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Research Article

Updated Review: Pharmacological Activities and Bioactive Constituents of *Terminalia Chebula*

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ABSTRACT

Terminalia chebula belongs to the family Combretaceae and its fruits are widely used as crude drugs in different traditional medicine systems such as Ayurveda and Unani. This review article aims to collect the available scientific information regarding traditional uses, bioactive chemical constituents and the pharmacological activities of T. chebula. Various research conducted on T. chebula plants has proven the presence of different types of phytoconstituents such as tannins, flavonoids, phenolic acids, and other compounds. Fruits and other parts of T. chebula are widely studied for their pharmacological activities which mainly include hepatoprotective, antioxidant, cytotoxic, neuroprotective, anti-inflammatory antidiabetic activities. However, in the future more clinical and in vivo studies for mechanism-based pharmacological evaluation should be conducted to provide stronger scientific evidence for their traditional uses.

Keywords: Tannins, antioxidants, phenolic acids, bioactivity, *Terminalia chebula*, Combretaceae.

1 INTRODUCTION

There are 200-250 species from the genus Terminalia which belongs to the family Combretaceae[1-7]. The highest diversity of these plants found in Southeast Asia, although plants of the Terminalia genus are globally distributed in tropical regions. Name Terminalia is derived from the Latin word terminus, because the leaves of these plants exist at top of the shoot[8-14]. Well, studied species of this genus include T. Travancorensis, T. alata, T. procera, T. paniculata, T. coriacea, T. myriocarpa, T. manii, T. chebula, T. citrine, T. catappa, T. bellirica, T. bilata and T. arjuna. In Ayurveda different parts of species T. chebula, T. bellerica, and T. arjuna are used from ancient times[15-16]. Pharmacologically most explored species T. chebula Retz is native to south Asia and southeast Asia[17-18]. T. chebula fruits are known as harro in Nepali and haritaki in Sanskrit, it is used Ayurvedic formulation Triphala churna, which contain an equal quantity of T. bellirica, T. chebula, and Phyllanthus emblica. Extensive studies performed on the formulation, traditional uses, pharmacological activities, and bioactive chemical constituents of T. chebula. Traditional uses have been supported by preclinical studies and explore its ability to develop new therapies[19-20]. To understand the mechanism of action characterization of active constituents, proper formulations, and isolation methods have to be developed. Polyherbal formulations of T. chebula and pharmacological activities of Triphala churna have been reported in different studies[21-24]. This study has aims to review traditional uses, pharmacological activities, scientific information, and bioactive chemical compounds of T. chebula. Literature information was collected from PubMed, SciFinder, published books, proceedings, and Google Scholar. In this article, current research gaps and future recommendations for T. chebula are discussed.

2. TRADITIONAL USES

In many of the Asian countries, T. chebula is used in medicine since ancient times. Fruit kernels are edible[25-27]. Chebulae Fructus also known as pericarp of mature fruits is traditionally used as a crude drug. T. chebula have local names in different languages: Haritaki (Bengali & Sanskrit), Harad (Hindi), Harro (Nepali), Karakkaya (Telugu), Halela (Urdu), Kadukkai (Tamil), Hirdo, Himaja, Pulo-harda (Gujrati), Harada (Marathi), Halela, Harar (Panjabi), Alalekai (Kannada), Katukka (Malayalam), Halela (Kashmiri).

In many Ayurvedic formulations such as Triphaladi Taila, Triphala Churna, Agastya Haritaki Rasayana, Abhayarista, Danti Haritaki, Dasamula Haritaki, Citraka Haritaki, Abhaya lavana, Brahma Rasayana and Pathyadi Lepa haritaki is one of the ingredients. T. chebula fruits have carminative, purgative, alternative, astringent, and stomachic properties[28-29]. In traditional Ayurveda and Siddha medicines, fruits are used for the treatment of gastroenteritis constipation, chronic diarrhea, malabsorption syndrome, ulcer, asthma, dyspepsia, dyspnea, hemorrhoids, candidiasis, cough, hepatomegaly, antiparasitic, antitumor, urinary discharge, skin disease, epilepsy, loss of memory, cardiovascular disease, anorexia, diabetes, homeostatic, diuretic, wound healer and antitussive[30-32]. It is also used for spleen enlargements, hepatic problems, curing skin ailments, as an astringent for treating hemorrhoids, treating loose gums, as a dentifrice, bleeding in gums,

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and ulceration. For the treatment of hemorrhoids and asthma fruit past is used[33].

3. BIOACTIVE CHEMICAL CONSTITUENTS

Phenolic compounds including tannins, flavonoids, and phenolic acids are widely reported in T. chebula fruits, it also has high vitamin c content. Other tannin-containing compounds include chebulagic acid (CA), punicalagin, terchebulin, terflavin A, corilagin, and chebulinic acid[34]. list of these compounds is provided in table 1.for For determination of 14 phenolic constituents in T. chebula fruits reverse-phase HPLC method was developed by Juang et al. (2004)[35].

Forty-eight (48) phenolic constituents were reported from methanolic extract of T. chebula by Lee, Kim, et al. (2017). During the extraction and isolation process, various methyl and methyl esters of phenolic constituents were reported[36]. Other Terminalia species and plant such as Punica granatum and rheum species also contains tannins and other phenolic compounds [37-41]. Different phenolic compounds such as ellagic acid, gallic acid, hydroxycinnamic acids, and their derivatives also reported (Table 1). Flavonoids such as quercetin, rutin, and methylated derivatives of quercetin were also reported from fruits. (Table 1).

