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Phytochemical and Pharmacological Profile of *Terminalia chebula*

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Review Article
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Abstract

Plant secondary metabolites have been of interest to man for a long time due to their pharmacological relevance. In this search *Terminalia chebula* is widely used to enhance the natural resistance to various diseases. It is called the "king of medicines" and always listed first in the Ayurvedic meteria medica because of its extraordinary powers of healing. Traditionally it has been used as a popular folk medicine for homeostatic, antitussive, laxative, diuretic and cardio tonic treatments. Recent studies showed that it has also been used as antidiabetic, antiviral, cardioprotective, anticancer, antioxidant, free radical scavenging and hypolipidemic agent. The present review is an attempt to highlight the various ethnopharmacological and traditional uses as well as phytochemical and pharmacological aspect of *Terminalia chebula*.

Keywords: *Terminalia chebula*; Pharmacological Effect; Gastrointestinal Activity; Anticariogenic Effect; Antidiabetic Effects; Cardiotonic Activity; Phytochemical Constituents

Abbreviations: ITM: Iranian Traditional Medicine; STZ: Streptozotocin; IFHP: Isolated Frog Heart Perfusion Technique; LDL: Low Density Lipoprotein; VLDL: Very Low Density Lipoprotein; HDL: High Density Lipoprotein; MIC: Minimum Inhibitory Concentration; HSV: Herpes Simplex Virus; CA: Chromosomal Aberration; MN: Micronucleus; HETC: Hydroalcoholic Fruit Extract of *Terminalia chebula*; MES: Maximal-Electroshock; EPM: Elevated Plus Maze; PI: Phagocytic Index; AI: Avidity Index, NBT: Nitro Blue Tetrazolium; MT: Mother Tincture.

Introduction

Terminalia chebula is a native to various parts of Southern Asia including India, Nepal, China (Yunnan), Sri Lanka, Malaysia and Vietnam [1]. It is found all over India from eastern to western region and is commonly known as "black Myroblans" in English and 'Harad' in Hindi. It is known as the "king" of Mongolian and Tibetan medicines, a drug for a wide range of diseases [2]. This tree is known in Iranian traditional medicine (ITM) as halileh or halilaj and the fruit is used to develop treatments [3]. In Ayurveda *Terminalia chebula* is considered to destroy all diseases and eliminate all waste from the body. At the same time, it is known to promote tissue growth and health. It is most powerful Ayurvedic herb used in the treatment of any kind of gastric infection in any part of the body. It is found to be an effective product for infections caused by *E. coli* and other parasites of the digestive system. Recent studies have demonstrated that *T. chebula* exhibits a wide range of biological activities including cardioprotective [4], antispasmodic [5], antioxidant [6], free radical scavenging [7] and hypolipidemic [8]. Its antimicrobial [9], antiviral [10,11], anticancer [12], antianaphylaxis [13] and antidiabetic [14] activities.

Habitat

Terminalia chebula is a deciduous tree growing upto 30 mts. tall with a trunk up to 1 mt. diameter. The leaves are alternate to sub opposite in arrangement, oval, 7-18 cm

long and 4.5-10 cm broad with a 1-3 cm petiole. The fruit is drupe-like, 2-4.5 cm long, 1.2-2.5 cm broad and blackish with five longitudinal ridges [15] (Figures 1 & 2).

Figure 1: Leaves of *T. chebula.*

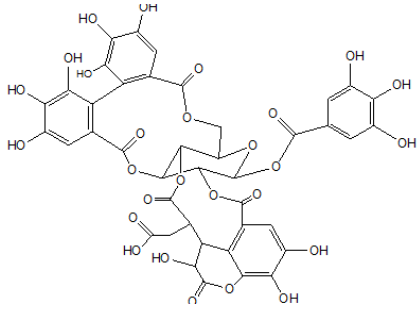
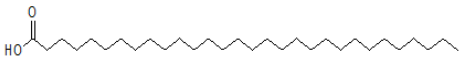
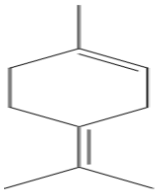
Figure 2: Fruits of *T. chebula.*

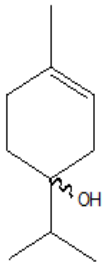
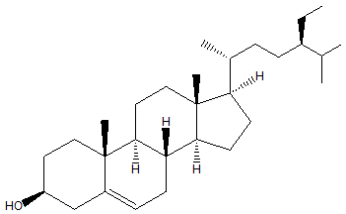
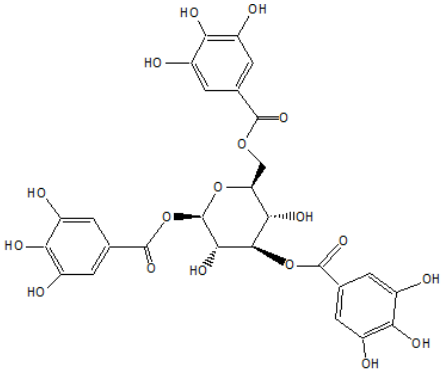
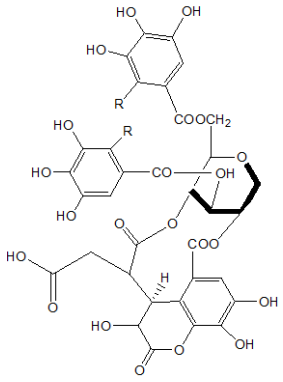
Taxonomical Classification

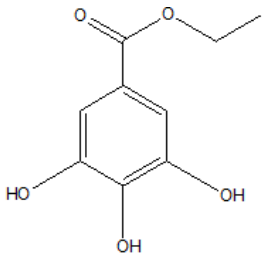
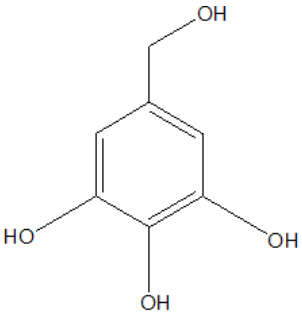
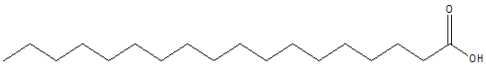
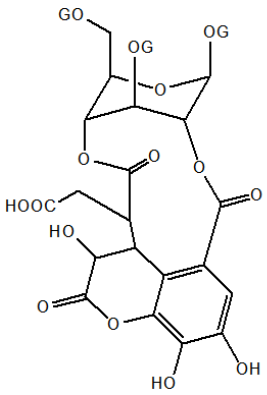
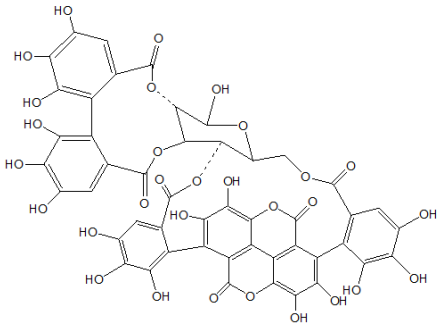
Kingdom: Plantae
Division: Magnoliophyta
Class: Magnoliopsida
Order: Myrtales
Family: Combretaceae
Genus: *Terminalia*
Species : *Terminalia chebula*

