriptase [35]. Hot water extract of *T. chebula* showed anti-herpes simplex virus (HSV) activity *in vivo* and anti-cytomegalovirus (CMV) activity both *in vitro* and *in vivo* in a study [36]. Ledretan-96 and each of its 23 individual components were tested on an epithelial tissue culture cell line for their protective activity against cytotoxic effects caused by influenza A virus. Of the 23 components tested, only one component showed a significant protective effect when applied to the epithelial cells individually [37]. A study proved that *T. chebula* fruits contain four human HIV-type 1 integrase inhibitors such as gallic acid and three galloyl glucoses, and suggested that galloyl moiety had a major role for inhibition of the 3′-processing of HIV-1 integrase by these compounds [38]. *T. chebula* can also be used in sexually transmitted diseases and AIDS [39]. Recently, acetone extract of *T. chebula* has emerged as a new alternative to treat pandemic swine influenza A infection due to its low cost, easy preparation and potential effect [40]. Herpes simplex virus 1 (HSV-1) is the cause of lifelong latent infection of sensory neurons. Two hydrolyzable tannins, chebulagic acid and punicalagin, isolated from the dried fruits of *T. chebula* inhibited HSV-1 entry at non-cytotoxic doses in A549 human lung cells by preventing binding, penetration, and cell-to-cell spread, as well as secondary infection [41].

Antimutagenic and anticarcinogenic activities

The effect of 70% methanolic fruit extract of *T. chebula* was studied on growth of several malignant cell lines including a human (MCF-7) and mouse (S115) breast cancer cell line, a human osteosarcoma cell line (HOS-1), a human prostate cancer cell line (PC-3) and a non-tumorigenic, immortalized human prostate cell line (PNT1A) using assays for proliferation (^{3}H-thymidine incorporation and coulter counting), cell viability (ATP determination) and cell death (flow cytometry and Hoechst DNA staining).). In all cell lines studied, the extract decreased cell viability, inhibited cell proliferation, and induced cell death in a dose dependent manner [13]. Acetone extract of *T. chebula* has been reported to contain phytochemicals with promising antimutagenic and anticarcinogenic properties [42]. One of the fractionated compounds from ethanolic fruit extract of *T. chebula*, chebulagic acid, showed potent dual inhibition against COX and 5-LOX. It also showed anti-proliferative activity against HCT-15, COLO-205, MDA-MB-231, DU-145 and K562 cell lines [43]. A recent study has shown the ability of Triphala to inhibit cytochrome P450 [44].

Antioxidant activity

T. chebula is an excellent anti-oxidant. In a study, 6 extracts and 4 pure compounds of *T. chebula* exhibited anti-lipid peroxidation, anti-superoxide radical formation and free radical scavenging activities at different magnitudes of potency [45]. The aqueous extract of *T. chebula* protected the antioxidant enzymes from reactive oxygen species (ROS) produced by gamma radiation in the rat liver

microsomes and mitochondria [5]. The ethanolic extract of the fruits of *T. chebula* decreased the level of lipid peroxidase in albino rats [46]. Both treatment and pretreatment of the cultured rat primary hepatocytes with *T. chebula* aqueous fruit extract (500 or 1000 mg/kg body weight for 5 days) significantly reversed the *t*-BHP-induced cell cytotoxicity and lactate dehydrogenase leakage. In addition, *T. chebula* extract exhibited *in vitro* ferric-reducing antioxidant activity and 2,2-diphenyl-1-picryhydrazyl free radical-scavenging activities. Histopathologic examination of the rat livers showed that *T. chebula* extract reduced the incidence of liver lesions including hepatocyte swelling and neutrophilic infiltration, and repaired necrosis induced by *t*-BHP [47]. Further, a hepatoprotective compound, isolated from the ethanolic extract of the fruits of *T. chebula*, was identified as a mixture of chebulic acid and its minor isomer, neochebulic acid that also reduced the tert-butyl hydroperoxide (t-BHP)-induced cell cytotoxicity in isolated rat hepatocyte experiment [48]. An aglycone isolated from the fruits of *T. chebula*, triethylchebulate, significantly inhibited $FeSO_4$ /Cys-induced microsomes lipid peroxidation and protected both H_2O_{2-} -induced RBCs hemolysis and RBCs auto-hemolysis in a dose-dependent manner. Furthermore, triethylchebulate demonstrated potent DPPH free-radical scavenging ability and moderately suppressed azide-induced mitochondria ROS formation. The results demonstrated that triethylchebulate was a strong antioxidant and free-radical scavenger, which might contribute to the anti-oxidative ability of *T. chebula* [49].

