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Phytochemistry and Medicinal Value of Harad (*Terminalia chebula* Retz.) the 'King of Medicinal Plants'

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ABSTRACT

Terminalia chebula, popularly known as Harad, black- or chebulic myrobalan contains hydrolysable tannins. This dominantly contains many phytochemicals viz., casuarinin, chebulanin, chebulagic acid, chebulinic acid corilagin, ellagic acid, gallic acid, neochebulinic acid, punicalagin, 1,2,3,4,6-penta-O-galloyl-β-D-glucose,1,6-di-o-galloyl-D-glucose,3,4,6-tri-o-glloyl-D-glucose, terchebulin. There are many medicinal investigations recording viz., antiulcer, antioxidant, anticarcinogenic, antimutagenic, radio protective, hepatoprotective, cardioprotective, cytoprotective, antidiabetic, renoprotective, antibacterial, antifungal, antiviral, antiprotozoal, anti-inflammatory, antiarthritic, antispasmodic, wound healing and anticonceptive, molluscidal, anthelmintic, anaphylactic, hypolipidemic, hypocholesterolemic. Also having chemopreventive potential and adaptogenic activities. This has purgative property, immunomodulatory, analgesic, antiallergic, neuroprotective, acetylcholine inhibition activity and have gastrointestinal motility improving activity. This is beneficial in bronchial asthma and also useful as dye for fabrics.

Keywords: *Terminalia chebula*, Phytoconstituents, Antiulcer, Anticarcinogenic, Antimutagenic, Anthelmintic, Cardioprotective, Cytoprotective

INTRODUCTION

Terminalia chebula Retz. (*Harad*) belonging to Family-Combretaceae grows abundantly especially in Northern India and in the forests of Assam, West Bengal, Bihar and also Konkan. This have applications in Ayurveda, Homoeopathic and Unani system of medicines. The plant *T. chebula* is a gentle purgative, astringent and is used in prescriptions for treating constipation, flatulence, dysentery, diarrhoea, cyst, digestive disorders, vomiting, enlarged liver and spleen, cough, bronchial asthma since antiquity and for metabolic harmony. Its bark is diuretic. The fruits of the tree give various health benefits. The powder of mature fruits has also been in use in intermittent fevers, chronic fevers, anaemia and polyuria [1] and against various human ailments [2,3] including diabetes [4].

T. chebula (Harad) is widely used in the traditional medicine of India and Iran to treat diseases that include constipation, dementia and diabetes [5]. It is one of the three constituents of triphala used in India as common herbal medicine.

This contains many phytoconstituents that is useful in various human related diseases. The main purpose of this essay is to find information conducted on different pharmacological and phytochemical investigations done on different parts of the *T. chebula* plant. It may be useful in removing human health problems.

Vernacular names

English-Chebulic Myrobalan, Black Myrobalan; Hindi; Harra, Harad; Ayurvedic-Haritaki, Kaayasthaa, Pathyaa, Shreyasi, Shivaa. (Jivanti Puutanaa, Vijayaa, Abhayaa, Rohini, Chetaki, Amritaa; Unani-Harad, Halelaa siyaah, Halelaa zard, Halelaa Kaabuli (varieties); Siddha/Tamil-Kadukkai.

Ecology and distribution

T. chebula shows its distribution as mixed deciduous tree in forests of teak and uses light strongly. This can withstand some shade and can benefit in protection from sun effect (Figure 1). This being drought and frost tolerant can withstand fire so can recover well in burning. It shows poor regeneration. This is mainly because the fruits are taken away by farmers of local area and through animal's predation. This being medium to large deciduous tree attains 98 ft (30 mt) tallness and having a trunk up to 3 ft 3 in (1 m) in range. The leaves being subopposite to alternate in sequence. They are oval 4.5-10 cm (1.8-3.9 in). Petioles are in the range of 0.39-1.18 in (1-3 cm) and 2.8-3.1 in (7-8 cm) long. It bears cordate base with acute tip. The flowers circulates an unpleasant odour. They are monoecious and white-yellow in colour (Figure 1). Broadness of fruit is 0.47-0.98 in (1.2-2.5 cm) and length 0.79-1.77 in (2-4.5 cm). Longitudinal ridges on fruits are five and blackish in dry form. Fresh fruits ellipsoidal, ovoid, smooth, orange-brown-yellow and stony drupes (Figure 2).