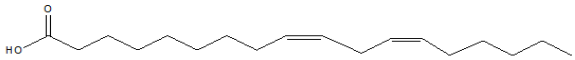
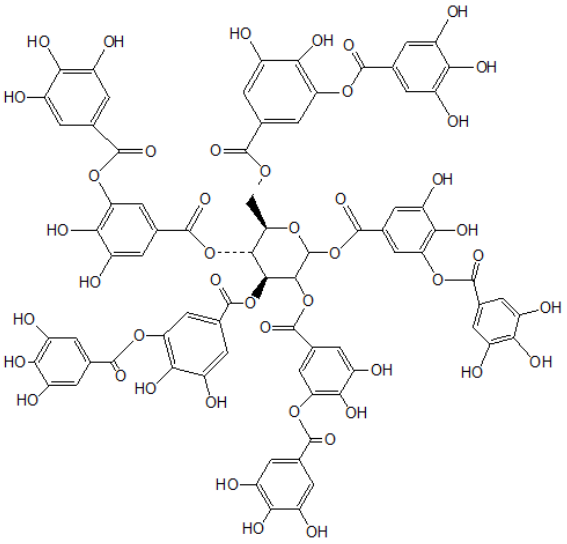
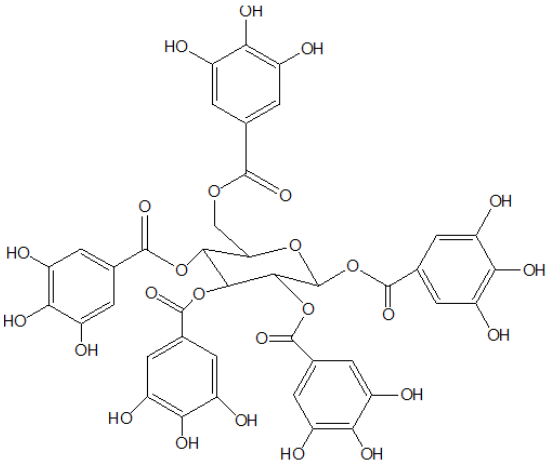
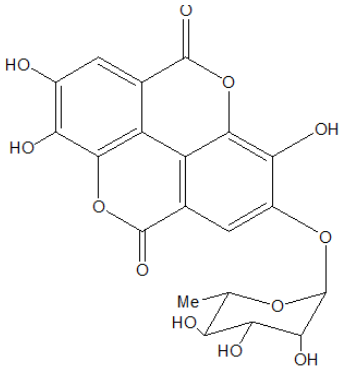
Chemical Constituents

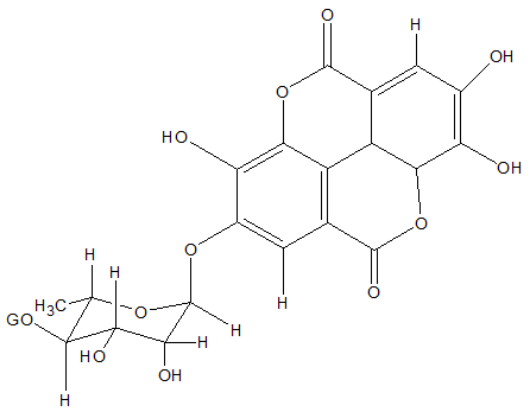
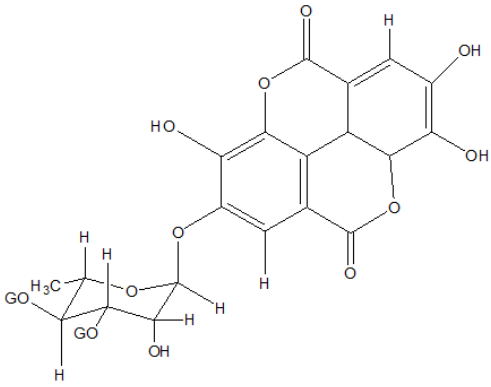
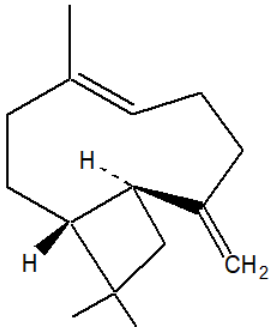
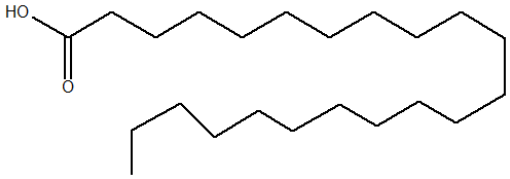
Table 1: Phytochemical Constituents Isolated from *Terminelia* and Their Pharmacological Activity.

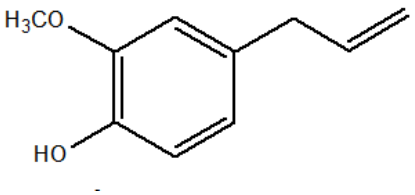
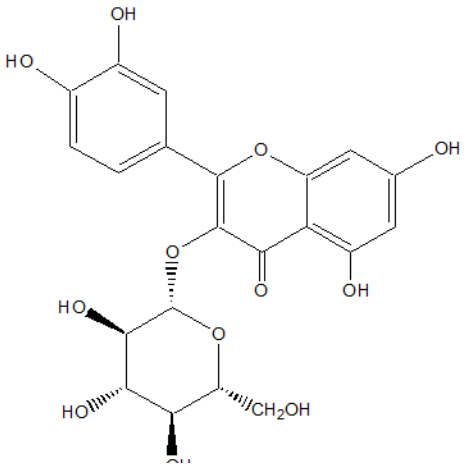
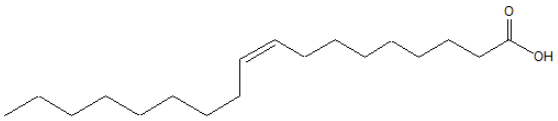
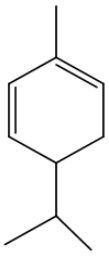
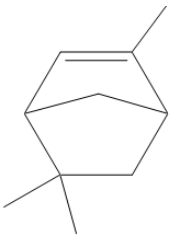
S. No.	Chemical constituent	Plant part	Pharmacological activity	References
1.	 Chebulagic Acid	Fruit	Immuno- suppressive effects	[20] [39,40,41] [46,47]
2.	 Triacontanoic Acid			[10]
3.	 Terpinolene			[10]

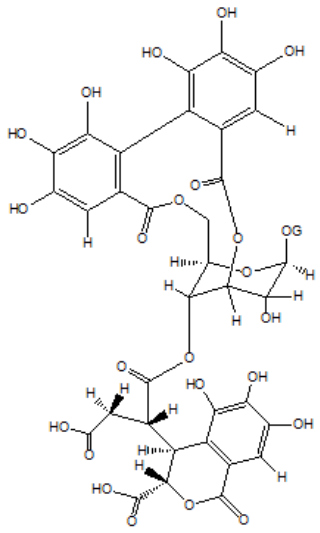
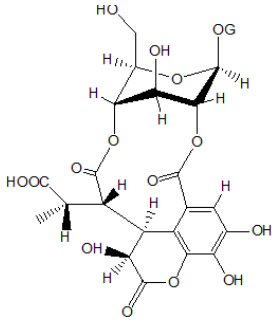
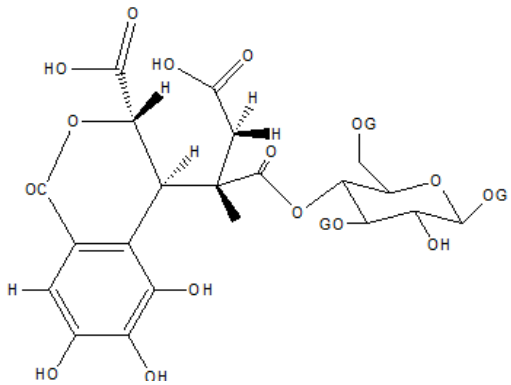
4.	 Terpinen-4-ol			[10]
5.	 β Sitosterol	Fruit		[47]
6.	 Corilagin			[47]
7.	 Chebulic Acid	Fruit	Hepatoprotective	[45] [47]

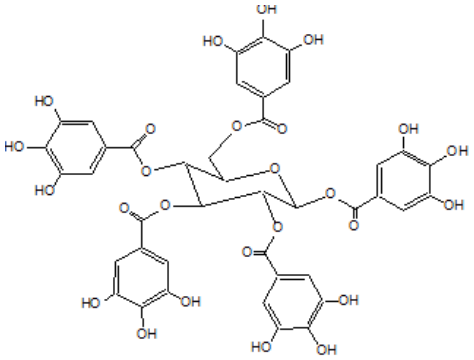
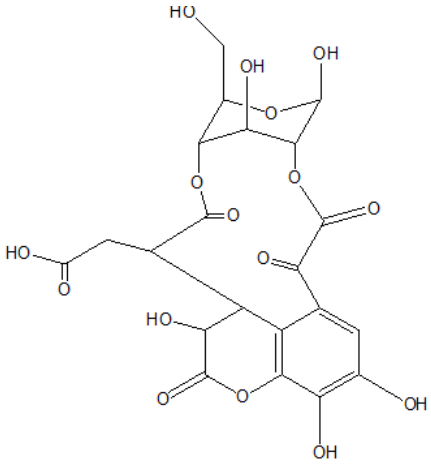
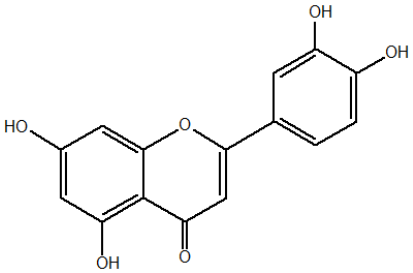
8.	 Ethyl Gallate	Fruit	Anticancer	[49]
9.	 Gallic Acid	Fruit	Anticancer	[47] [49]
10.	 Stearic Acid			[46]
11.	 (G = Galloyl) Chebulinic acid	Fruit	Anticancer	[40] [46][47] [49]
12.	 Punicalagin			[47]