Table 1: List of some of the bioactive phenolic compounds isolated from the fruits of *Terminalia Chebula*

Compound class	Compound name	Reference
Tannin	Terflavin A	32 ,36
	Terchebulin	32
Simple phenolic acid derivatives	Punicalagin	32, 35, 36
	Chebulagic acid	32,35
	Chebulinic acid	32,35
	Corilagin	32 , 36
	Casuarinin	35
	Chebulanin	35
	Tercatain	36
	Gemin	36
	Tellimagrandin I	36
	Punicacortein C	36
	Punicacortein D	36
	10-O-Methyl neochebulanin	36
	10-O-Methyl neochebulinate	36
	Dimethyl neochebulinate	36
	Chebulic acid	35
	60-O-Methyl chebulate	36
	70-O-Methyl chebulate	36
	Methyl chebulagate	36
	Neochebulagic acid	36
	60-O-Methyl neochebulagate	36
	Dimethyl neochebulagate	36
	Dimethyl 40-epi-neochebulagate	36
	Eschweilenol C	36
	Phyllanemblinin E	36
	Phyllanemblinin F	36
	6-O-Galloyl-β-D-glucose	36
	1,3-Di-O-galloyl-β-D-glucose	36
	1,6-Di-O-galloyl-β-D-glucose	35,36
	1,3,4-Tri-O-galloyl-β-D-glucose	36
	1,3,6-Tri-O-galloyl-β-D-glucose	36
	3,4,6-Tri-O-galloyl-β-D-glucose	35
	2,3,4,6-Tetra-O-galloyl-β-D-glucose	156
	1,3,4,6-Tetra-O-galloyl-β-D-glucose	36
	1,2,4,6-Tetra-O-galloyl-β-D-glucose	36
	1,2,3,4,6-Penta-O-galloyl-β-D-glucose	36,35
	1,2,3,-Tri-O-galloyl-6-O-cinnamoyl-β-D-glucose	36
	1,3,-Di-O-galloyl-2-O-cinnamoyl-β-D-glucose	36
	1,2,-Di-O-galloyl-6-O-cinnamoyl-β-D-glucose	36
	1,2,3,6-Tetra-O-galloyl-4-O-cinnamoyl-β-D-glucose	36
	4-O-(200,400-Di-O-galloyl-α-L-rhamnosyl)ellagic acid	36
	4-O-(400-O-Galloyl-α-L-rhamnosyl)ellagic acid	36
	4-O-(300,400-Di-O-galloyl-α-L-rhamnosyl)ellagic acid	36

	4-O-Galloyl-(-)-shikimic acid	36
	5-O-Galloyl-(-)-shikimic acid	36
	Gallic acid	35, 36
	Digallic acid	36
	Ellagic acid	36
	Ethyl gallate	156
	Methyl gallate	35,36
	4-O-Methylgallic acid	156
	Ferulic acid	157
	Vanillic acid	157
Flavonoids	Rutin	158
	Quercetin	158
	Luteolin	159
	Isoquercetin	159
	3-Methoxy quercetin	23
	3,40-Dimethoxy quercetin	23

4. PHARMACOLOGICAL ACTIVITIES

Extracts or isolated individual compounds from T. chebula fruits have reported various pharmacological activities. The most widely studied activities were antioxidant or free radical scavenging ability. The following sections provide details about individual activities.

4.1 Antioxidant activity

It is well-studied research that pathogenicity to oxidative stress and effects of antioxidants in inflammatory conditions. in this context methanolic extract of T. chebula fruits were assessed for antioxidant activity with DPPH assay (IC50 = 2.08 µg/mL) and antioxidant activity was found in methanolic extract, chebulic ellagitannins were identified compound reported as among different components with total 61.8g/kg of dry weight[42]. A similar result for methanolic extract was reported for fruits with IC50 value of 5.5 µg/ mL Devkota et al[43]. another study also reported antioxidant activity for an aqueous methanolic extract for different parts of T. chebula and barks had antioxidant activity (85.2 ± 1.1%) compared to fruits and leaves (79.8 ± 0.5%, and 80.1 ± 0.9% respectively), phenolic compounds were attributed for antioxidant activity[44]. flavonol aglycones and their derivatives, hydroxybenzoic acid derivatives and hydroxycinnamic acid have been reported as major phenolic compounds for their antioxidant profile[45].

70% ethanolic extract of fruits had potential antioxidant activity in vitro DPPH radical scavenging activity and assaying liver lipid peroxidation (LPO). The extract showed noticeable reduction information of in vivo thiobarbituric acid substances in rat liver carrageenin induced (IC50 = 94.96 mg/kg) and DPPH free radicals scavenged with 42.14 mg/mL IC50 value[46]. ethanolic extract of T. chebula fruits ree radical scavenging activity was analyzed by DPPH, nitric oxide (NO) assay, and 2,20-azinobis(3 ethylbenzothiazoline-6-sulfonic acid) (ABTS). IC50 values for extract were 6.04, 2.27, and 4.37 µg/mL for the DPPH, ABTS, and NO radical scavenging assays, respectively[47].