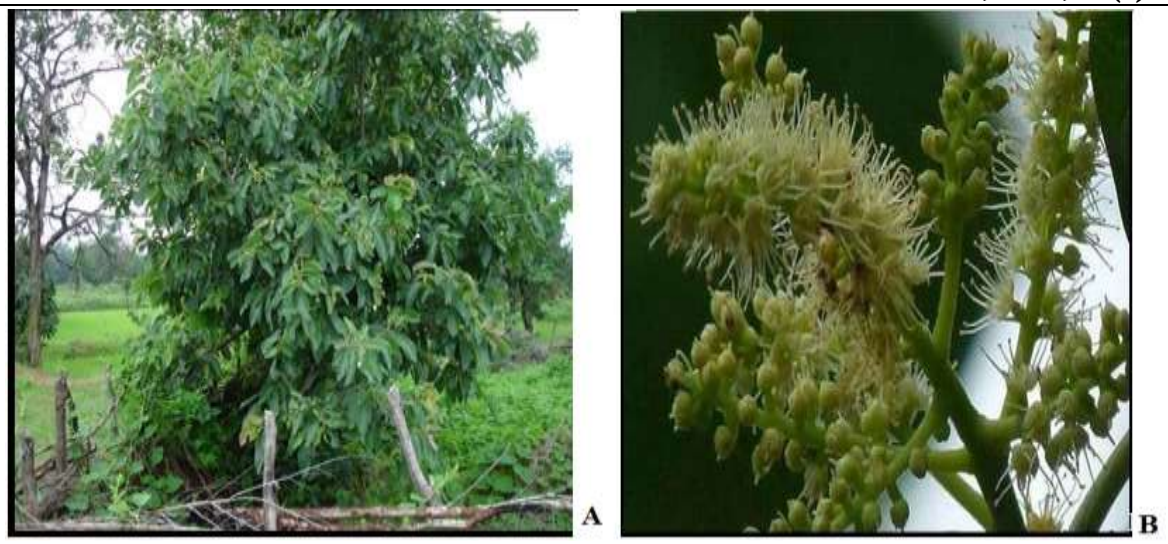

Figure 1: (A) *Terminalia chebula* tree and (B) Close up of inflorescence

Figure 2: (A) Green fresh/unripe fruits on plant and (B) Fruits of *Terminalia chebula* in dried form

T. chebula phytoconstituents

Time to time researchers have recorded *T. chebula* for having many bio-active phytochemicals in various segments. It contains tannins 32%-34% [6-8]. The imp ones are presented in Table 1.

Table 1: Phytochemical constituents on different portions of Harad

Source	Different constituents	Reference
Body of the Plant	Pyrogallol, phloroglucimol, ferulic, vanillic, p-coumaric, caffeic acids	Khare [9]
Kernels portion of the seed	Oleic, linoleic, stearic, palmitic, behenic, linoleic, oleic and arachidic acids	Khare [9]
Fruits	Mannitol, ethyl gallate, gallic, tannic, ascorbic, ellagic, chebulic corilagin	Grover and Bala [10]
	Tannins, anthraquinones, chebulinic acid, chebulagic acid, chebulic acid, ellagic acid and gallic acid. The other minor compounds include polyphenolic compounds, triterpene glycosides, terchebulin, punicalagin, terflavin-A, flavonoids like rutin and quercitin, terpenene glycosides, arjungenin and arjunglucoside-I and a small quantity of phosphoric, succinic, syringic and quinic acids	Inamdar et al.[11], Khanna et al. [12]
	Oleic, palmitic and linoleic acid	Zhang et al. [13]
	Punicalagin, polyphenols corilagin, galloyl glucose, terflavin A, maslinic acid	Williumson, [14]
	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)	Juang et al. [15]
	Gallic acid, chebulic acid, punicalagin, chebulanin, corilagin, neochebulinic acid, ellagic acid, chebulagic acid, chebulinic acid, 1,2,3,4,6-penta-Ogalloyl-β-D-glucose, 1,6-di-O-galloyl-D-glucose, casuarinin, 3,4,6-tri-O-galloyl-D-glucose, terchebulin and Hydrolysable tannins	Lee et al., [16]
	Bioflavonoids and Polyphenols	Newairy and Abdou [17]
	Betasitosterol, fructose, amino acids, resin and purgative principle of anthraquinone	Thakur et al., [18]; Tubtimdee and Shotipruk [19]

	Coumarin conjugated with gallic acids called chebulin triterpenoids, glycosides, flavonol	Yoganarasimhan [20]; Rangsriwong et al., [21]; Muhammad et al., [22]
	Betasitosterol, purgative principle of anthraquinone, fructose, amino acids, succinic acid, resin	Tubtimdee and Shotipruk [19]; Thakur et al., [18]
	Alkaloids, flavonoids, carbohydrates, glycosides, tannins, terpenoids, Phenols and absence of fixed oils and steroids	Raju et al., [23]
	Flavonol, glycosides, triterpenoids, coumarin conjugated with gallic acids called chebulin	Rangsriwong et al., [21]
	Hydrolysable tannins, gallic acid, chebulic acid, chebulic ellagitannins, and gallate esters	Pfundstein et al., [24]
	Glycosides-Triterpenoid such as chebulosides I and II, arjunin, 2α-hydroxyursolic acid, 2α-hydroxymicromiric acid and arjunglucoside	Mammen et al., [25]
	Triterpenoid contents maximum in methanolic extract while water extract contained max. total tannin and phenolics	Chang and Lin [26]
	Tannins, saponins, flavonoids and alkaloids	Saha and Verma [27]
Leaf	Polyphenols such as sterflavins B, C and D, punicalagin, punicalin	Bruneton [28]; Juang et al., [15]; Han et al., [29]
	Increasing order of phenolics, tannins, flavonoids and flavonol contents in various solvent extracts were for acetone > ethyl acetate > methanol > water > chloroform > petroleum ether	Kathirvel and Sujatha [30]
	Phenolics, triterpenoids, and flavonoids, gallic acid	Eshwarappa et al., [31]; Shankara et al., [32]

Pharmacological attributes

The herbal products are measured to be the symbols of safety in comparison to the synthetic products that are regarded to be hazardous to human life and environment. This plant has immense medicinal potentials as follows-

Antiulcer

Antiulcer activity in *T. chebula* Methanolic Extract (METC) was recorded through work of Raju et al. [23] in ethanol induced ulcer models through pylorus ligation in Wistar rats. They found that METC produced reduction of the gastric lesions induced through Pylorus ligation $^{@}$250, 500 mg/kg significantly. During application of hydrochloric extract $^{@}$200 and 500 mg/kg it was able to produce significant reduction in total affected area, lesion index and lesion per centage when compared with control ($P < 0.05$ and $P < 0.01$) through stress induced ulcer models in the aspirin, ethanol and cold restraint. But at 200 and 500 mg/kg it produced antisecretory actions [33,34].