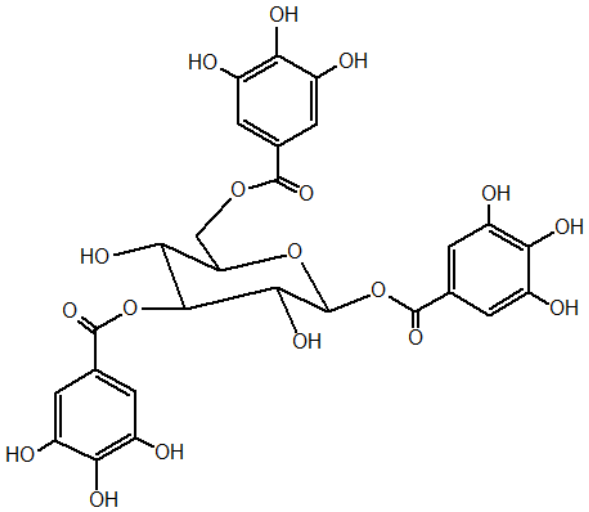
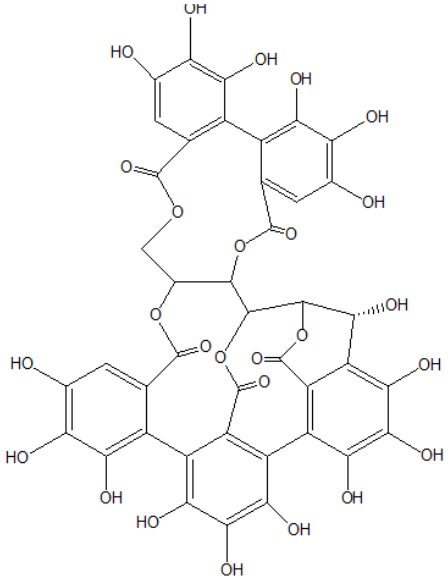
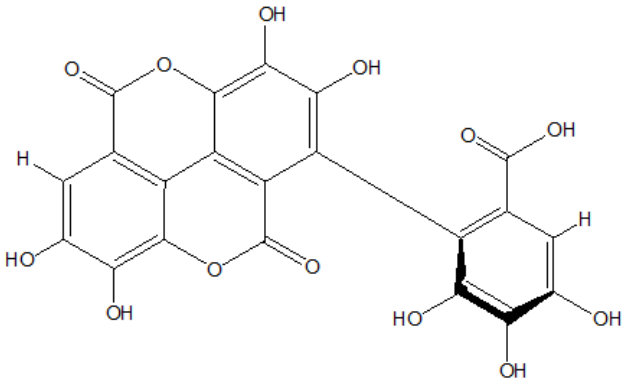
13.	 Linoleic Acid	Fruit		[48]
14.	 Tannic Acid	Fruit	Anticancer, Antioxident	[37] [49]
15.	 Galloyl Glucose		Anti HIV	[9]
16.	 Ellagic Acid	Fruit	Anticancer, Anti HIV	[9,10] [47,49]

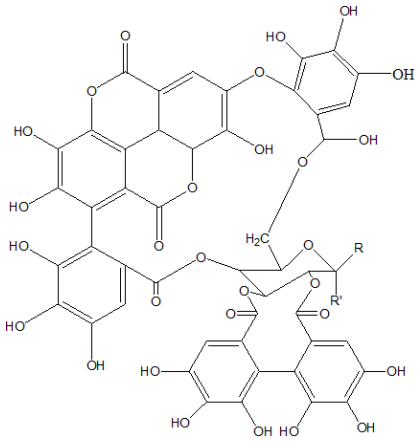
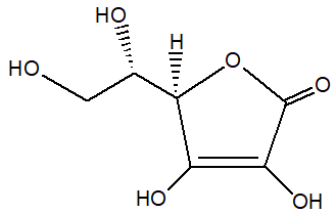
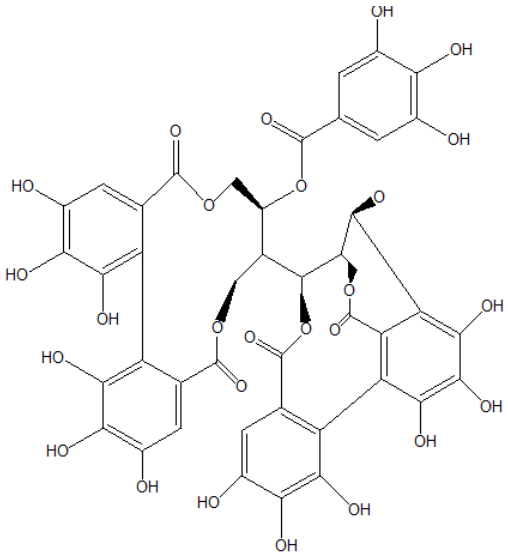
17.	 (G = Galloyl) 4-O-(4″-O-galloyl-α-l-rhamnopyranosyl)ellagic acid			[40]
18.	 (G = Galloyl) 4-O-(3″,4″-di-O-galloyl-α-l-hamnopyranosyl)ellagic acid			[40]
19.	 β Caryophyllene			[10]
20.	 Behenic acid			[10]

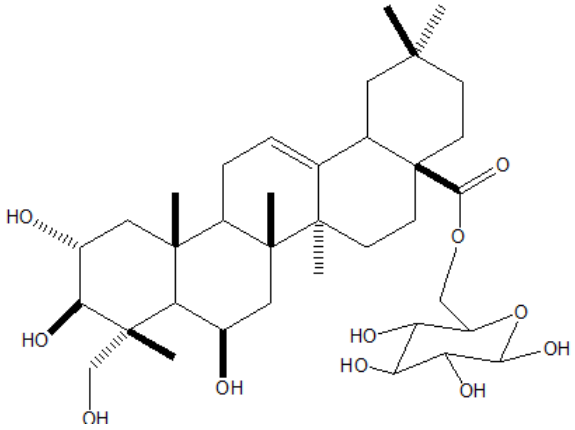
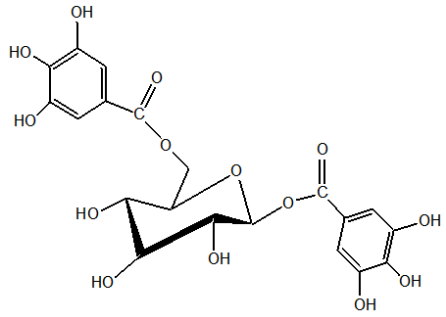
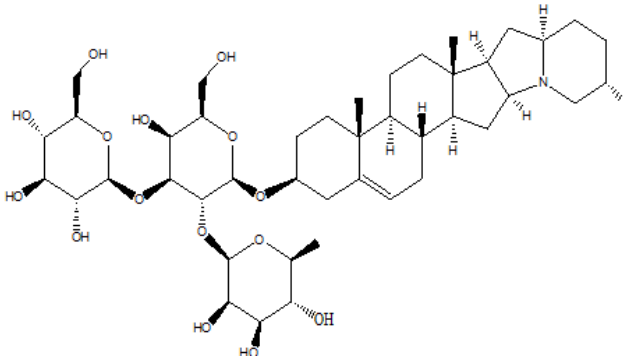
21.	 Eugenol			[10]
22.	 Isoquercetin			[10]
23.	 Oleic acid	Fruit		[10] [48]
24.	 $[Ca]^{2+}$ Ca-phellandrene			[10]
25.	 Alpha terpine			[10]