In one study T. chebula fruits extract had to delineate the repressive effect on the action of the digestive enzymes linked to diabetes and oxidative stress, it had shown potent in vitro scavenging action as evident by superoxide dismutase, glutathione S-transferase and induced oxidative stress analyses[48]. T. chebula fruits reported antioxidant activity was attributed to its cardio-protective effect. The study assessed ethanolic extract's capability to alleviate oxidative stress, induced by isoproterenol by measuring the concentration of iron, lipid peroxidase, vitamin E, and ascorbic acid plasma binding capacity. The study further investigated alteration in antioxidant enzymes activity as superoxide dismutase, the glutathiones (peroxidase, reductase, and S-transferase), and catalase in the heart tissue. The study found administration of a dose of 500 mg/kg body weight of EtOH extract for 30 days has maintained normal antioxidant status[49].

4.2 Hepatoprotective activity

Extract of T. chebula reported to suppress oxidative stress and 2-acetylaminofluoreneinstigated drug resistance in the hepatic tissue and nullify possible transformation of the liver to hepatocarcinoma by inhibiting the expression resistance to multidrug via preventing ROS generation and cyclooxygenase-2 (COX-2) expression through MAPK and Akt signaling[50]. Membrane stabilizing and anti-oxidative activities of T. chebula averted the hepatotoxicity by rifampicin, pyrizinamide, and isoniazid (in combination) in a sub-chronic mode[51].

Interestingly, reduction in elevation of hepatic GSH, ROS level, and tert-butyl hydroperoxide- (t-BHP-) induced cytotoxicity was reported with treatment by chebulic acid obtained from T. chebula[52]. Similarly, an aqueous extract of T. chebula attenuated the increase of serum liver enzymes alanine transaminase, lactate dehydrogenase, and aspartate transaminase exerting a hepatoprotective effect in t-BHP-induced liver injury in C57/BL6 mice. Gallic acid, chebulic acid, phyllanemblinin E, punicalagin, geraniin, CA and chebulinic acid found in aqueous extract of T. chebula were likely to contribute to the hepatoprotective effect[53].

4.3 Neuroprotective effect

T. chebula showed pharmacological activities against Alzheimer's disease. tannic acid, Ellagic acid, and gallic acid derived from the fruits of T. chebula reported inhibiting butyrylcholinesterase and acetylcholinesterase (AChE)[54]. In one study T. chebula extracts showed neuroprotective action especially ellagic acid its mechanisms of action were studied in an undifferentiated pheochromocytoma (PC12) cell line by using beta-amyloid25-35 (Aβ25-35)-induced cell toxicity. Results of this study revealed that T. chebula (water and methanol extracts) defended PC12 cells from Aβ25-35-induced cell damages and by the declining influx of calcium ion and retarding ROS production increased the cell viability[55]. Nootropic activity of T. chebula (ethanolic extract) was analyzed In mice models to document its beneficial effect on learning aspects and memory, administration of extracts on an acute level in mice enhanced learning capability and dose-dependent manner memory recall[56].

T. chebula was reported for Neuroprotective activity using in vitro oxygen-glucose deprivation followed by reoxygenation ischemia and H2O2 induced cell injury in pheochromocytoma cells of rat, T. chebula safeguards neuronal cells by reducing oxidative damage and inflammation as evident by reducing level of malondialdehyde, NO and increased cell survival, suggested it as medication for ischemia, oxidative stress and activated microglia-instigated secondary damage, these features reported in neurodegenerative ailments[57]. In recent study formulation of T. chebula in to functional beverages with other herbal materials reported the anti-cholinesterase inhibitory activity, its promising acetylcholinesterase inhibition (22.54%) property may attributed to high content of total flavonoids (375.44 ± 3.85 mg catechin eq./100 mL beverage), total phenolic compounds (330.25 ± 2.47 mg gallic acid eq./100 mL beverage) and total tannins (261.55 ± 3.55 mg tannic acid eq./100 mL beverage)[58]. Chebulagic acid (CA) has been reported to have neuroprotective activity through autophagyinduction on human neuroblastoma SH-SY5Y cell lines, this compound had a pronounced effect on the expression level of autophago-marker proteins, showed a protective effect against -methyl-4-phenylpyridinium (MPP+)- induced cytotoxicity which is similar to a pathological symptom of Parkinson's disease[59].

4.4 Nephroprotective activity

Bilvadi agada (antivenom formulation containing T. chebula as one of the ingredient) shown nephroprotective activity based on various biochemical changes observed in urine creatinine, serum creatinine, and potassium levels[60]. T. chebula Administration has been reported to protect the kidney performance from toxicity induced by cadmium (Cd) and it was indicated by notable restoration of serum urea, uric acid creatinine and its clearance[61]. Protective effect of T. chebula against acetaminophen-induced hepato and nephro toxicities in Wister kyoto rats, T. chebula at a dose of 125 mg/kg reversed the alterations of the elevated serum creatinine, blood urea nitrogen and provided better protection[62]. Recently, protective effects against imidacloprid-induced renal damage have reported with T. chebula with other plants; P. emblica, T. bellirica and their formulation called Triphala (1:1:1)[63]. T. chebula had shown a protective effect against nickel chloride) induced renal oxidative stress, where the application of extract down-regulated the renal glutathione content, glutathione reductase, LPO, glutathione-S-transferase with associated GPx activity rehabilitation[64]. Supplementation of T. chebula has been reported in Wistar rats to reduces cisplatin-induced nephrotoxicity by amelioration of oxidative stress and modifying apoptotic signaling as evident by inhibition of the elevated serum creatinine, blood urea nitrogen, cytokines and oxidant stress markers[65].