Antioxidant role

The oxidative stresses may pose serious problem the reason is that diseases persists through a dis-balance in detoxifying pro-oxidants. So a right alternative may be the use of natural antioxidants which has been in use as traditional medicines. Now interest increasing in use medicinal plants having antioxidant activity. The work on antioxidant nature of *T. chebula* is compiled in Table 2.

Table 2: Antioxidant potential of *Terminalia chebula*

Source	Observed antioxidant potential	Reference
Leaf	Methanol Extract (METC), Water Extract (WETC), 95% Ethanol Extract (EETC), fermented product of dried powder at 15°C and fermented product of water extract at 25°C exhibited antioxidant activity based on the pyrogallol-luminol assay	Chang and Lin [26]
Fruit	Highest antioxidant function was found in the ethanolic extract	Kushwaha et al., [33]
	Checked nitric oxide release and free radical induced haemolysis through lipopolysaccharide stimulated murine macrophages while using polyherbal formulation (NR-A2/Aller-7)	Mahesh et al., [35]
	Acetone extract showed stronger antioxidant activity	Chen et al., [36]
	Water extract appeared to have good antioxidant activities in cupric sulfate-Phen-Vc-H_2O_2 and luminol-H_2O_2 assays. Pyrogallol-luminol assay showed the 95% ethanol extract to have good antioxidant activity	Chang and Lin [26]
	Showed various magnitudes of potency as antioxidant activity	Hazra et al., [37]
	Lipid peroxidation inhibition in microsomes of rat liver in different doses through radiation	Lee et al., [16]
	Methanolic extract inhibited formation of lipid peroxide and also scavenge superoxide hydroxyl and radicals *in vitro*	Lee et al., [38]
	The aqueous *T. chebula* extract showed potent antioxidant activity when microsomes exposed $^{@}$100 Gy to 600 Gy. Considerable reduction in the extent of lipid peroxidation was observed	Naik et al., [39]
	Significant antioxidant nature in methanolic extract when compared to ascorbic acid through dose dependent mode. In nitric oxide scavenging assay, the IC_{50} value 51.3 µg/ml while the IC_{50} value of ascorbic acid was 77.4 µg/ml. showed strong reducing power and total antioxidant activity of the extract also increased at different doses	Sarwar et al., [40]
	Depicted better antioxidant activity (IC_{50} 0.032 mg/ml) to reduce 2, 2-Diphenyl-1-Picrylhydrazyl (DPPH)	Mathen et al., [41]
	Possessed powerful reducing ability, nitric oxide scavenging activity which also scavenges hydrogen peroxide induced radicals.	Saha and Verma., [27]
Leaf extract	Showed inhibition of xanthine/xanthine oxidase activity and also as DPPH radicals excellent scavenger	Naik et al., [39]
	Antioxidant potential of leaves, evaluated *in vitro* DPPH-radical scavenging activity and reported it to be safe source of functional food as natural antioxidant resource	Kathirvel and Sujatha [30]

Anticarcinogenic

Plants have been an important source for discovery of anticancer compounds. With the current decline in the number of new molecular entities from the pharmaceutical industry, novel anticancer agents are being sought from traditional medicines therefore the anticancer efficacy has been evaluated using various cell lines and information generated is compiled below (Table 3).

Table 3: Observed anticarcinogenic activity

Source	Anticarcinogenic potential	Reference
Fruit	Inhibited growth of cancer cells	Saleem et al., [42]
Fruit	Induced death of cell, inhibited proliferation of cell in ethanolic extract of many cell lines being malignant in human Prostate Cancer Cell (PC-3), Human Osteosarcoma Cell Line (HOS-1), Mouse (S115) Breast Cancer Cell Line including Human (MCF-7), in Non-tumorigenic Immortalized Human Prostate Cell Line (PNT1A)	Reddy et al., [43]
Bark and fruit powder	Acetone extract showed promising anticarcinogenic activity	Reddy et al., [43]
	Inducer of apoptosis in lung cancer cell lines potently	Saleem et al., [42]
Fruits	Increase of lifespan of the mice through restoration of haematological parameters $^{@}$200 mg/kg when given orally and found to be cytotoxic in the *in vitro* showing its significant anticancer potential.	Ahuja et al., [44]
	Fruit powder $^{@}$500 µg/ml of each fraction was used against cells of the A549 lung cancer cell line using the MTT assay, at 48 h Fraction 3 exhibited the lowest rate of growth inhibition while fraction 4 exhibited the highest rate	Wang et al., [45]
Leaf gall extract	Ethanolic leaf gall extract was evaluated against buffalo rat liver 3A, MCF-7 (Human mammary gland adenocarcinoma) and A-549 (Human lung cancer) cell lines by MTT assay. The extract was potent and effective in inducing cytotoxic effects in all the cell lines as IC_{50} value of 305.18 ± 1.7 µg/ml, 643.13 ± 4.2 µg/ml and 208.16 ± 3.7 µ/ml, respectively. The extract was more effective against A549 cell lines than the others.	Shankara et al., [32]

Antimutagenic, radio protective and chemopreventive potential

The acetone and chloroform extracts showed mutagenicity inhibition through induction of direct and S9-dependent mutagens in TA98 and TA100 tester strains of *Salmonella typhimurium* [10,46].