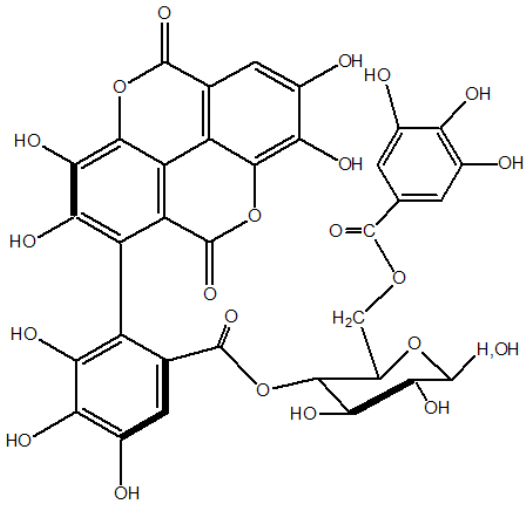
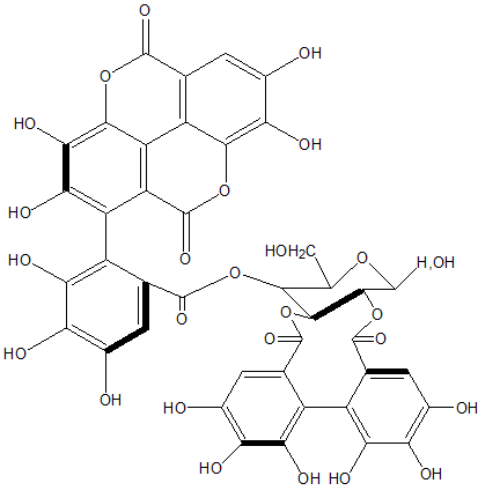
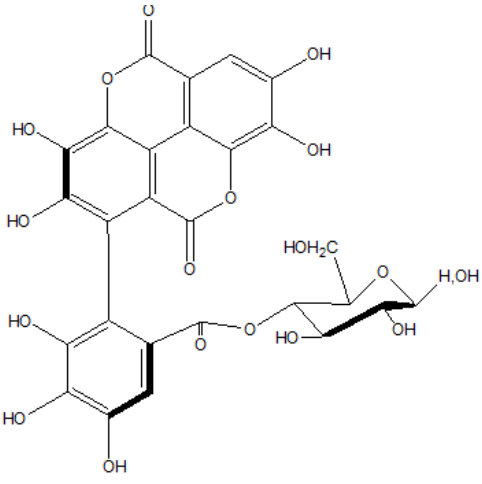
26.	 (G = Galloyl) Neochebulic acid		Hepatoprotective	[45]
27.	 (G = Galloyl) Chebulanin	Fruit		[47]
28.	 Neochebulinic acid			[47]

29.	 1,2,3,4,6-penta-o-galloyl-beta-d-glucose	Fruit		[47]
30.	 Palmitic acid	Fruit		[48]
31.	 2,4-Chebulyl-beta-d-glucopyranose	Fruit	Anticancer	[49]
32.	 Luteolin		Anticancer	[49]

33.	 1,3, 6-Tri-O-galloyl-ß-D-glucose			[51] [55]
34.	 Castalagin			[52]
35.	 Flavogallonic acid			[52]

36.	 (α- R=H, R'=OH) (β- R=OH,R'=H) Terchebulin			[52]
37.	 Ascorbic acid	Fruit		[37]
38.	 Casuarinin	Fruit		[53]

39.	 Chebuloside II	Fruit		[54]
40.	 1,6-di-O-galloyl-β-D-glucose	Fruit		[53]
41.	 Saponin	Fruit		[55]

42.	 Terflavin B	Leaves		[56]
43.	 Terflavin C	Leaves		[56]
44	 Terflavin D	Leaves		[56]

Ethnic Uses

Plants of the genus Terminalia are amongst the most widely used plants for traditional medicinal purposes worldwide [16]. Plant-derived medicines have been a part of our traditional health care system and the antimicrobial properties of plant-derived compounds are well documented. It is one of the main ingredients of the Triphla (*Terminalia chebula*, *Terminalia belerica*, and *Emblica officinalis*). Triphla is an Ayurvedic preparation that is used for correcting the digestive ailments. It is also useful in asthma, mouth ulcers, stomach infections, gastritis, hepatitis, skin diseases, piles and cough. It is used as gargle against inflammation of mucous membrane of mouth. Its paste with water is found to be anti-inflammatory, analgesic and having purifying and healing capacity for wounds. Its decoction as a lotion is used in surgical dressing for healing the wound earlier. The dried ripe fruit of herb has traditionally been used as a popular folk medicine for homeostatic, antitussive, laxative, diuretic and cardiotonic treatments [16,17].

Study of Pharmacological Effects

In recent years, there is an upsurge in the clinical usage of indigenous drugs, because of their efficacy and being free from serious toxic effects. Moreover constant increase in the antibiotics resistant strains and various side effects caused by the synthetic drugs has prompted scientists to look for herbal immunomodulators to treat various infections [18]. Herbal drugs are believed to enhance the natural resistance of the body against infection and their immunomodulatory activities have been reported in numerous plants [19]. Herbs are selected and combined for their ability to inhibit microbial overgrowth in various parts of the body and support those organ systems responsible for immune functions [20].

Anticariogenic Effect

The aqueous extract of *T. chebula* is used as a mouth rinse seems to be a potential anticariogenic mouthwash. A mouth rinse of 10% concentration was prepared by diluting the concentrated aqueous extract of the fruit of *T. chebula* in sterile distilled water. The efficacy of the mouth rinse was assessed by testing on 50 salivary samples. Salivary samples were collected from subjects assessed to be at high risk for caries. Salivary pH, buffering capacity and microbial activity were assessed before rinsing, immediately after, and 10 min, 30 min and 1 h after rinsing. There was an increase in the pH and buffering capacity and decrease in microbial count [21].

The total phenol content of aqueous extract was found to be 21.33 ±1.633 (mean ± SD) and total flavonoids as found to be 23.17 ± 2.317 (mean ± SD). There was a gradual increase in pH till 45 minutes post-rinse when compared to pre-rinse was observed. Antimicrobial effect of *Terminalia chebula* aganist microbes showed that there was a significant reduction between the pre-rinse and post-rinse samples [22].

Activity Against Anaphylactic Shock

The water soluble fraction of methanol extract of *T. chebula* fruit was tested in an anaphylactic shock model *in vivo*, by the death of Spague-Dawley rats (200-300 g) and ICR mice (20-30 g). Doses of 0.01-1.0 g/kg of the extract, administered 1 h before the experiment inhibited the anaphylactic shock with 100 %. Administration 5-10 mins after decreased the mortality dose dependently. Oral application reduced the cutaneous anaphylaxis with 63.5 +/- 7.8 %. From the rat mast cells the release of histamine was hindered in a dose dependent manner [13].

Gastrointestinal Activity

Terminalia chebula is a commonly advocated agent in Ayurveda for improving gastrointestinal motility. Charles Foster rats (150-200 grams of either sex) were divided into four groups as follows - Group 1 (n = 15) normal animals; Group II (n = 6) rats administered metoclopramide (1.35 mg/kg); Group III (n = 8) rats given atropine (0.45 mg/kg). These agents were injected intramuscularly, 30 mins before the experiment. Rats from Group IV (n = 8) were administered *Terminalia chebula* (100 mg/kg/day for 15 days orally). All rats were then given a test meal of methyl cellulose (1.5%) mixed with phenol red (50 mg/100 ml) orally and gastric emptying was measured 20 mins later. Gastric emptying of normal rats (Group I) was found to be 51.6 +/- 7.79%. Metoclopramide significantly increased the gastric emptying (76.33 +/- 12.37%; $p < 0.01$) and atropine inhibited the motility (% gastric emptying being 7.26 +/- 19.76%; $p < 0.01$). *Terminalia chebula* was found to increase the percent gastric emptying (86.57 +/- 6.65%; $p < 0.01$). Thus from this study it appears that *Terminalia chebula* can serve as a useful alternative to prokinetic drugs available today [23].