Antidiabetic and retinoprotective activities

Oral administration of 75% methanolic extract of *T. chebula* (100 mg/kg body weight) reduced the blood sugar level in normal and alloxan diabetic rats significantly within 4 h. Continued daily administration of the drug produced a sustained effect [50]. The chloroform extract of *T. chebula* seeds (100, 200 and 300 mg/kg body weight) produced dose-dependent reduction in blood glucose of diabetic rats in both short term and long term study (300 mg/kg body weight for 8 weeks). Further, remarkable renoprotective activity was also observed in *T. chebula* treated rats [51]. Oral administration of ethanolic extract of fruits of *T. chebula* (200 mg/kg body weight for 30 days) reduced the levels of blood glucose and glycosylated hemoglobin in streptozotocin (STZ)-induced experimental diabetic rats [52]. In a similar study, aqueous extract of *T. chebula* (200 mg/kg body weight for two months) reduced the elevated blood glucose and increase in glycosylated hemoglobin. The same dose also showed a marked improvement in controlling the elevated blood lipids as well as decreased serum insulin levels. The *in vitro* studies with pancreatic islets showed that the insulin release was nearly two times more than that in untreated diabetic animals. The treatment did not have any unfavorable effect on liver and kidney function tests [53].

Antianaphylactic and adaptogenic activities

T. chebula along with several other medicinal plants helps to resist against a number of stressors in different ways [54]. *T. chebula,* when given following anaphylactic shock, reduces the serum histamine level showing a strong antianaphylactic activity [55].

Antinociceptive activity

The petroleum ether, chloroform, ethanol and water extracts of *T. chebula* fruits were evaluated for their analgesic activity using the tail immersion model in mice. The ethanolic extract of the plant exhibited analgesic response at 200,400 and 800mg/kg body weight in acute pain and in chronic pain studied for 15 days with maximum analgesic response on 14th day. The results suggested that *T. chebula* could be a potential candidate for bioactivity-guided isolation of natural analgesic agents in the management of chronic pain [56].

Antiulcerogenic activity

Animals pretreated at 200 and 500 mg/kg body weight with hydroalcoholic extract of *T. chebula* showed reduction in lesion index, total affected area and percentage of lesion in comparison with control groups in the aspirin, ethanol and cold restraint stress-induced ulcer models. The *T. chebula* extract increased mucus production in aspirin and ethanol-induced ulcer models and showed antisecretory activity in pylorus ligated model leading to a reduction in the gastric juice volume, free acidity, total acidity, and significantly increased gastric pH [57].

Anti-arthritic activity

The hydroalcoholic extract of *T. chebula* produced a significant inhibition of joint swelling as compared to control in both formaldehyde-induced and CFA-induced arthritis. *T. chebula* treatment also reduced serum TNF-α level and synovial expression of TNF-R1, IL-6 and IL-1β. The authors believed that *T. chebula* could be used as a disease-modifying agent in treatment of rheumatoid arthritis [58].

Wound healing activity

Topical administration of alcoholic extract of the leaves of *T. chebula* caused much faster healing of rat dermal wounds *in vivo* due to improved rates of contraction and a decreased period of epithelialization. Biochemical studies revealed increase in total protein, DNA and collagen contents in the granulation tissues of treated wounds. The levels of hexosamine and uronic acid also increased up to day 8 post-wounding. The tensile strength of tissues in extract-treated incision wounds increased by about 40%. These results strongly documented the beneficial effects of *T. chebula* in the acceleration of the healing process [59]. In another study, healing activity of ethanol extract of *T. chebula* against the indomethacin-induced stomach ulceration was reported [60]. In alloxan induced diabetic rats, the hydroalcoholic extract of *T. chebula* fruit exhibited 82% reduction in the wound area due to faster epithelialization compared to controls [61]. Tannins extracted from immature fruits of *T. chebula* inhibited *Staphylococcus aureus* and *Klebsiella Pneumonia in vitro* and promoted cutaneous wound healing in rats due to a powerful anti-bacterial and angiogenic activity of the extract [62]. The wound healing activity of ethanolic extract of fruits of *T. chebula* in the form of an ointment with two concentrations (5% and 10% w/w ointment of bark extract in simple ointment base) showed significant response in excision and incision models in albino rats compared to controls [63].