Grover and Bala [10] found antimutagenic activity in hydrolyzable tannins and aqueous extract of *T. chebula* against *Salmonella typhimurium*. Gandhi and Nayar [47] studied mice liver and reported peroxidation reduction in membrane lipids. There was a decrease in radiation damage to DNA through application of *T. chebula* aqueous extract. This protected from undergoing induced damage from gamma radiation to DNA of human lymphocytes when exposed *in vitro*. The tannin fraction of *T. chebula* extract showed efficacy as highly significant against 2AF-S9-dependent mutagen. However, chebula tannins though partly effective against NPD mutagen may not be effective against mutagen 4NQNO [48]. Prasad et al. [49] reported chemopreventive effect of *T. chebula* on nickel chloride-induced toxicity, proliferation response in cells of male wistar rats and renal oxidative stress.

To obtain experimental evidence and assess the antimutagenic activity, Chromosomal Aberration (CA) and Micronucleus (MN) formation in C57BL hybrid mice were examined. In MN formation test, single application of *T. chebula* methanolic fruit extract at different doses of 50, 100 and 150 mg/kg dry weight 24 h prior to administration of Cyclophosphamide (CP) at $^{@}$50 mg/kg significantly reduced the frequency of MNCPE and at the same time significantly increased PCE/NCE ratio as compared to CP alone. Concerning CA test, fruit extract at all different doses significantly reduced the % CA and at the same time increased the % degree of protection in dose dependent manner in bone marrow cells of mice as compared to CP alone treated group. However *T. chebula* fruit extract alone did not show any chromosomal aberration and/or micronucleus formation. These results clearly, indicate the antimutagenic activity of the TC fruit extract [50].

In a radiation dose 270 Gy the lipid peroxidation was studied in varying concentration (5 to 35 µg/ml) of the extract which showed protection efficacy in varying concentrations. At 15 µg/ml of the extract the peroxidation is inhibited by 50% (IC_{50} value) [39]. The traditional ayurvedic decoction of *T. chebula* harbours its efficacy as a low cost, safe chemopreventive agent if given according to the ayurvedic specifications at the intestinal level [51].

Hepatoprotective

This is the liver which may control various physiological actions of the entire body. If any injury happens it will damage liver. Since Harad have radical scavenging activity it may be useful in prevention of liver damage. It has been recorded that 95% ethanolic fruit extract of *T. chebula* showed hepatoprotective activity against toxicity induced antituberculosis drug which in turn might be due to prominent antioxidative and membrane stabilizing activities [52].

The ethanol extract prevented hepatotoxicity through *T. chebula* when rifampicin/isoniazid and in combination of pyrazinamide was applied in sub-chronic model (12 weeks) [52]. The herbal formulation (HP-1) of *T. chebula* was found exhibiting hepatoprotective activity in rat hepatocytes against induced toxicity of carbon tetrachloride [53]. The Chebulic Acid (CA) and neochebulic acid in a combination of 2:1 extracted from ethanolic extracts of fruit of *T. chebula* exhibited strong hepatoprotective activity [38].

Fruit of *T. chebula* is an ayurvedic remedy and if given orally it can work as detoxifying agent and a generic intestinal [51]. Which was studied on 2-Acetylaminofluorene (2-AAF) activated hepatocellular carcinoma of mice. There was liver aberration and Multidrug Resistance-1 (MDR1), generation of reactive oxygen species (ROS), Cyclooxygenase-2 (COX-2) expression through phosphorylation of Akt-MAPKs and nuclear translocation of NF-κ at B25 $mg.kg^{-1}$ b.w. 2-AAF. The pre administration of 50 $mg.kg^{-1}$ TCE along with 25 $mg.kg^{-1}$ 2-AAF inhibited the expression of MDR1 by preventing ROS generation and COX-2 expression through Akt and MAPK signalling pathway. This is useful in preventing the possible neoplastic transformation leading to hepatocarcinoma [53].

In iron dextran injection model 70% methanol and 95% ethanol extract of *T. chebula* showed hepatoprotective effects in animal models [54]. I t was observed that t-BHP injection notably increased in the liver tissue in the presence of malondialdehyde, total reactive oxygen species and nitric oxide. It showed again a drop in the antioxidant activities including total antioxidant capacity, glutathione peroxidase, superoxide dismutase, total glutathione contents and catalase. TCW pretreatment ameliorated remarkably these alterations and also relevant in gene expressions [55].

Forty four rats of age group 90-120 days having 150-200 g were chosen and after 14 days of settlement they were divided equally in two experimental and control groups. The control set was again divided into paracetamol treated control (PC, n=11) and base line control (BC, n=11). The experimental group were again kept in 2 groups as pretreated *T. chebula* and paracetamol treated (TCP-PCT, n=11). They were given basal diet up to 21 consecutive days. It was concluded from this study that *T. chebula* has hepatoprotective effect against paracetamol induced rat liver damage [56].