The antimicrobial action of *Teminalia chebula* especially on gastrointestinal tract is considered in supplementation of soothing to mucosal lining. Ellagic acid present in *T. chebula* has a potent inhibitory action on microorganisms like *C. perfringens* and *E. coli*. It is commonly advocated for increasing the gastrointestinal motility thus relieving the symptoms of gastroparesis for better bioavailability and fast absorption of the micronutrient. The presence of anthraquinone and sennoside are responsible for the purgative action. Studies have also shown the additional antibacterial activity of *T. chebula* on *Helicobacter pylori*. Reports have shown the extract of *T. chebula* to be effective against a broad spectrum of pathogens comprising of both gram positive as well as gram negative microorganisms [24].

Immunosuppressive Effects

Gallic acid and chebulagic acid, isolated from fruits of *T. chebula* inhibited the killing activity of CD8 and CTL clones at IC_{50} values of 30 and 50 µM, respectively. Granule exocytose in response to anti-CD3 stimulation was also blocked by both substances at the equivalent concentrations [25]. Chebulagic acid from immature seeds of *T. chebula* was found as a potent suppressor of the T cell activity. In DBA/1J mice arthritis was induced by subcutaneous immunization with bovine type II collagen on days 0 and 21. Chebulagic acid was administered intraperitoneally for 3 weeks, either as prophylaxis (10 or 20 mg/kg) before disease onset or as a therapy (20 mg/kg) after disease onset. In both the prophylactic and either in the therapeutic model, all clinical scores, like serum levels of total and anticollagen IgG and levels of interleukin-10 and interleukin-6 were reduced. The serum levels of the transforming growth factor beta were markedly elevated. The number of the granulocytes was reduced, but the proportion of CD4+, CD25+ T cells was greater in the knee joints of the chebulagic acid-treated mice. It concludes that chebulagic acid significantly suppressed the onset and progression the disease in mice [26].

The biologically active compounds such as chebulagic acid, gallic acid and ellagic acid make *T. chebula* highly potent antioxidant, which may be responsible for its immunomodulatory activity [17,27,28]. Its extract neutralizes reactive oxygen species (ROS) and scavenges free radicals. The free radicals are responsible for causing inflammation by stimulating release of cytokines such as IL-1, TNF-α and IFN-β, which stimulate additional neutrophils and macrophages at site of inflammation [29]. Thus, different antioxidants of the extract exhibit immunosuppressive properties, which help in neutralizing these important inflammatory mediators [30].

Antidiabetic Effects

The chloroform extract of *T. chebula* seed powder, produced significant antidiabetic effects with various doses in Streptozotocin-induced diabetic rats using short term and long term study protocols. In short term studies, *T. Chebula* extract produced a maximum reduction of blood glucose of 20.85% ($p < 0.01$), 28.45% ($p < 0.001$) and 42.20% ($p < 0.001$) at 4 h with doses of 100, 200 and 300 mg/kg respectively, whereas glibenclamide (0.04 mg/kg) produced a maximum reduction of 50.44% (4 h, $p < 0.001$) compared to control group. While the long term administration of *T. chebula* (300 mg/kg) for four weeks produced significant reduction in blood glucose. The reduction was significant after treatment for one week in both the extract and glibenclamide treated groups and continued to increase up to four weeks. At the end of 4th week, *T. chebula* extract produced significant blood glucose reduction of 53.09% ($p < 0.01$). On the other hand, glibenclamide produced significant blood glucose reduction of 60.10% ($p < 0.01$). The hepatic and skeletal muscle glycogen content decreased to 75 % and 62.2 % in the diabetic controls. In the *in vitro* investigation the pancreatic islets showed that the insulin release was nearly two times more than that in untreated diabetic animals. The treatment did not bring any unfavourable effects on the other blood parameters of the liver and the kidney function tests. The LD_{50} value was above 3 g/kg. There were no deaths of animals even at this dose [31].

Oral administration of ethanolic extract of the fruits (200 mg/kg body weight/rat/day) for 30 days significantly reduced the levels of blood glucose and glycosylated hemoglobin in streptozotocin (STZ)-induced experimental diabetes in rats. Electron microscopic studies showed significant morphological changes in the mitochondria and endoplasmic reticulum of pancreatic β cells of STZ- induced diabetic rats. Also, a decrease in the number of secretory granules of β-cells was observed and these pathological abnormalities were normalized after treatment with *T. chebula* extract. The present study shows that the ethanolic extract of *T. chebula* fruit has potential hypoglycemic action in STZ-induced diabetic rats and the effect was found to be more effective than glibenclamide [32].

Study was conducted to evaluate the anti-diabetic effects of ethanolic extract of *Terminalia chebula* Retz. Fruits by using alloxan-monohydrate induced diabetic control by using Wistar Albino rats for 30 days. The effect of this extract (200 mg kg^{-1} b.wt.) was compared with the glibenclamide (600 mg kg^{-1} b.wt.). This extract showed nil toxicity up to 500 mg kg^{-1} b.wt. After the completion of the study, collected samples were performed under parameters like biochemical and anti-oxidant enzymes related to diabetes. The histopathological changes caused after induction of alloxan showed the granular cytoplasm, dilatation, shrunken nuclei and inflammation, which were reduced after treatment of the ethanolic extract (200 mg kg^{-1} b.wt.). Excess proliferation of epithelium in the pancreas was observed in diabetic rats, which was reduced. From the evaluation of the present study has been confirmed that having the pharmacological action against the diabetic condition, even though the mechanism of the action is unknown [33]. The 80%-ethanolic extract of *Terminalia chebula* Retz. Has also significant hypoglycemic effect on alloxaninduced diabetic rats and it been comparable with standard drug, metformin. The effective dose was 200 to 400 mg/kg [34].

The aqueous extract of the fruits of *Terminalia chebula* Retz. Has been evaluated for its antidiabetic activity in streptozotocin (STZ) induced mild diabetic rats and compared with a known drug, tolbutamide. Oral administration of 200 mg / kg body weight of aqueous extract of *T. chebula* daily

once for two months reduced the elevated blood glucose by 43.2% ($p < 0.01$) and significantly reduced the increase in HbA1c ($p<0.01$). Hepatic and skeletal muscle glycogen content decreased by 75% and 62.9% respectively in diabetic controls, these alterations were partly prevented (34.9% and 21.17%) in aqueous extract treated group when compared to the healthy controls. 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 other blood parameters of liver and kidney function tests [35].

Chebulagic acid, isolated from *T. chebula* proved to be a reversible and non-competitive inhibitor of maltase with a KI value of 6.6 mμM. The inhibitory influence of chebulagic acid on the maltase-glucoamylase complex was more potent than on the sucrase-isomaltase complex. The magnitude of the inhibition is greatly affected by its origin [36].

Cardiotonic Activity

The different extracts of fruits of *T. chebula* exhibited cardiotonic activity when tested on isolated frog hearts. The benzene and chloroform extracts showed a moderate cardiotonic activity, though at high doses because they were not completely soluble in the experimental Ringer solution. Ethyl acetate, butanone, butanol and aqueous extracts exerted fairly potent cardiotonic activities. These all gave easily dispersible solutions, produced dose-dependent positive isotropic effects and an increase in the cardiac output. There was no appreciable change in the heart rate. The extracts being tested here stimulated the isolated perfused frog heart without inducing depression [37].

Cardiotonic effect of aqueous extract of stem bark of *Terminalia chebula* was studied by using isolated frog heart perfusion technique (IFHP). This was studied on both normal and hypodynamic hearts. Calcium free Ringer solution was used as vehicle for administration of aqueous extract of *Terminalia chebula* as a test extract and digoxin as a standard. A significant increase in height of force of contraction (positive inotropic effect) with increase in dose, no change in heart rate was observed with test extract as compared to dose of a standard digoxin. The test extract produced cardiac arrest at 3 mg/ml, a higher concentration, as compared to standard, digoxin (15μg/ml). Compared to digoxin, a drug with narrow therapeutic window, *Terminalia chebula* showed wide therapeutic window [38].

An ethanolic extract of *T. chebula* fruits (500 mg/kg) was tested in rats with isoprotenerol (200 mg/kg) induced myocardial damage. In them the level of lipid peroxidase increased significantly in the serum and the heart. The activity of the myocardial marker enzymes decreased with a concomitant increase in the activity of the serum. The myocardial necrosis was confirmed by histopathological examination. Pre-treatment with the extract ameliorated the effect of isoprotenerol on the lipid peroxide formation and retained the activities of the diagnostic marker enzymes [39].