4.5 Gastroprotective activity

In Ayurveda T. chebula is a frequently used agent for improvement of gastrointestinal motility hence it can be used as a substitute for currently available prokinetic drugs. vivo effect of T. chebula on gastric emptying have reported that the methanolic extract at a dose of 100 mg/kg/ day for 15 days orally has increased the percent gastric emptying($86.57 \pm 6.65\%$; $p < .01$)[66]. T. chebula fruits containing, Chebulinic acid is reported to exhibit a gastroprotective activity against ulcers, Chebulinic acid reduced total acidity, free acidity and upregulates mucin secretion[67]. Chebulinic acid It also inhibits H+ K+-ATPase activity that proves its antisecretory activity[68]. T. chebula methanolic extract exhibited antiulcerogenic as well as ulcer healing activity, attributed to declining in the secretion of gastric acid and gastric cytoprotection as supported by histopathological study of experimental rats[69]. Hydroalcoholic extract of T. chebula reported to have antiulcerogenic activity, pre-treatment with T. chebula in a dose of 200 and 500 mg/ kg has reduced ulceration as inhibition of ulcers percentage was 76% and 85% for a dose of 200 and 500 mg/kg, respectively, and the pre-treated animals have shown inhibition of mucosa lesion by 60% and 72% compared Omeprazole (20 mg/ kg) as a standard drug which had a percentage of inhibition 83%[70]. Gastric emptying time was elevated by T. chebula via its protective action on gastrointestinal tract mucosa with the refinement in the secretory action of Brunner's gland[71].

4.6 Cytoprotective and antiaging activities

T. chebula fruit ethanolic extract reported to reduce oxidative stress In HEK-N/F cells and showed cytoprotective effect against damage induced by UV B, these effects were due to the suppressive property of the T. chebula on the shortening of the telomere length with aging[72] in one study T. chebula was analyzed on the prevention of dermal photodamage using mice model and human skin fibroblasts, ethanolic extract of the fruits found to decrease the UVB-instigated matrix metalloproteinases-13 and 1 expression with an upregulation in the expression of type I procollagen in UVB radiated human skin fibroblasts[73]. Chebulic acid derived from T. chebula had inhibitory activity on advanced glycation end products-induced dysfunction

of endothelial cell reported using human umbilical vein endothelial cells model[74]. T. chebula fruits extract containing Chebulic acid and gallic acid ameliorated the cytotoxic T lymphocyte-mediated cytotoxicity, hence showed their immunosuppressive and cytoprotective properties[75]. T. chebula reported the notable protective effect against oxalate- induced cell injury of NRK-52E and MDCK renal epithelial cells, an aqueous extract of the fruits explored the antilithiatic activity against the formation of Calcium oxalate with 95.84% at a dose of 25 µg/mL and extract also has increased the cell viability and alleviated the cells' injury in a dose-dependent manner[76].

4.7 Cardioprotective activity

In traditional medicines, T. chebula has been extensively used as a cardio-protective agent. It was found that the effect of isoproterenol-induced alterations was attenuated by pre-administration of T. chebula extract led to the retention of near-normal activities of the lysosomal enzymes heart tissue and serum possibly attributed by the membrane-stabilizing effects[77-78]. cardioprotection activity of T. chebula pericarp has also been documented in isolated frog heart model and evident by increased contraction of force without disturbing the heart rate and cardiac output[79].

4.8 Anti-diabetic activity

Excessive production of ROS is linked with Diabetes, as more concentration and inadequate secretion of ROS finales in mutilation to cellular proteins, membrane lipids, nucleic acids, and vascular dysfunction. A previous study had explored that T. chebula fruits and seeds exhibited a decrease in blood glucose in streptozotocin-induced diabetic rats[80]. T. chebula fruit extracts containing Ellagitannins and gallotannins were also reported to increase the peroxisome proliferator-activated receptor α/γ signaling[81]. Another study reported T. chebula fruits potential anti-diabetic activity on streptozocin (STZ)-induced diabetes in rats, oral administration of the extract to rat at a dose of 200 mg/kg body weight/day has stimulated the action of insulin, reduced glucose level and, and ameliorate STZ induced pathological abnormalities of β-cells[82]. Another similar study on fruits aqueous extract has reported the anti-diabetic activity STZ-induced diabetic rats; administration of extract orally at a dose of 200 mg/kg body weight has reduced glucose level by 55.6% in the oral glucose tolerance test and 43.2% reduction upon 2 month's prolonged administration[83].

T. chebula evaluated for the hypoglycaemic properties by in vitro enzymatic assays, the study investigated the inhibitory activities against, rat intestinal α-glucosidase, yeast α-glucosidase, and α-amylase enzymes, three polyhydroxytriterpenoid derivatives along with other 14 compounds from T. chebula were responsible for this effect,23-O-galloylarjunolic acid, 23-O-galloylarjunolic acid (IC50 21.7 µM) and 28-O-β-Dglucopyranosyl ester (IC50 64.2 µM) showed potent inhibitory activities against yeast α-glucosidase[84] .

Another similar study identified α-glucosidase inhibitors active compounds from the methanolic extract of T. chebula fruits. 4-O-(200,400-di-O-galloyl-α-L-rhamnosyl) ellagic acid and 1,2,3,6-tetra-O-galloyl-4-O-cinnamoyl-β-Dglucose were identified hydrolyzable tannins, showed inhibitory activities (IC50 values of 6.4 and2.9 µM, respectively) and both compounds have mixed-type inhibitory activities(inhibitory constants Ki = 4.0 and 1.9 µM, respectively)[85] in one study aqueous extract of the fruits has shown good α-glucosidase inhibitory activity but for methanol extract activity was not detected, among many compounds ellagic acid and corilagin have shown a dose-dependent manners α-glucosidase inhibition with IC50 values of 6.28 and 2.64 µM, respectively[86].