Cytoprotective and antiaging activities

Gallic acid and chebulagic acid, isolated from fruit extract of *T. chebula*, blocked cytotoxic T lymphocyte (CTL)-mediated cytotoxicity. Granule exocytosis in response to anti-CD3 stimulation was also blocked by the above phytochemicals at the equivalent concentrations [64]. The ethanol extract of the fruits of *T. chebula* inhibited oxidative stress and the age-dependent shortening of the telomeric DNA length. In the peroxidation model using *t*-butanol, *T. chebula* extract showed a notable cytoprotective effect on HEK-N/F cells. In addition, the *T. chebula* extract exhibited cytoprotective effect against UVB-induced oxidative damage. The life-span of the HEK-N/F cells was elongated by 40% as a result of the continuous administration of 3 µg/ml of *T. chebula* extract compared to controls [65]. The extracts of *T. chebula* gall were tested for antioxidative and tyrosinase inhibition activities as well as for proliferative and MMP-2 inhibition activities on early aging human skin fibroblasts to evaluate *in vitro* anti-aging activity. The cold water extract of *T. chebula* gall indicated the highest stimulation index (SI) on normal human fibroblast proliferation. The extract also demonstrated MMP-2 inhibition on fibroblasts 1.37 times more potent than ascorbic acid. The study confirmed the traditional use of *T. chebula* gall in many Thai medicinal plant recipes for longevity [66].

Radioprotective activity

Treatment of mice with aqueous extract of Triphala in different doses consecutively for five days before irradiation delayed the onset of mortality and reduced the symptoms of radiation sickness compared to controls [67]. In an experiment, aqueous extract of the fruit of *T. chebula* (50µg) was able to neutralize 1,1-diphenyl-2-picrylhydrazyl, a stable free radical by 92.9% and protected the plasmid DNA pBR322 from undergoing the radiation-induced strand breaks. The administration of *T. chebula* (80 mg/kg body weight, i.p.) prior to whole body irradiation of mice resulted in reduction of peroxidation of membrane lipids in the liver and decrease in

radiation-induced damage to DNA. *T. chebula* extract also protected the human lymphocytes from undergoing the gamma radiation-induced damage to DNA exposed *in vitro* to gamma-radiation [68].

Cardioprotective activity

Cardioprotective effect of ethanolic extract of *T. chebula* fruits (500 mg/kg body weight) was investigated in isoproterenol induced myocardial damage in rats. It was reported that the pretreatment with *T chebula* extract had cardioprotective effect due to the lysosomal membrane stabilization preventing myocardial necrosis and inhibition of alterations in the heart mitochondrial ultrastructure and function in the experimental rats [69,70,71].

Hepatoprotective activity

The 95% ethanolic extract of *T. chebula* fruit showed hepatoprotective activity against anti-tuberculosis (anti-TB) drug-induced toxicity which could be attributed to its prominent anti-oxidative and membrane stabilizing activities [72].

Chemomopreventive activity

In an investigation, *T. chebula* extract treatment prevented nickel chloride induced renal oxidative stress, toxicity and cell proliferation response in male Wistar rats. The authors suggested that *T. chebula* extract could be used as therapeutic agent for cancer prevention as it blocked or suppressed the events associated with chemical carcinogenesis [73].

Hypolipidemic and hypocholesterolemic activities

T. chebula extract administration showed hypolipidaemic activity against experimentally induced atherosclerosis[74] and hypocholesterolemic activity against cholesterol-induced hypercholesterolemia and atherosclerosis [75]. Triphala formulation was found to have hypolipidaemic effects on the experimentally induced hypercholesteremic rats [76].

Antispermatogenic activity

The oral administration (300 mg/kg body weight for 28 days) of bark of *T. chebula* extracted in acetone, methanol, 50% ethanol, and in aqueous solvents caused histological alterations in seminiferous tubules in testes of treated mice. However, aqueous bark extract of the plant showed more testicular alterations than those treated with other extracts. The level of sialic acid in the epididymis and that of fructose in the seminal vesicle were significantly reduced in aqueous extract-treated mice compared to controls. Sperm parameters, however, were adversely affected in mice in all extracts-treated groups compared to controls. The results of the study in mice suggested that the aqueous bark extract of *T. chebula* is more effective in its suppressive effect on the male reproductive end points than the other extracts [77].

CONCLUSION

In spite of the overwhelming influences and our dependence on modern medicines and tremendous advances in synthetic drugs, a large segment of the world population still likes drugs of plants origin. Of the 2,50,000 higher plant species on earth, more than 80,000 are medicinal. However, only 7000-7500 species are used for their medicinal values by traditional communities. *Terminalia chebula* (haritaki) is one of the most important medicinal plants used in medicines of ayurveda, siddha, unani and homeopathy because of having a number of pharmacological properties. It is the source of a variety of biologically active phytoconstituents such as chebulic acid, chebulinic acid, chebulagic acid, gallic acid, corilagin ellagic acid and other related compounds which are responsible for antimicrobial, antioxidant, antihyperglycemic, anticancer and protective effects on various vital organs such as nerves, heart, kidney and liver. Traditionally, this plant is used to treat a huge variety of health problems. Therefore, there is an urgent need to investigate the biological activity of its phytoconstituents for development of an effective, safe and cheap herbal drug.

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