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 cheblic myrobalan contains hydrolysable tannins. This dominantly contains many phytoc hemicals viz., casuarinin, chebulagic acid, cheblic acid, chebulanic acid corilagin, ellagic acid, gallic acid, neochebulin acid, punicalagin, 1,2,3,4,6-penta-O-galloyl-β-D-glucose, 1,6-di-O-galloyl-β-D-glucose, 3,4,6-tri-O-galloyl-β-D-glucose, terechubulin. 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, anhelminthic, 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, Phytocconstituents, 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 phytocconstituents 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, Abbhayaa, Rohini, Chetaki, Amritaas; Unani-Harad, Haleelaa siyaah, Haleelaa zard, Haleelaa 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). Pettyoles 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 monocious and white-yellow in colour (Figure 1). Breadness 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).
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**

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

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-

Antilulcer
Antilulcer 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 *a*250, 500 mg/kg significantly. During application of hydrochloric extract *a*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 [19,24].

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*

<table>
<thead>
<tr>
<th>Source</th>
<th>Observed antioxidant potential</th>
<th>Reference</th>
</tr>
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<tbody>
<tr>
<td>Leaf</td>
<td>Methanol Extract (METC), Water Extract (WETC), 95% Ethanol Extract (EEETC), 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</td>
<td>Chang and Lin [26]</td>
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<td>Checked nitric oxide release and free radical induced haemolysis through lipopolysaccharide stimulated murine macrophages while using polyherbal formulation (NR-A2/Aller-7)</td>
<td>Kashwaha et al., [33]</td>
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<td></td>
<td>Acetone extract showed stronger antioxidant activity</td>
<td>Chen et al., [36]</td>
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<td></td>
<td>Water extract appeared to have good antioxidant activities in cupric sulfate-Phen-Vc-H2O2 and luminol-H2O2 assays. Pyrogallol-luminol assay showed the 95% ethanol extract to have good antioxidant activity</td>
<td>Chang and Lin [26]</td>
</tr>
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<td>Lipid peroxidation inhibition in microsomes of rat liver in different doses through radiation</td>
<td>Hazra et al., [37]</td>
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<tr>
<td></td>
<td>Methanolic extract inhibited formation of lipid peroxide and also scavenge superoxide hydroxyl and radicals in <em>vivo</em></td>
<td>Lee et al., [16]</td>
</tr>
<tr>
<td>Fruit</td>
<td>The aqueous <em>T. chebula</em> extract showed potent antioxidant activity when microsomes exposed to 100 Gy to 600 Gy. Considerable reduction in the extent of lipid peroxidation was observed</td>
<td>Naik et al., [39]</td>
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<td></td>
<td>Significant antioxidant nature in methanolic extract when compared to ascorbic acid through dose dependent mode. In nitric oxide scavenging assay, the IC50 value 51.3 µg/ml while the IC50 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</td>
<td>Sarwar et al., [40]</td>
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<td>Depicted better antioxidant activity (IC50 0.032 mg/ml) to reduce 2, 2-Diphenyl-1-Pcrylichydrazyl (DPPH)</td>
<td>Mathen et al., [41]</td>
</tr>
<tr>
<td></td>
<td>Possessed powerful reducing ability, nitric oxide scavenging activity which also scavenge hydrogen peroxide induced radicals</td>
<td>Saha and Verma., [27]</td>
</tr>
<tr>
<td>Leaf extract</td>
<td>Showed inhibition of xanthine/xanthine oxidase activity and also as DPPH radicals excellent scavenger</td>
<td>Naik et al., [39]</td>
</tr>
<tr>
<td></td>
<td>Antioxidant potential of leaves, evaluated in <em>v</em> <em>v</em> <em>i</em> <em>v</em> <em>i</em> <em>o</em> <em>v</em> <em>i</em> <em>o</em> <em>o</em> <em>o</em> <em>o</em> <em>o</em> <em>e</em> <em>c</em> <em>a</em> <em>e</em> <em>r</em> <em>a</em> <em>d</em> <em>i</em> <em>c</em> <em>a</em> <em>l</em> scavenging activity and reported it to be safe source of functional food as natural antioxidant resource</td>
<td>Kathirvel and Sujatha [30]</td>
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</table>
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 MNCE 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 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% (IC50 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-k 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 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 a significant drop in the antioxidant activities including total antioxidant capacity, gluthathione 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

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Source | Anticarcinogenic potential | Reference
--- | --- | ---
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) | Sales et al., [42]
Fruit | Inhibited growth of cancer cells | Reddy et al., [43]
Fruit | Acetone extract showed promising anticarcinogenic activity | Reddy et al., [43]
Fruits | 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 80-200 mg/kg when given orally and found to be cytotoxic in the in vitro showing its significant anticancer potential | Ahuja et al., [44]
Fruits | The extract was potent and effective in inducing cytoxic effects in all the cell lines as IC50 value of 305.18 ± 1.7 μg/mL, 643.15 ± 4.2 μg/mL and 208.16 ± 3.7 μg/mL, respectively. The extract was more effective against A549 cell lines than the others. | 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 against 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. | Shankara et al., [32]

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

Antifungal activity

Antifungal activity of \textit{T. chebula} has also been found as compiled below (Table 5).

<table>
<thead>
<tr>
<th>Source</th>
<th>Antifungal potential</th>
<th>Reference</th>
</tr>
</thead>
</table>
| Fruit       | Exhibited antifungal activity against \textit{Candida albicans} and dermatophytes \textit{Microsporum gypseum}, \textit{Floccoccum}, \textit{Epidermophyton} and \textit{Trichophyton rubrum} in aqueous extract  
Strongly antidermatophytic on \textit{(Trichophyton spp.)} and on three yeasts (\textit{Candida spp.})  
Strongly antifungal against clotrimazole resistant \textit{Candida albicans} in methanolic extract | Dutta et al., [81]  
Barazani et al. [82]  
Mehnood et al., [83]  
Bonjar [80] |

Antiviral activity

Antiviral activity has also been investigated for \textit{T. chebula} as compiled in Table 6.
Antiprotozoal

A study was done in rats caecal amoebiosis 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 amoebiosis 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 amoebiosis 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 1,2,3,4,5-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 antiarthritic 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 cytotoxic 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. Also 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 folk lore 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 anaphylactoion. The serum histamine release levels from rat peritoneal mast cells were reduced in a dose dependent manner [104].

Hypolipidemic and hypcholesterolemic

A study revealed that T. chebula extract are effective in atherosclerosis when induced experimentally and hypolipidemicrole [105]. It also have power of hypcholesterolemic 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 induced 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 ulcers in [113]. The *T. chebula* hydromalcholomic 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 cholesterolera. 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 of [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].

Analgic
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 LC₅₀ 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 H₂O₂-induced toxicity toward PC12 cells methanol and water extracts. This have bio-potential for the treatment of H₂O₂-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 H₂O₂ by 91.4%; (2) Scavenges the DPPH free radical by 94% and decreases malondialdehyde levels from 23.70 ± 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 Avalaha. The results of the study indicate that the Vasa Haritaki Avalaha 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 (KIS) 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 H2O2-induced toxicity toward PC12 cells. This is potential candidate for treatment of H2O2-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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