The fruits of *T. chebula* are claimed to be useful against heart diseases. Besides the known effects of extracts on isolated frog hearts in this investigation, extracts are applied on (Na^+, K^+ and Mg^{2+}) ATP ases of a whole homogenate prepared from ventricular portion of frog heart. The extracts exerted the following inhibition: Butanolic extract 13.5 % and 57.4 % with doses of 0.5 and 1.0 mg respectively. Aqueous extract 31.22 %, 40.68 %, and 49.18 % with doses of 0.1, 0.5, and 1.0 mg. The inhibition of the ATPase system with the dose of 1 mg is enormous. It is higher than that caused by ouabain, which is a specific inhibitor of this ATPase [4].

Wound Healing

The alcoholic extract of leaves from *T. chebula* was topically administered on dermal wounds of rats. The treated wounds healed much faster, indicated by improved rates of contraction and a decreased period of epithelisation. The granulation tissue increased in total protein DNA and collagen content. The levels of hexosamine and uronic acid in these tissues also increased up to 8 days post-wounding. In addition, the extract was active against *Staphylococcus aureus* and *Klebsiella*. These results document the beneficial effects of *T. chebula* extract for the healing process [40].

The hydroalcoholic extract of *T. Chebula* fruit was evaluated for its wound healing activity in alloxan induced diabetic rats using excision and dead space wound models. Extract treated animals exhibited 82% reduction in the wound area when compared to controls which was 40%. The extract treated wounds were found to epithelize faster as compare to controls. The wet and dry granulation tissue weight content was increased significantly when compared to controls. This extract promotes significant wound healing in diabetic rats and further evaluation of this activity in humans is suggested [41].

Different concentrations of various organic and aqueous extracts (solvent-free) of *T. chebula* were tested on fibroblast (L929) and keratinocytes cells to evaluate its biocompatible concentration by using MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] and live-dead viability/cytotoxic assay. These extracts were found to be effective in decreasing the ammonia accumulation in the media, thereby reducing its toxic effect on cells. The cytoskeletal structure and extracellular matrix secretion of the cells treated with extracts showed higher cellular activity in comparison to control. In conclusion, we have demonstrated the effect of

these extracts of *T. chebula* on both types of skin cells and optimized concentration in which it could be used as a bioactive component for wound healing applications by increasing cell proliferation and decreasing free-radical production without affecting the normal cellular matrix [42].

Hypolipedemic Effect

Hypercholesteremia is one of the risk factors for coronary artery disease. The present study highlights the efficacy of Ayurvedic herbal formulation Triphala on total cholesterol, low density lipoprotein (LDL), very low density lipoprotein (VLDL), high density lipoprotein (HDL) and free fatty acid in experimentally induced hypercholesteremic rats. Four groups of rats were employed namely control, Triphala treated, hypercholesterolemia rats (4% Cholesterol + 1% cholic acid + egg yolk) and Triphala pre-treatment in hypercholesteremic rats. Results showed significant increase in the total cholesterol, LDL, VLDL, and free fatty acid in hypercholesteremic rats were significantly reduced in Triphala treated hypercholesteremic rats [43].

In atherogenic diet induced hyperlipidemic model, the rats receiving treatment with Haritaki (*Terminalia chebula*) showed significant reduction in total cholesterol, triglycerides, total protein and elevation of high density lipoprotein cholesterol. The results also suggest that Haritaki at 1.05 and 2.10 mg/kg b.wt. concentrations is an excellent lipid-lowering agent. It can be utilized for providing dietary management in the prevention of atherosclerosis in hyperlipidemic patients [44]. Treatment with *Terminalia chebula* ameliorated the biochemical parameters, histological and histochemical results [45].

Antibacterial

The ethanolic extract of *T. chebula* fruit was tested for its activity against methicillin-resistant and methicillin-sensitive *Staphylococcus aureus* strains from clinical isolates. The extract showed a broad spectrum of antibacterial activity with an inhibition zone size of 11 to 27 mm, against all the test bacteria. There was a synergistic interaction of the crude extract with tetracycline, too. TLC analysis indicated phenols and flavonoids as major active compounds [46]. In a similar investigation gallic acid and its ethyl ester could be verified on the basis of spectroscopic evidence [47].

Ether, alcohol and water extracts of *T. chebula* and black myrobalan (*Teminalia chebula* Retz) were tested against *Helicobacter pylori* in an agar diffusion test. The water extract had a MIC value of 125 mg/L and a MBC of 150 mg/L. Plant powder, incorporated in agar gave higher MIC and MBC values (150 and 175 mg/l). The extract was active after autoclaving for 30 min at 121°C. The water extract at a concentration of 1-2.5 mg/L inhibited the activity of urease [9]. The aqueous extract of *T. chebula* strongly inhibited the growth, the sucrose induced adherence and the glucan-induced aggregation of *Streptococcus mutans.* Mouth rinsing with a 10 % solution of the extract significantly reduced the total bacterial counts and the total streptococcal counts in the saliva samples. It successfully inhibited glycolysis of salivary bacteria for up to 90 min after rinsing [9,21].

An ethanol extract of *Terminalia chebula* fruit was studied for its antibacterial activity against clinically important standard reference bacterial strains. The antimicrobial susceptibility was screened using the disc diffusion method and the minimum inhibitory concentration (MIC) was determined using the broth micro dilution method. The results showed that it was active against both gram-positive and gram-negative bacteria. The *T. chebula* fruit extract was highly effective against *Salmonella typhi* SSFP 4S, *Staphylococcus epidermidis* MTCC 3615, *Staphylococcus aureus* ATCC 25923, *Bacillus subtilis* MTCC 441 and *Pseudomonas aeruginosa* ATCC 27853. The MIC was determined as 1 mg/ml for *S. typhi*. These results indicate that the *T. chebula* dry fruit possesses a potential broad spectrum of antimicrobial activity [48]. This extract demonstrated a strong antimicrobial activity against all the test isolates and found to be most effective over others. Phytochemical analysis revealed the presence of high concentration of phenolics and low concentration of flavonoids and terpenoids. In acute oral toxicity study, no gross behavioral changes were observed in mice at recommended dosage level and 24 h LD_{50} was found to be >4 g/kg, p.o. in mice. The results provide that *Terminalia chebula* fruit could be useful for the development of alternative/complementary medicine for multidrug–resistant uropathogens [49].

Antiviral

HSV-1 (Herpes simplex virus) is a common human pathogen that causes lifelong latent infection of sensory neurons. Non-nucleoside inhibitors that can limit HSV-1 recurrence are particularly useful in treating immunocompromised individuals or cases of emerging acyclovir-resistant strains of herpes virus. The extract of *T. chebula* showed a strong anti-HSV-1activity in combination with acyclovir. With doses, corresponding to the human use it limited the development of skin lesions and prolonged the mean survival times of infected mice compared with both acyclovir and with the mice treated alone with the herbal extract ($p<0.01$ and $p<0.05$). It reduced virus yields in the skin and brain stronger than acyclovir alone. It exhibited a stronger anti-HSV-1 activity in the brains than in the skin, in contrast to acyclovir treatment alone. The combination

was not toxic to mice [50]. Chebulagic acid and punicalagin inhibit HSV-1 entry at noncytotoxic doses in A549 human lung cells. Experiments revealed that both tannins targeted and inactivated HSV-1 viral particles and could prevent binding, penetration, and cell-to-cell spread, as well as secondary infection. Results indicated that both blocked interactions between cell surface glycosaminoglycans and HSV-1 glycoproteins [51,52].

Chebulagic and chebulinic acids have higher direct antiviral activity against HSV-2 and efficacy to inhibit virus attachment and penetration to the host cells as compared to acyclovir. Hence, it may be a useful candidate for developing alternative therapy for prevention of sexually transmitted HSV-2 infection [53].

Chebulinic acid and chebulagic acid can effectively inhibit IAV (The influenza A virus) replication. These compounds act as neuraminidase inhibitors and show antiviral potency to both wild-type and oseltamivir-resistant IAV strains [54]. Chebulagic acid and/or its hydrolysis fragments as new chemical leads to restores growth of M2(S31N)-expressing yeast and inhibits *in vitro* influenza A replication regardless of M2 sequence [55].