4.9 Anti-hyperlipidemic activity and hypocholesterolemic activity

Treatment with T. chebula in rats' hyperlipidemic model induced by atherogenic diet shown a decline in total cholesterol, triglycerides, total protein and increase in high-density lipoprotein cholesterol revealing its hypolipidemic activity[87]. one study reported that administration of T. chebula orally to mice on atherogenic diet had alleviated the effects related to high cholesterol diet as; serum cholesterol, body weight, thickening of the walls of the aorta, triglyceride and shrinkage in its lumen[88] in another study Wistar male albino rats to analyze the anti-hyperlipidemic profile of T. chebula methanol bark extract, finding suggested that there is dose-dependent anti-hyperlipidemic activity against hyperlipidemia induced by high-fat diet as depicted by a significant decline in, serum total cholesterol, triglyceride level and a notable decrease in serum VLDL and LDL levels[89]. It was reported that T. chebula extracts exhibit hypolipidemic action against cholesterol-induced atherosclerosis and hypercholesterolemia as evident by a decline in serum cholesterol, aortic sudanophilia, and cholesterol contents of liver and aorta[90]. Triphala containing T. chebula had been reported to have hypolipidemic activity on an experimentally induced hypercholesteraemic rat model, which shows a significant decrease in the VLDL, LDL, total cholesterol, and free fatty acid[91].

4.10 Anti-inflammatory activity and anti-arthritic activity

Anti-arthritic activity of hydroalcoholic extract of T. chebula was explored using formaldehyde or Freund's adjuvant-induced arthritic rat models, it was found that application of a hydroalcoholic extract of T. chebula inhibited joint swelling in both the models and lessened the level of serum TNF-R1, IL-6, TNF-α and IL-1β in synovial fluid indicated that anti-arthritic profile of T. chebula[92]. Twelve(12) compounds isolated from the methanolic extract of T. chebula fruits were investigated for anti-inflammatory activity and the inhibitory activity was determined in terms of their potential to restrain inducible nitric oxide synthase (iNOS) and COX-2 in lipopolysaccharide-stimulated macrophages, four compounds were potentially effective and remarked good IC50 values as 55.2, 53.4, 48.8 and 38.0 µM for2,3,6-tri-O-galloyl-β-D-glucose,

chebulinic acid, arjunic acid, and arjunolic acid respectively, aforementioned compounds have efficiently reduced the protein expression of iNOS and COX-2 in macrophages[93]. Another study found fruit extract of T. chebula had anti-inflammatory activity against carrageenin-induced inflammation in rats. The study revealed that ethanol extract (70%) at a dose of 250 mg/kg was capable to induce a 69.96% reduction in carrageenin-induced rat paw edema, it also had a protective effect on human RBC membrane stability[94]. anti-arthritic activity of chebulanin was reported in collagen-induced arthritis in DBA/1 mice, it was documented that chebulanin ameliorated the severeness of arthritis, evident by downregulation of enzymes MMP-3 and COX-2 and TNF-α, IL-6 inflammatory cytokines responsible to induce inflammation with a reduction in cartilage destruction and bone erosion, finding suggested chebulanin as potential In collagen-induced arthritis in DBA/1 mice, the anti-arthritic activity of chebulanin was reported, where it was documented that severeness of arthritis ameliorated by chebulanin as evident by downregulation of inflammation-induced enzymes (MMP-3 and COX-2) and inflammatory cytokines (TNF-α, IL-6) with a reduction in cartilage destruction and bone erosion. Thus findings suggested chebulanin to be a potential alternative for treating rheumatoid arthritis[95]. Similarly, T. chebula fruits were investigated for anti-arthritic effect, formulated as a standardized ethanol extract with the traded name of NDI10218, administration of this extract at dose ranged from 62.5, 125 or 250 mg/kg dissolved in 0.5% methylcellulose has reduced the arthritis index against collagen-induced arthritis, pro-inflammatory cytokines serum levels were prominently decreased as; IL-1β, IL-6 and TNF-α, it also reduced quantity of T cell subpopulations in the regional lymph nodes of the arthritis mice[96].

4.11 Immunomodulatory activity

CA and gallic acid, isolated from T. chebula shown immunosuppressive response as they found to block the CTL mediated cytotoxicity, in response to anti-CD3 stimulation, granular exocytosis was blocked[97]. Alcoholic extract of T. chebul reported for immunomodulatory activity on male Wistar rats as evident by increased in lymphocytes, neutrophils, and time-dependent linear significant phagocytic activity with an increase in the immunoglobulin level[98]. Dried ripe fruits of T. chebula shown an immunomodulatory effect at the cellular level. Treatment with T. chebula extract had elevated the level of superoxide dismutase, glutathione, and catalase (252.22,25.36, and 273.32 units/mg protein, respectively), the extract has decreased the level of LPO to 68.01 nmol MDA/g Hb. The extract also increased the levels of cytokines expression as TNF-α mRNA and as IL-2, IL-10 several-fold to 6.23 and 7.46-, 73.52 respectively[99] in the study to find the function of T. chebula extract for increasing the antigen-specific Th1/Th2 immune responses in mice model, T. chebula increased T-cell proliferation, enhanced the Ig secretion elevate macrophage-mediated phagocytosis and considered an inclination towards Th1-type immunity.it proved T. chebula as a stimulator of innate, cell-mediated, and humoral[100]. Aqueous and alcoholic extracts of T. chebula intensify the activation of macrophages[101]. T. chebula immunostimulatory effect in relation to antigenic stimulation was reported an aqueous extract of the fruits at doses of 300, 400 and 500 mg/kg produced a noticeable increase in both the delayed-type hypersensitivity and humoral antibody titer in a dose-dependent manner in mice[102].