To assess the effect of ethanolic fruit extract of *T. chebula* induced Hepatotoxicity in rats, they were divided into six different groups each having six rats. Group 1 served as the control, Group 2 received 40% ethanol (2 ml/100 g, oral), in sterile water, group 3, 4 and 5 served as

extract treatment groups and orally received 50, 100 & 200 mg/kg, orally, ethanolic fruit Extract of *T. chebula* (TCE) and group 6 served as the standard control and received Silymarin 25 mg/kg. All the treatment protocols followed 21 days after which rats were sacrificed and blood samples taken for biochemical studies. The ethanol treated group rats (G2) showed variable increase in serum Amino Transferase (AST), Alanine Amino Transferase (ALT) and Alkaline Phosphatase (ALP) levels. Moreover, total protein and total bilirubin levels were significantly increased in treatment groups. The effect of extract was compared with a standard drug, silymarin. It was concluded that the ethanolic fruit extract of *T. chebula* protects against ethanol-induced oxidative liver injury in rats [57].

Cardioprotective

In a study it was noticed that extract of *T. chebula* can retain enzymes role as a diagnostic marker in rats myocardial damage which is induced through isoproterenol. This ameliorated isoproterenol activity during lipid peroxide formation [58] but its pericarp have cardioprotective activity [59].

Cytoprotective

The two chemicals such as Gallic acid (GA) and CA extracted from *T. chebula* fruit can block lymphocyte-mediated cytotoxic cytotoxicity [60]. The ethanolic extract of fruits have cytoprotective effect on the HEK-N/F cells. While in UV-induced oxidative damage this have significant cytoprotective activity. This is because of the *T. chebula* extract inhibitory effect in age dependent telomere length shortening which might be due to terminal restriction fragments of DNA Southern Blots obtained in sub culture passages [61]. This formed duodenal ulcers and showed cytoprotective effect *in vitro* in the gastric mucosa [62]. The *T. chebula* fruit extract produced cytoprotective effect on oxidative stress and it was inhibitory to cellular aging [63].

Renoprotective and antidiabetic

In an animal study *T. chebula, T. belerica, Emblica officinalis* methanolic extract individually and their combination 'Triphala' were found to reduce the blood sugar level significantly within 4 h comparable to standard control [64]. The ethanolic extract of *T. chebula* fruit has potential hypoglycemic action in Streptozotocin induced diabetic rats. *T. chebula* showed more hypoglycemic effect than standard therapeutic drug, glibenclamide [65].

In other long term/short term investigation revealed that chloroform extract of *T. chebula* showed dose dependent reduction of blood glucose in diabetic rats in comparison to standard drug, glibenclamide. It also revealed action of *T. chebula* in reduction blood glucose which got mediated through enhanced secretion of insulin through β-cells of Langerhans. There was significant reno-protective activity in *T. chebula* treated rats [66]. The *T. chebula* seeds and fruit showed reduction in blood glucose which was dose dependent in streptozotocin induced diabetic rats both in short and long term studies. It also showed an effective renoprotective potential [67,68].

Antibacterial. Time to time researchers have investigated antibacterial activity of *T. chebula* as summarised below (Table 4).

Table 4: Antibacterial nature of *Terminalia chebula*

Source	Antibacterial activity	Reference
Fruit	Ethyl ester and GA obtained from ethanolic extract showed antibacterial activity against methicillin-resistant *Staphylococcus aureus*	Sato et al., [69]
	Inhibited the urease activity of *Helicobacter pylori* effectively	Malckzadeh et al., [70]
	Methanolic extract of leaf proved potent equally effective antibiotics such as kanamycin, gentamycin, ciprofloxacin, ofloxacin and cephalexin in comparison to the aqueous extract.	Ghosh et al., [71]
	Inhibited the growth of salivary bacteria *Streptococcus mutants* through aqueous extract	Aneja and Joshi [72]
	Strong antibacterial against many bacteria which is human pathogenic for both Gram-positive and Gram-negative	Khan et al., [73,74]
	Strongly useful in the management of citrus canker disease through inhibitory action on strain X-100 of the bacterium *Xanthomonas campestris* pv. citri	Kannan et al., [75]
	Strong inhibitory activity on *Salmonella typhi, Klebsiella* and intestinal bacteria	Rani and Khullar [76]; Agrawal et al., [77]
	T. chebula fruit extract highly active against *Bacillus subtilis Staphylococcus aureus Salmonella typhi, Staphylococcus epidermidis,* and *Pseudomonas aeruginosa*	Kannan et al., [68]
	Strong antibacterial activity against multidrug-resistant uropathogenic *Escherichia coli in ethanolic fruit extract*	Bag et al. [78,79]
Ripe seeds	Exhibited strong antibacterial potential against *S. aureus*	Bonjar [80]
Leaves	Acetone extract showed higher inhibitions for *B. subtilis, E. faecalis, K. pneumoniae, S. aureus* and *C. diphtheria* for. Particularly *B. subtilis, E. faecalis, K. pneumoniae* showed higher activity than the standard, Streptomycin while *S. boydii* responded to acetone extract *S. typhi* however showed higher antibacterial activity for water extract.	Kathirvel and Sujatha [30]

Antifungal activity

Antifungal activity of *T. chebula* has also been found as compiled below (Table 5).