Hot water extracts of *T. chebula* were examined for ant cytomegalovirus activity *in vitro* and *in vivo*. *In vitro* they inhibited the replication of human cytomegalovirus. *In vivo* they were tested in an infection model on immune suppressed mice. The herbal extract was orally administered to the mice treated with 50 mg/kg cyclosporine for one day before the intraperitoneal infection. The efficacy was evaluated by the reduction of the virus yield in the lung. The *T. chebula* extract significantly suppressed the virus yields in the lungs of the treated mice compared with the water treated animals [10].

Antioxidant and Cytoprotective Effects

Treatment and pretreatment of the hepatocytes with the *T. chebula* extract significantly reversed the *t*-BHP-induced cell cytotoxicity and lactate dehydrogenase leakage. In addition, extract exhibited *in vitro* ferric-reducing antioxidant activity and 2,2-diphenyl-1-picryhydrazyl free radical-scavenging activities. The *in vivo* study showed that pretreatment with extract (500 or 1000 mg/kg) by gavage for 5 days before a single dose of *t*-BHP (0.1 mmol/kg) significantly lowered the serum levels of the hepatic enzyme markers aspartate aminotransferase, alanine aminotransferase and reduced the indicators of oxidative stress in the liver, such as the glutathine disulfide content and lipid peroxidation, in a dose dependent manner. Histopathologic examination of the rat livers showed that extract reduced the incidence of liver lesions, including hepatocyte swelling and neutrophilic infiltration, and repaired necrosis induced by *t*-BHP [17]. Triphala extracts inhibit 50 % of lipid peroxidation, induced with Fe^{2+} ascorbate were 85.5, 27, 74, and 69 µg/mL *in vitro*. The concentrations needed for inhibition of the hydroxyl radical scavenging were 165, 71, 155.5, and 12.5 µg/mL. A continued daily administration sustained the effect [14].

The water extract of *T. chebula* fruits was tested for its radio protective ability. The free radical neutralizing ability was comparable to that of ascorbate (100 µM) 93.5 % and gallic acid (100 µM) 91.5 %, respectively. It protected the plasmid DNA pBR322 from the radiation-induced strand breaks. The administration of 80 mg/kg prior to whole body irradiation of mice (4 Gray) reduced the peroxidation of membrane lipids in the mice liver from radiation-induced DNA damages. Human lymphocytes also were protected from DNA damages exposed *in vitro* by 2 Gray [56]. It inhibits xanthine oxidase activity. It is an excellent scavenger of DPPH radicals. A HPLC analysis showed the presence of ascorbate, gallic acid and ellagic acid. The extract seems to be able to protect cell organelles from radioinduced damages [57].

The percentage inhibition of CaOx nucleation was found 95.84% at 25µg/mL of *Terminalia chebula* aqueous extract which remained almost constant with the increasing concentration of the plant extract; however, plant extract inhibited CaOx crystal growth in a dose dependent pattern. When MDCK and NRK-52E cells were injured by exposure to oxalate for 48 hours, the aqueous extract prevented the injury in a dose-dependent manner. On treatment with the different concentrations of the plant extract, the cell viability increased and lactate dehydrogenase release decreased in a concentration dependent manner. This study indicates that *T. chebula* is a potential candidate for phytotherapy against urolithiasis as it not only has a potential to inhibit nucleation and the growth of the CaOx crystals but also has a cytoprotective role [58].

The polyphenolic extract of *T. chebula* fruits was evaluated for antioxidant activity by determining the reducing power, total antioxidant capacity, DPPH radical concentration (IC_{50} 14 µg/mL), nitric oxide radical concentration (IC_{50} 30.51 µg/mL) and hydrogen peroxide scavenging activity (IC_{50} 265.53 µg/mL) under *in vitro* conditions. Moreover, the phytochemical characterization of the extract was also measured by determining the total phenolic, flavonoid, tannin and ascorbic acid contents. It also scavenges hydrogen peroxide-induced radicals. The activity of the extract may be due to the total polyphenolic content. The antioxidant activity of the extract is significantly higher than the standard ascorbic acid, and its activity is concentration-dependent. It is concluded that a polyphenolic-rich fraction of *T. chebula* fruits is a potential source of natural antioxidants

[59].

Antimutagenic

Tannin fractions and gallic acid from the dried pulp of *T. chebula* were evaluated for their antimutagenic potential. They all were highly significant active against S9-dependent mutagen 2AF. The effect corresponds with the nature of the fractions; the monomeric gallic acid was the least effective [60]. The water extract of dried *T. chebula* fruits inhibited the direct acting mutagens sodium azide and 4-nitro-o-phenylendiamine in the strains TA100, TA1535, TA97a, TA98 of *Salmonella typhi* murium and S9-dependent mutagen 2-aminofluoren in TA97, TA98 and TA100 strains. Autoclaving the water extract reduced the effect not significantly [61]. In the VITOTOX Test for detection of DNA damages in prokaryotic and eucaryotic cells extracts from *T. chebula* were not genotoxic. This result is consistent with another Ames Test. But in the COMET assay the extracts increased DNA damages with content above 500 ppm [62].

Study showed that ethyl acetate portion of of *Emblica officinalis*, *Terminalia chebula* and *T. bellirica* extracts contain two major compounds, gallic acid and ellagic acid which might be responsible for potent antimutagenic activity induced by different genotoxic compounds in a dose dependent manner [63].

To obtain experimental evidence on the therapeutic efficacy of the *Terminalia chebula* fruit extract, we examined its effect on chromosomal aberration (CA) and micronucleus (MN) formation in C57BL hybrid mice, to assess the anti-mutagenic activity. In MN formation test, single application of *Terminalia chebula* methanolic fruit extract at different doses of 50, 100 and 150 mg/kg dry weight 24 hours prior to administration of cyclophosphamide (CP) at the dose of 50 mg/kg significantly reduced the frequency of MNCPE and at the same time significantly increased PCE/NCE ratio 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 *Terminalia chebula* fruit extract alone did not show any chromosomal aberration and/or micronucleus formation. The anti-mutagenic activity observed in this study can be attributed to the presence of flavonoids and polyphenols. Thus it could be a better choice to treat cancer without inducing mutations in healthy body cells [64].

Protective Drugs against Stress

The IC_{50} value of hydroalcoholic fruit extract of *Terminalia chebula* (HETC) in *in vitro* antioxidant assays i.e. ABTS, DPPH and NO radical scavenging assay was found to be 2.27µg/ml, 6.04µg/ml and 4.37µg/ml respectively. In experimental study, PTZ (pentylenetetrazole) and MES (maximal-electroshock) treated groups exhibited 100% seizures with increased oxidative stress ($p < 0.001$) and cognitive deficits ($p < 0.01$) as compared to control group. HETC at highest dose (1000mg/kg) showed 83.33% (5/6) protection in MES induced seizures while 66.66% (4/6) protection in PTZ induced seizures. However, HETC (1000mg/kg) and co-administration of sub-therapeutic dose of HETC with valproate and phenytoin showed complete protection. In addition, it also attenuated the seizure induced oxidative stress and cognitive impairment as indicated by significant ($p < 0.01$) improvement in the transfer latencies in elevated plus maze (EPM) and passive avoidance test (PA) as compared to PTZ and MES treated group. The findings suggest that HETC exhibited significant anticonvulsant activity and also potentiated the subtherapeutic dose of phenytoin and valproate indicate its usefulness as an adjuvant to antiepileptic drugs with an advantage of preventing cognitive impairment and oxidative stress [65].

Pretreatment with an ethanol extract of *T. chebula* is found to retain near normal activities of lysosomal enzymes in rats compared with isoproterenol alone. Isoproterenol administration produced significant cardiac damage (as seen by the triphenyltetrazolium chloride assay) and significantly altered lysosomal enzyme activities. Results showed that *T. chebula* extract stabilizes the lysosomal membrane and prevents myocardial damage [66].