4.12 Analgesic effect

To analyze the analgesic effect of ethanolic extract of T. chebula fruits in Swiss albino mice and Long Evans rats hot plate method employed, the result showed that ethanolic extract remarkably increased the latency time in comparison to control with notable analgesic action. Duration and intensity of analgesia were dependent on dose[103]. T. chebula was evaluated for analgesic activity in a single oral dose by employing mechanical hot air pain model and pain model in healthy human participants, finding suggested remarkable enhance in pain threshold time and pain tolerance in comparison to placebo[104-105]. In another study aqueous extract of T. chebula fruits in which pain was induced by 0.1% formalin in mice, extract exhibit analgesic activity attributed to its inhibitory action on the release and/ or synthesis of inflammatory factors[106] in vivo analgesic effect reported in another study for a standardized extract of T. chebula(NDI10218) on ICR mice using acetic acid-induced writhing model Oral administration of NDI10218 at a dose of 300,100 and 30 mg/kg has reduced the number of abdominal contractions and made the mice writhed 38.5 ± 5.8, 43.7 ± 7.2 and 58.4 ± 10.2times, respectively[107].

4.13 Wound healing activity

Dried immature fruits of T. chebula can accelerate cutaneous wound healing by angiogenic and powerful anti-bacterial activity (as evident by the inhibition of Staphylococcus aureus and Klebsiella pneumonia)[108]. T. chebula ethanolic extract has alleviated the acute lesions of the gastric mucosa, induced by indomethacin. at a dose of 200 mg/kg body weight, ethanolic extract performed a relatively low healing capacity of 48.5% in comparison to misoprostol at a dose of 1.43 µg/kg body weight, that gave 85.4% reduction in the ulcer index[109] .in comparison to topical application of silver sulfadiazine, application of T. chebula in rats is competent in speeding up the healing by more wound contraction, used for the treatment of burns[110].

4.14 Anti-convulsant activity

ethanolic extract of fruits of T. chebula was studied for anticonvulsant property in Swiss mice model by giving picrotoxin (PC), pentylenetetrazole (PTZ)-induced seizures and maximal electrical shock (MES), administration of T. chebula extract was found to delay the latency PC, PTZ and MES instigated seizures suggesting anticonvulsant activity by the opening of GABA neurotransmitter receptors associated chloride channels[111]. Fruits of T. chebula have been reported for a protective role on seizure-induced cognitive

impairment in experimental models. hydroethanolic extract of T. chebula showed 66.66% protection in PTZ-induced seizures while83.33% protection in MES-induced seizures which was relatively similar to the effect of the standard Valproate (a dose of 150 resulted in 66.6% protection), and also reported in a combination of ethanolic extract (at 500 mg/kg) has produced 100% protection and Valproate (at a sub-therapeutic dose of 150 mg/kg)[112].

4.15 Antitumour, antimutagenic and radioprotective activities

Chebulinic acid, tannic acid, and Ellagic acid of T. chebula fruit reported as the major cytotoxic compounds, that its administration has reduced proliferation, cell viability, and further stimulation of cell death in many cancerous cell lines (S115, MCF-7, PC-3, and PNT1A) dose-dependently. At higher doses, they induced necrosis whereas induced apoptosis[113]. Aqueous extract of T. chebula evaluated on lung cancer cells (A549), it was reported to induce apoptosis via Bcl-2 (family protein)-linked mitochondrial pathway which involves the release of Caspase-3 activation, cytochrome c and PARP cleavage[114]. Another research proposed that T. chebula methanolic extract derived silver nanoparticles possessed remarkable anticancer activity against colon cancer cells[115]. In a study to isolate and identify active molecules from the fruit extract of T. chebula, compounds CA had been found to work as a dual inhibitor of COX and 5-LOX exhibited antiproliferative action against HCT-15, COLO-205, K562, DU-145, and MDA MB-231 cancer cell lines[116]. Anticancer activity of the T. chebula fruits ethanolic extract was analyzed) against Ehrlich ascites carcinoma cells in Swiss albino mice, the extract significantly reduced the tumor growth so enhanced the lifespan of the mice[117]. Chemo-modulatory profile of T. chebula has investigated in male Wistar rats against oxidative stress and nickel chloride instigated tumor promotion, T. chebula found to restrains or blocks the chemical carcinogenesis[118]. Chebulagic acid (CA) reported synergizing with doxorubicin-induced cytotoxicity in human hepatocellular carcinoma cells via COX-2 associated downregulation of MDR-1 by inactivating Akt, NF-κB, p38, JNK, and ERK pathways[119]. Moreover, Chebulagic acid (CA) has also been reported to restrain growth/ the proliferation of retinoblastoma cells by induction of Cytochrome c release, modulating mitochondrial membrane permeabilization, and imbalancing the Bax/Bcl2 ratio towards cell death and activation of caspase 3, it also activates G1 cell cycle arrest by enhancing expression of CDK, p27 inhibitor[120]. Many studies have reported antimutagenic activity of T. chebula, it was assessed against two direct-acting mutagens4-nitro-o-phenylenediamine (NPD) and sodium azide in strains TA1535, TA100, TA98 and TA97a of Salmonella typhimurium, respectively and S9-dependent mutagen, 2-aminofluorene (2-AF) in TA98, TA97a, and TA100 strains. The study reported the activity for water extract against2-AF as well as NPD induced in strains of Sa. Typhimurium but chloroform extract was inactive[121].