Table 5: Potential of *Terminalia chebula* against fungi

Source	Antifungal potential	Reference
Fruit	Exhibited antifungal activity against *Candida albicans* and dermatophytes *Microsporum gypsum, Floccosum, Epidermophyton* and *Trichophyton rubrum* in aqueous extract	Dutta et al., [81] Barazani et al., [82]
	Strongly antidermatophytic on (*Trichophyton* spp.) and on three yeasts (*Candida* spp.)	Mehmood et al., [83]
	Strongly anticandidal against clotrimazole resistant *Candida albicans in methanolic extract*	Bonjar [80]
Seed extract	Antifungal activity against *Trichophyton glabrata* in aqueous seed extract	Barazani et al., [82]

Antiviral activity

Antiviral activity has also been investigated for *T. chebula* as compiled in Table 6.

Table 6: Antiviral potential of *Terminalia chebula*

Source	Antiviral potential	Reference
Fruit	Showed strong inhibitory effects on human immunodeficiency virus-1 reverse transcriptase in acetone extract of *T. chebula* fruits	Mekkaway et al., [84]
	Strong therapeutic potential in fighting herpes simplex virus both *in vitro* and *in vivo* tests	Kurowa et al., [85]
	Strongly effective in inhibiting the replication of human cytomegalovirus (CMV) *in vitro*	Yukawa et al., [86]
	Strongly effective in protecting epithelial cells against influenza A virus	Badmaev and Nowakowski [87]
	Strong inhibition against the 3′-processing of HIV-1 integrase of the compounds	Ahn et al., [88]; Jeong et al., [89]
	Strongly effective for control of AIDS and sexually transmitted diseases	Vermani and Garg [90]
	Significant inhibitory activity with $IC_{50} \leq 5$ µg/ml on human immunodeficiency virus-1 reverse transcriptase in methanolic and aqueous extracts	Gambari and Lampronti [91]; Ahn et al., [88];
	Tannins strongly effective against potato virus X	Ma et al., [92]
	Useful in treatment of pandemic swine influenza A infection	Ma et al., [92]
	Herpes Simplex Virus-1 (HSV-1) causes 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	Lin et al., [93]

Antiprotozoal

A study was done in rats caecal amoebiasis which showed curative rate of 89% at 500 mg/kg body weight through inhibition of enzyme activities such as RNase, DNase, aldolase, α-amylase, acid phosphatase, protease and alkaline phosphatase in axenically cultured amoebae of varying degree [94,95]. In another study of amoebic liver abscess in golden hamsters and in immunomodulation studies TC showed maximum cure rate against hepatic amoebiasis up to 73% in 800 mg/kg body weight. The humoral immunity got enhanced in immunomodulation studies while T-cell counts remained unaffected while cell-mediated immune response got stimulated [94]. The four botanicals (*Boerhavia diffusa*, *Berberis aristata*, *Tinospora cordifolia*, and *Zingiber officinale*) along with TC showed maximum cure up to 73% in amoebic liver abscess [96] but 89% in caecal amoebiasis in rats producing strong inhibitory activity on *Entamoeba histolytica* [95]. The anti plasmodial activity against *Plasmodium falciparum* was found to be present in acetone extract of *T. chebula* seeds [97].

Acetylcholine inhibition

For the control of alzheimer's disease acetylcholinesterase inhibitors are useful. The phytochemical 1,2,3,4,6-penta-O-galloyl-β-D-glucose isolated from TC was compared with tacrine which revealed strong acetylcholinesterase and butyrylcholinesterase inhibitory effects [98]. The *T. chebula* aqueous extract showed highest efficacy to inhibit acetylcholinesterase when tested in comparison with other herbs viz. *Emblica officinalis*, *Terminalia bellirica*, *Emblica officinalis* and Triphala [99].

Antiarthritic and anti-inflammatory

The *T. chebula* dried fruit extract inhibited nitric oxide synthesis and showed antiinflammatory activity when used in aqueous form [100]. Chebulagic Acid (CA) obtained *T. chebula* immature seeds checked development of collagen induced arthritis in mice [101]. The polyherbal formulation (Aller-7) *T. chebula* showed a dose dependent antiinflammatory effect on Freund's adjuvant induced arthritis in rats [102].

Nair et al. [101] reported anti-arthritic effect in *T. chebula* hydroalcoholic extract (TCHE) through experimental models to compare the effect of treatment on macrophage-derived pro-inflammatory cytokine expression and extent of disease activity. This resulted a potent inhibition of joint swelling when caparisoned with the control in both CFA and formaldehyde produced arthritis. TCHE use reduced serum TNF-α level and synovial expression of TNF-R1, IL-6 and IL-1β. This also resulted antiarthritic activity in TCHE which showed it was at least in part due to its modulatory action on pro-inflammatory cytokine expression in the synovium [101].

Lipoxygenase (LOX) inhibitors are the promising therapeutic target for treating a wide spectrum of inflammation diseases such as cancer, asthma, lymphoma, leukaemia, and autoimmune disorders. The photochemical constituents, anti-LOX potential of *T. chebula* leaf galls was evaluated to find out development of medicine. Extracts of *T. chebula* galls were tested for anti-LOX activity using linoleic acid as substrate and lipoxidase as an enzyme and also the total content of polyphenols with phytochemical analysis of the extract were determined. The higher LOX inhibitory activity was positively correlated to the high content of total polyphenols/flavonoids. This confirms the folklore use of *T. chebula* leaf gall extracts as a natural anti-inflammatory agent [31].