Immune Activation

In recent years, much attention is being focused on the immunological changes occur during stress. The immunomodulatory activities of Triphala were assessed by testing the various neutrophil functions like adherence, phagocytosis [phagocytic index (P.I) and avidity index (A.I)] and nitro blue tetrazolium (NBT) reduction in albino rats. Noise (100 dB) stress for 4 h/d for 15 d, was employed to alter the neutrophil functions. The neutrophil function tests and corticosterone levels were carried out in eight different groups of animals, namely control, Triphala, noise-stress, Triphala noise-stress, and corresponding immunized groups were used. Sheep red blood cells (SRBC 5 x 10(9) cells per ml) were used for immunizing the animals that belongs to immunized groups. In Triphala administration (1g/kg/d for 48 d), A.I was found to be significantly enhanced in the Triphala group, while the remaining neutrophil functions and steroid levels were not altered significantly. However the neutrophil functions were significantly enhanced in the Triphala immunized group with a significant decrease in corticosterone level was observed. Upon exposure to the noise stress, the neutrophil functions were significantly

suppressed and followed by a significant increase in the corticosterone levels were observed in both the noise-stress and the noise-stress immunized groups. These noise-stress induced changes were significantly prevented by Triphala administration in both the Triphala noise-stress and the Triphala noise-stress immunized groups. Hence study has divulged that oral administration of Triphala appears to stimulate the neutrophil functions in the immunized rats and stress induced suppression in the neutrophil functions [67].

Study reports the effect of dry fruit extract of *T. chebula* (TCE) on Th1/Th2-mediated immune responses in mice. TCE was administered orally for 10 consecutive days, after which mice were immunized with goat RBC (gRBC) or ovalbumin. TCE enhanced the expression of Th1 cytokine, interferon γ, decreased interleukin 4, and increased the number of plaque-forming cells in gRBC-immunized mice. The percentage of CD4+ cells and delayed-type hypersensitivity response also increased in these mice. Treatment is reported to increase lymphocyte proliferation and macrophage phagocyte response, but decrease nitrite production. The bone marrow cellularity and WBC count also increased in the treated mice. None of the group showed any sign of toxicity. The data indicate that TCE elicits a significant dose-dependent Th1 response [68].

Immunomodulatory activity of ripe *T. chebula* fruits evidenced by increase in the concentration of antioxidant enzymes, GSH, T and B cells, the proliferation of which play important roles in immunity. This phenomenon also enhances the concentration of melatonin in pineal gland as well as the levels of cytokines, such as IL-2, IL-10 and TNF-α, which play important roles in immunity [69].

α-Glucosidase Inhibitor

Mammalian α-glucosidase inhibitory activity by *Terminalia chebula* Retz. fruits was investigated. The aqueous methanolic extract was found to have potent rat intestinal maltase inhibitory activity, whereas neither intestinal sucrase nor isomaltase activity was inhibited by this extract. Using bioassay-guided separation, three active ellagitannins were identified as chebulanin (1), chebulagic acid (2) and chebulinic acid (3) and were shown to possess potent intestinal maltase inhibitory activity, with the IC_{50} values of 690 μM, 97 μM and 36 μM, respectively. The intestinal maltase inhibitory activities of 2 and 3 were even higher than that of 1,2,3,4,6-penta-*O*-galloyl-β-d-glucose (PGG) (4, IC_{50}=140 μM), which is a known potent α-glucosidase inhibitor. Comparison of the activities of 1–4, 1,2,3-*O*-trigalloyl-β-d-glucose (5), neochebulagic acid (6) and corilagin (7) suggested that the positions of chebulloyl and galloyl groups mostly affected the potency. Kinetic studies revealed that 2, 3, and 4 inhibited maltose-hydrolyzing activity of intestinal α-glucosidase, noncompetitively. This is the first report on mammalian α-glucosidase inhibition by 1, 2 and 3 isolated from *T. chebula* fruits. These results suggest a use of the extract of *T. chebula* fruits for managing Type 2 diabetes [70].

Chebulagic acid, isolated form *Terminalia chebula* proved to be a reversible and non-competitive inhibitor of maltase with a K_i value of 6.6 μM. The inhibitory influence of chebulagic acid on the maltase glucoamylase complex was more potent than on the sucrase-isomaltase complex. The magnitude of α-glucosidase inhibition by chebulagic acid was greatly affected by its origin. These results show a use for chebulagic acid in managing type-2 diabetes [36]. Compounds, 23-*O*-galloylarjunolic acid (IC_{50} 21.7 μM) and 23-*O*-galloylarjunolic acid 28-*O*-*β*-d-glucopyranosyl ester (IC_{50} 64.2 μM) from *Terminelia chebula* also showed potent inhibitory activities against Baker's yeast *α*-glucosidase compared to the positive control, acarbose (IC_{50} 174.0 μM) [71].

Anticancer Activity

Homeopathic preparations of *Terminalia chebula* known as Mother tincture (*MT*) decreased the viability of breast cancer (MDAMB231 and MCF7) and non-cancerous (HEK293) cells. However, other homeopathic preparations of *Terminalia chebula* (*3X*, *6C* and *30C*) decreased the viability of only breast cancer cells without affecting the viability of the non-cancerous cells. All the potencies, *MT*, *3X*, *6C* and *30C*, reduced growth kinetics of breast cancer cells, more specifically at 1:10 dilution at 24, 48 and 72 h. Under SEM, *MT* appeared as a mesh-like structure whereas under TEM, it showed presence of nanoclusters. On the other hand, 6C potency contained 20 nm sized nanoparticles. The current study reports the anticancer activity of homeopathic preparations of *Terminalia chebula* against breast cancer and reveals their nano particulate nature. These preliminary results warrant further mechanistic studies at both *in vitro* and *in vivo* levels to evaluate the potential as nanomedicine in breast cancer [72].

In several human malignant cell lines a 70 % methanolic extract of *T. chebula* fruits decreased the cell viability, inhibited the cell proliferation and induced the cell death in a dose dependent manner. In lower concentrations some apoptosis was induced, but at higher concentrations necrosis was the major mechanism of the cell death. The following IC_{50} values could be revealed: Chebulinic acid: 53.2+/-0.16 μM, tannic acid 59.0+/-0.19 μM, ellagic acid 78.5+/-0.24 μM, respectively [14].

Potent Suppressor of T- Cell Activity

In both the prophylactic and therapeutic Chebulagic acid (CHE) dosing models, all clinical scores, serum levels of total and anticollagen IgG, and levels of interleukin-10 (IL-10) and IL-6 were reduced, while serum levels of transforming growth factor (TGF) were markedly elevated. The number of granulocytes was reduced, but the proportion of CD4+, CD25+ T cells was greater in the knee joints of CHE-treated collagen-induced arthritis (CIA) mice. Expression of Foxp3 and TGF β messenger RNA was also augmented significantly in the knee joints of CHE-treated CIA mice in the therapeutic dosing model. It concludes that CHE significantly suppressed the onset and progression of CIA in mice. Immune suppression via the induction of TGF β and CD4+, CD25+ T cells may represent a new strategy in the development of therapies for managing rheumatoid arthritis and other inflammatory diseases [26].

Study assessed *T. chebula* extract-dependent protein expression changes in Jurkat cells. Matrix-assisted laser desorption/ionization–time-of-flight mass spectrometry and Ingenuity Pathways Analysis (IPA) were performed to assess protein expression and networks, respectively. A comparative proteomic profile was determined in *T. chebula* extract (50 μg/mL)-treated and control cells; the expressions of β-tubulin, ring finger and CHY zinc finger domain containing 1, and insulin-like growth factor 1 receptor kinase were significantly down-regulated in *T. chebula* extract-treated Jurkat cells. Treatment with the *T. chebula* extract significantly inhibited nuclear factor-κB activity and affected the proteomic profile of Jurkat cells [73-89].

Conclusion

Terminalia chebula have extensive medicinal potential to explore. It is called the "king of medicines" and always listed first in the Ayurvedic meteria medica because of its extraordinary powers of healing. This review describes the key bioactive phytochemicals isolate from it and their role in various system of traditional medicine to cure various diseases. Phytochemical constituents of this plant show anticariogenic effect, gastrointestinal activity, immunosuppressive effects, antidiabetic effects, hypolipedemic effect, antimutagenic, α-glucosidase inhibitor, potent suppressor of T- Cell Activity etc. The present review summarizes the ethnic use, pharmacological activities of extracts and phytochemicals of *Terminelia Chebula* for last 40 years.

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