T. chebula derived hydrolyzable tannins assessed for antimutagenic effect against two direct-acting mutagens 4-nitroquinoline-N-oxide (4NQNO), NPD, S9-dependent mutagen and2-AF in TA100 and TA98 strains of Sa. Typhimurium, Tannins-containing extract was highly effective against S9-dependent mutagen, 2AF. The tannin of T. chebula was found to be partially effective against NPD but not at all effective against 4NQNO[122].

T. chebula antimutagenicity has been documented by the prevention of strand breaks formation by application of gamma-radiation in a plasmid (pBR322) DNA, attributed to the compounds ellagic acid, gallic acid, and ascorbate, these compounds act as antioxidants and defend cell organelles harm due to radiation hence considered the radioprotective properties of T. chebula[123].

4.16 Antimicrobial activity

4.16.1 Anti-bacterial activity

The antibacterial property of T. chebula was reported against various pathogenic gram-positive and gram-negative bacteria. Antibacterial action of ethanolic extract (T. chebula fruits) was studied against standard reference bacterial strains of clinical importance and extract was found to be highly effective against S. epidermidis, Bacillus subtilis, Sa. Typhi, S. aureus, and Pseudomonas aeruginosa [124]. Antibacterial action of T. chebula was studied against enteric pathogens, namely Salmonella sp, Shigella sp, Escherichia coli, and Vibrio cholera, where they found the potential antibacterial activity compared with traditional antibiotics [125]. The leaf gall was evaluated for antibacterial activity against 10 bacterial strains, namely S. citreus, S. aureus, B. polymyxa, B. cereus and E. coli. Best zone of inhibition was reported with the ethanolic extract compared with the aqueous extract. Results has showed that both extracts were unique against different microorganisms such as Se. marcescens, Pr. Mirabilis, while S. aureus was more susceptible to both extracts [126]. T. chebula barks were evaluated for Antibacterial activities against mutant type and wild-type of B. subtilis. methanolic extract has an antibiotic activity in a dose-dependent manner. Extract kept the growth of the rec- strain under control more effectively than that of the rec+ strain [127]. different extraction solvents of T. chebula fruits was investigated against fourteen Gram-negative bacteria and nine Gram-positive bacteria Among petroleum ether, chloroform, dimethylformamide, ethanol, and water extracts, ethanol extract showed maximum antibacterial activity while chloroform and petroleum ether extracts showed minimum antibacterial activity [128] . Fresh matured fruits of T. chebula(different extraction preparation) was examined against dental caries pathogens. Highest bactericidal activity was reported by acetonic extract with a minimum inhibitory concentration (MIC) of 25 mg/mL and mean diameter of inhibition zone being 25.32 mm against Streptococcus mutants and a MIC of 12.5 mg/mL and a

mean diameter of 32.97 mm against S. aureus followed by ethanolic, hot aqueous, cold aqueous and methanolic extracts [129]. T. chebula-derived compounds reported for antibacterial activity in several studied. Ethyl gallate and Gallic acid were reported as the chief components for antibacterial action against methicillin-resistant S. aureus [130]. T. chebula extracts acetone fraction containing Ethanedioic acid showed strong and moderate inhibitory action against Clostridium perfringens and E. coli respectively, while ellagic acid exhibited strong inhibitory activity against both E. coli and C. perfringens [131]. Methyl gallate obtained from T. chebula was considered as a potential antibacterial agent for the curing intense infections caused by multi-drug resistant Shigella spp [132].

4.16.2 Antiviral activity

Repressive action of T. chebula was investigated on viral diseases caused by cytomegalovirus (CMV), herpes simplex virus-1 (HSV-1) influenza, and human immunodeficiency virus type 1 (HIV-1) [133-136] . Gallic acid and tannins obtained from fruits of T. chebula were reported as human HIV type I integrase inhibitors and galloyl component reportedly perform a pivotal function in hindering the 30-processing of HIV-1 integrase [137] . T. chebula reported to show a stronger antiviral activity in conjunction with acyclovir as opposed to HSV-1 infection in vitro and in vivo as evident by a decrement in the yield of the virus in the brain of mice [138]. hydrolyzable tannins CA and Punicalagin obtained from dried fruits of T. chebula was found to restrain the entry of HSV-1 in human lung cells via inactivating and targeting HSV-1 viral particles thus averting, binding, penetration cell-to-cell spread and secondary infection as well [139] . It was documented that T. chebula notably inhibited the replication process of human CMV in vitro and in vivo [140]. The potential of T. chebula was recently explored for its potential against sexually transmitted herpes simplex virus-2 (HSV-2) infection. CAs and chebulinic obtained from T. chebula extract have remarkably greater direct antiviral efficacy and activity as opposed to HSV-2 to impede virus attachment and penetration to the host cells compared with standard medication acyclovir used for the management of HSV infection [141]. T. chebula aqueous extract was been documented for prominent activity against hepatitis B virus (HBV) by decreasing the level of extracellular HBV virion DNA, suggesting its potential use as an effective anti-HBV drug in the future [142]. The antiviral activity of methanolic extract of T. chebula barks was assessed in terms of the effects on cell surface expression and inhibition of syncytium formation of BHK cells infected with the Newcastle disease virus (NDV) virus. The extract has blocks the cell surface expression of NDV-hemagglutininneuramidase (-HN) glycoprotein in a dose-dependent manner [143].