Adaptogenic and antianaphylactic

The adaptogenic potential of fruit of *T. chebula* has been studied along with 6 herbs when administered in animals it was able to relieve in different stresses in different ways [103]. But when administered for anaphylactic shock levels of serum histamine got reduced showing its strong antianaphylactic activity [104]. The aqueous fraction of *T. chebula* showed inhibition of 48/80-induced anaphylaxis both locally as well as at systemic level. The effect is pronounced in pretreatment when compared with induction of anaphylactogen. The serum histamine release levels from rat peritoneal mast cells were reduced in a dose dependent manner [104].

Hypolipidemic and hypocholesterolemic

A study revealed that *T. chebula* extract are effective in atherosclerosis when inducted experimentally and hypolipidemicrole [105]. It also have power of hypocholesterolemic activity on cholesterol produced hypercholesterolemia in rabbits [106].

Gastrointestinal motility improving and anti-ulcerogenic

The gastric emptying time may be increased while using the fruit of *T. chebula* but traditionally it has laxative power [107]. This can protect gastro intestinal mucosa. It prevents Brunner's gland secretions which may be useful in duodenal ulcer formation protection [34].

Antispasmodic

A study revealed that *T. chebula* have antispasmodic activity and useful in reduction of blood pressure as well as intestinal spasms. It is also beneficial in intestinal disorders and spastic colon [108].

Anticaries agent

A study reported that aqueous *T. chebula* extract found inhibitory effect on sucrose inducted accumulation of *Streptococcus mutans* in the saliva samples up to 3 h after rinsing. It also inhibited upto 90 min even after post rinsing [109]. Another study revealed that mouth rinsing through 10% solution inhibited salivary bacterial count [72,110].

Wound healing

The alcoholic extract of *T. chebula* leaves showed in rat much faster healing in dermal wounds. This is mainly due to decreased period for epithelialization and improved rates of contraction [111]. The studies recorded increase of DNA, collagen, total protein contents in the granulation tissues of treated wounds. The hexosamine and uronic acid levels were got increased up to day 8 on post-wounding. It is helpful in healing process promotion [112]. The healing activity in ethanol extract of *T. chebula* was reported through indomethacin induced stomach ulceration [113]. The *T. chebula* hydroalcoholic extract of fruit exhibited 82% reduction in the wound area due to a faster epithelialization when compared to controls in alloxan induced diabetic rats [114].

The tannins immature fruits *T. chebula* inhibited *Klebsiella pneumonia* and *Staphylococcus aureus in vitro.* This because of having powerful antibacterial and angiogenic activity of the extract accelerated cutaneous wound healing in rats [111]. An ointment at two concentrations (5% and 10% w/w ointment of bark extract) produced a very good result in incision and excision models in albino rats when compared to controls in wound healing action of ethanolic fruits extract of *T. chebula* [115].

The aqueous and organic extracts (Solvent-free) of *T. chebula* were evaluated on keratinocytes and fibroblast (L929) cells. This decreased accumulation of ammonia in the media so reducing toxic effect on cells. The DPPH assay resulted the free radical scavenging ability of the extracts. This got increased with the increase in concentration of each extract. The ECM secretion and cytoskeletal structure of the cells treated with extracts showed higher cellular activity when compared to control [116].

Hypolipidemic

A study revealed that rats receiving *T. chebula* treatment noticed reduction in total protein cholesterol, triglycerides. This significantly elevated high density lipoprotein cholesterol showing hypolipidemic activity significantly [105]. In an experimental study including rabbits *T. chebula* showed significantly lower cholesterolaemia. No cholesterol excretion was found hence the action may be mediated through enzymic degradation of cholesterol either in the liver or elsewhere [117].

Molluscicidal

The *T. chebula* fruit powder has potent molluscicidal activity on *Lymnaea acuminata* which is a vector snail. This activity is mainly due to tannic acid [118].

Anthelmintic activity

T. chebula fruit extracts were screened to evaluate anthelmintic activity in adult earthworm *Pheritima posthuma*. The alcoholic and aqueous extract of the fruits showed significant anthelmintic activity. It was higher in alcoholic extract than the aqueous extract and even the standard drug of albendazole [96].

The ovicidal and larvicidal activities were studied in *Haemonchus contortus*. The three extracts acetate, acetone and methanol were taken from dried leaves and seeds. This was based on egg hatching and larval development assays at 50, 25, 12.5, 6.25 and 3.13 mg/ml. The leaves and seed extracts 50 mg/ml concentration showed complete inhibition[@] [119].

Purgative action

The oil fraction in *T. chebula* seeds have Purgative activity [120].

Immunomodulatory

T. chebula have potential to increase humoral antibody titer and useful in delayed type of hypersensitivity [121]. The dried ripe fruits have immunomodulatory activity. The aqueous extract [@]100 mg/kg/p.o. can increase level of liver mitochondrial enzymes CAT and SO as well as GSH. This can decrease in the level of LPO in the liver when compared to the vehicle cyclophosphamide treated groups/Sheep Red Blood Cells (SRBC) [122].

Analgesic

The analgesic activity in *T. chebula* methanolic extract fruits was evaluated using acetic acid-induced writhing test in mice. The extract, [@]500 mg/kg, showed a maximum of 44.17% inhibition ($P < 0.05$) of writhing reaction compared to the reference drug diclofenac-sodium (66.96%). The extract also showed moderate cytotoxic activity in brine shrimp lethality bioassay and the LC_{50} value was found to be 97.36 µg/ml [40].

Antiallergic

This have got antiallergic activity. This was confirmed when polyherbal formulation of seven medicinal plants Aller-7 was prepared along with this and used in guinea pig [102].

Neuroprotective

This have neuroprotective activity against H_2O_2-induced toxicity toward PC12 cells methanol and water extracts. This have bio-potential for the treatment of H_2O_2-induced neurodegenerative disease at 0.5-5.0 µg/ml [123].

Another study with *T. chebula* extract: Showed (1) increase in the survival of cells subjected to OGD-R by 68% and H_2O_2 by 91.4%; (2) Scavenges the DPPH free radical by 94% and decreases malondialdehyde levels from 237.0 ± 15.2% to 93.7 ± 2.2%; (3) Reduces NO production and death rate of microglia cells stimulated by lipopolysaccharide; (4) Decreases the cerebral infarct volume and extent of

hemisphere swelling. This suggested that *T. chebula* fruit has a very high potential as a natural herbal medicine, to protect the cells from ischemic damage. This is through the inhibition of oxidative and inflammatory processes [124].

Effect of *T. chebula* on bronchial asthma

An ayurvedic clinical study reported evaluating two Ayurvedic formulations on bronchial asthma (Tamak shvasa) viz. Shvasahara Leha and Vasaharitaki Avaleha. The results of the study indicate that the Vasa Haritaki Avaleha containing *T. chebula* provided higher relief than Shvasahara Leha in Tamaka Shvasa [34].

Antinociceptive

The ethanol extract of *T. chebula* exhibited antinociceptive effect claimed to be due to triterpenoids present and may be partially acting through the cholecystokinin receptor pathways [125].

Natural dye

TC is useful in development of eco-friendly shades on woolen yarn for different hues and tones. In a study the effect of dye concentration on color strength (*K*/*S*) of woolen yarn dyed with *T. chebula* was assessed. This resulted that increasing concentration of dye can decrease lightness values of woolen yarn samples [126,127].

Clinical studies

In simple constipations small scale trials have been conducted. This can increase the stools and evacuate the bowel completely [128] (Singh and Sinha, 1978). Besides some Ayurvedic drugs, along with *T. chebula* have their effects on mental physical disability, mental stress, constipation, and allergic rhinitis [128,72]. For development of gingivitis and periodontitis Dental Plaque Bacteria (DPB) are associated. The growth of oral bacteria got suppressed through Ethanol Extract of *T. chebula* (EETC). This reduced the induction of proteases, inflammatory cytokines but abolishing the expression of PGE2 and COX-2. This inhibited the matrix damage so contributing in prevention of bone resorption [129].

Safety evaluation

T. chebula has no cellular toxicity on sheep erythrocytes as well as acute oral toxic effects on rats [130,131]. The hydroalcoholic extract of fruits of *T. chebula* have cytochrome P450 inhibition activity in rats [132]. This had no genotoxic effect [133]. The fruit extract of *T. chebula* can reduce the induced genotoxicity associated with lead and aluminium [134,135]. The cytotoxicity studies 80 μg/ml on 3T3 cell line revealed only negligible inhibition [41]. *T. chebula* fruits having hydrolysable tannins showed antimutagenic activity on mutagens like 4-nitro-O-phenylene diamine and sodium azide. These findings revealed that it is safe for used.

Drugs available in market

Haritaki (*T. chebula*) a mild laxative capsule (90 capsules) have been marketed by Wilson Drugs Jalandhar, Punjab which is effective in use for Constipation, loss of appetite and flatulence.

CONCLUSIONS AND RECOMMENDATIONS

T. chebula have a wide spectrum of pharmacological and medicinal attributes. Not much work has been conducted on its medicinal applications against multidrug resistant bacteria.

Cytotoxic activities are mainly because of higher concentration of phenolics/flavonoids viz., chebulinic, chebulic, chebulagic, gallic, ellagic acid and corilagin along with related compounds. They are responsible for antimicrobial, antioxidant, antihyperglycemic, anticancer activity and protective effects on the vital body organs. So we need to search mechanism of its action for development of cheap, safe and an effective drug. Extensive investigations are required to combat diseases mainly for drug resistant infections as well as the mechanism of action. Polyphenols being valuable plant constituents help protect the body from oxidative stress and may be used in nutraceuticals and the food industry. However, studies are required to develop fractionation methods and identification of the antioxidant compounds.

This has neuroprotective activities against H_2O_2-induced toxicity toward PC12 cells. This is potential candidate for treatment of H_2O_2-induced neurodegenerative diseases. This have immunomodulatory activity which might be because of inhibition of lipid peroxidation and/or indirect stimulatory effect on both cellular and humoral immunity; and proliferation of lymphocytes as indicated by increase in the number of β and T cells which release cytokines and growth factors regulating other immune cells and secrete antibodies in the blood. *T. chebula* extracts have potential to protect from radiation induced damage to cellular organelles. Natural products with well-established pharmacological history are the best suited candidates as they are gifted with none or lesser side effects.

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