4.16.3 Anti-fungal activity

The anticandidal action of T. chebula methanol extracts was evaluated and reportedly found to be active against Candida albicans(Clotrimazoleresistant). T. chebula has been reported to be active against A. flavus, Aspergillus niger, Al. alternate, Alternaria brassicicola, Fusarium oxysporum, Helminthosporium tetramera Phytophthora capsica and F. solani [144-146]. T. chebula seeds extract has been investigated for in vitro fungicides kinetics. three extracts; ethyl acetate, methanol, and chloroform shown fungal mycelial growth inhibition at a concentration of 1,500 ppm/disc against F. solani, F. oxysporum Ph. capsici, and Botrytis cinerea in the range of 41.6–61.3%, with MIC values ranging from 62.5 to 500 mg/mL. Extracts showed an attenuating effect on fungi spore germination at as time-dependent kinetic inhibition for Bo. cinerea [147] . Different findings reported for antifungal activity of the fruits against seven fungal strains. Chloroform, petroleum ether, ethanol, dimethylformamide, and water extracts from fruits did not show anticandidal activity against four Candida species; Ca. albicans ATCC18804, Ca. albicans ATCC2091, Ca. tropicalis ATCC4563, Ca. glabrata NCIM3448, also extracts has not shown inhibitory effect against fungal strains, namely Cr. neoformans ATCC34664, Cryptococcus luteolus ATCC32044, Trichosporon beigelii NCIM3404 and four moulds; A. flavus NCIM538, A. candidus NCIM883 A. niger ATCC6275, Mucor hiemalis wehmer NCIM873 [148] .

4.17 Molluscicidal activity

T. chebula was studied for functional molluscicidal composites, the acid and alkaline phosphatase (ACP/ALP) & AChE activities in nervous tissue of Lymnaea acuminate. Remarkable decline in the ACP, AChE and ALP activity was attributed to tannic acid that possibly inhibits these enzymes in a non-competitive- competitive manner as evidenced by the inhibition kinetics [149].

4.18 Antiprotozoal activity

Aqueous extract of T. chebula showed Antiplasmodial action against Plasmodium falciparum K1 by its potential to retard further incorporation and the uptake of [3H] hypoxanthine into nucleic acid and cause growth inhibition[150]. Notable antiplasmodial activity reported for acetone extract of seeds of T. chebula against the chloroquine-sensitive strain of Pl. falciparum[151]. Antimalarial and antileishmanial activities of three Nepalese plants, including T. chebula reported against intracellular amastigotes of erythrocytic stages of Pl. falciparum, and intracellular amastigotes of Leishmania infantum respectively. T. chebula alcoholic extract exhibited fairly good antiplasmodial activity with selectivity index values >5 and IC50 values of 4.5 ± 2.4 μg/mL[152]. anthelmintic activity of T. chebula fruits reported against adult earthworm Pheritima posthuma. Both aqueous and alcoholic extracts were active at a concentration range100–20 mg/mL, alcoholic extract was more effective than standard drug Albendazole[153].

5. TOXICOLOGICAL STUDIES AND POSSIBLE SIDE EFFECTS

T. chebula does not appear to have debilitating or toxic side effects hence it is one of the important aspects for

its future development as an herbal functional food/ nutraceutical product.

In a toxicity study and to evaluate the safety of T. chebula, the water extract from the dried fruits of T. chebula was orally administrated in rats. Results did not show visible signs of toxicity such as mortality, behavior changes, histopathological changes, or gross appearance of the internal organs of rats. Signs of chronic toxicity do not show abnormalities in the test groups as compared with the controls. blood chemical and Haematological values in treated groups were normal in comparison with the control group[154]. In another study mutagenicity and oral toxicity in rats was analyzed, the ethyl acetate -a soluble portion of ethanol extract of T. chebula does not induce any type of adverse effect[155-160].

6. CONCLUSION AND FUTURE PROSPECTIVE

T. chebula fruits have been widely used in various traditional medicine systems including Unani, Tibetan, and Ayurvedic traditional medicine among others. They are consumed for their nutritive values also. Various chemical classes have been isolated and identified. phenolic acids and tannins were found to be the most widely studied chemical classes. T. chebula fruits were also widely studied regarding pharmacological activities such as hepatoprotective antioxidant, cytotoxic, neuroprotective, anti-inflammatory, antidiabetic activities among others. Most of these studies have focused on in vitro assessment of the biological activities while very few studies were performed using in vivo models with the detailed mechanism of action. Similarly, identification and bioactivity guided isolation of active components studies were performed with limited studies regarding the screening of biological activities. Future studies should be designed to fill these gaps in its research. Designing studies to provide relevance of this plant to traditional therapeutic uses is also expected. Similarly future studies should also focus on the possible interactions of active compounds with other natural products or synthetic drugs should also be studied in detail with their pharmacokinetics.

CONFLICT OF INTEREST :

No conflict of interest is declared.

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