A phytochemical and biological review of *Terminalia paniculata* L.

Abstract

Terminalia is ~~2~~2nd second major genus ~~belonging to~~of family Combretaceae. Species ~~o~~from this genus ~~*Terminalia*~~ have been used in outmoded popular medicine globally. But then, a little study was stated on *Terminalia paniculata* L. *(TP).* This is a complete literature review of various *Terminalia* plants highlighting on *TP*, about its biological and isolated constituents. The objective of this study is to fascinate the attention of unfamiliar activities of *TP*, thus conducive to the growth of novel therapeutics which might benefit health of individuals suffering from illnesses. Existing data on *Terminalia* ~~accumulated~~was sourced from electronic databases like Scopus, Goggle Scholar, ScienceDirect, PubMed, Chemical Abstract earth and Springer Link~~s~~. Plant based studies have led to extraction of various categories of phytochemicals like, tannins, flavonoids, phenolic acids, triterpenes, triterpenoid glycosides, lignan and ligan derivatives in *Terminalia* plants. Extracts and their isolated constituents of various *Terminalia* plants reported a good spectrum of activities. *TP* consist of polyphenols such as ellagic acid, 3,3'-di-*O*-methyyl ellagic acid and 3,4,3'-*O*-trimethyl flavellagic acid. Studies on *Terminalia* genus has opened a diverse active chemical component. Many biochemical potentials have authenticated use of *Terminalia* in therapy of different ailments in plant-based medicine. Future studies desired to discover bioactive constituents' accountable ~~pharmacological mechanisms~~pharmacological mechanisms.

Keywords: *TP*, ellagic acid, hepato-protective, nephron-protective.

1. INTRODUCTION:

Terminalia ~~*paniculate*~~ *paniculate* L. (Combretaceae) is~~,~~ a tropical tree with huge

spreading in west and south India. In olden days, its extract was in the treatment of cholera, inflammation of parotid-glands, menstrual problems, cough, bronchitis, cardiac debility, hepatitis, diabetes and in obesity [1-6]. Juice of *TP* flowers and were used as medicines for cholera, inflamed parotid glands and menstrual disorders in folk medicine [2,3]. The bark has 14 % tannins with a pyrogallol nucleus with gallic acid. Heartwood has ellagic acid, dimethyl ellagic acid, penta methyl flavellagic acid, trimethyl flavellagic acidand β sitosterol [7].

The *Terminalia* genus is one of the largest ~~genus of~~ in family Combretaceae, ~~has~~with around 200 plant-species. These species are spread across tropical parts of the world, especially diverse in south-east Asia [1]. *Terminalia* gets its name after a latin word "*terminus"*, as leaves look at the tips of shoot. Mostly the trees are huge, in a height up to 75m^3. Plants of this genus were extensively used in folk medicine in several countries for the therapy of various diseases like abdominal problems, bacterial attacks, common-cold, sore throats, conjunctivitis, diarrhea, dysentery, fever, gastric ulcers, headaches, heart diseases, hookworm, hypertension, jaundice, leprosy, nosebleed, edema, pneumonia and skin diseases.

This review has 2 main sections, in first part, a phytochemical study of different components and their prevalence in *Terminalia* was reported, in the second part the bi2ological activities led on various species was emphasized.

2. ~~Part I: Research on Phytochemicals~~Phytochemistry

Phytochemical research performed on different *Terminalia* plant species have reported presence of tannins, pentacyclic triterpenes and their glycoside derivatives, flavonoids and other phenolic compounds [8-10].

Literature reveals rich source of tannins and pseudomamma, like gallic acid and its gallate esterase, chebulic and non-chebulic ellagitannins, ellagic acid derivatives and ellagic acid

glycosides polyphenolics, which are potent natural antioxidants, have created great interest as budding therapeutics in various ailments. Many studies showed flavonoids and tannins with strong hepatoprotective potential in many animal models [5,6].

3. Part II: Biological activities reported on *Terminalia* genus:

3.1 Hepatoprotective and nephroprotective studies

- *T. muelleri* constitutes polyphenolic-rich fraction having hepato-protective and nephron-protective potential in CCl_4-generated hepato-toxicity and nephron-toxicities in rodents [11,29].
- Oral route of *T. arjuna* fruit juice prevented liver toxicity and oxidation of cadmium-caused liver toxicity in rodents [12,31].
- Manna reported protective actions of arjunolic acid, separated from bark of *T. arjuna*, against sodium arsenate-generated oxidation in mice hepatic cells [13,32].
- *In vitro* studies of hepatic cell lines with chebulic acid and neochebulic acid, extracted from *T. chebula* fruit ethanolic-extract, potentially reduced tert-butyl hydroperoxide-caused cytotoxicity, suppressed active oxygen radicals, and increased the liver GSH [14, 33].
- Corilagin, from *T. catappa* acted against galactosamine and lipopolysaccharide-induced hepato-toxicity in rodents at 1 mg/kg by suppressing oxidation and cell death [15, 34].
- Prior treatment of *T. bellerica* leaves extracts in CCl_4-generated hepato-toxicity and nephron-toxicity, reported dose-dependent biochemical activity, while isolated gallic acid had strong hepatoprotective effects at 200 mg/kg [16, 35].

3.2 Anti-inflammatory studies

- Ethanolic stem extract of *T. phanerophlebia* and the isolated β-sitosterol from ethanolic stem extract prevented cyclooxygenase COX-II selectively [17, 36].

- *T. frdinandiana* fruit extract reported a potent anti-inflammatory action in lipopolysaccharide-induced murine macrophages, by preventing COX-II and iNOS, also by preventing the synthesis of prostaglandin E_2 [18, 38].
- Chebulagic acid isolated from seeds of *T. chebula*, potentially delayed the inception and development of collagen-induced arthritis in rodents [19, 39].
- Anolignan B from the ethylacetate extract of *T. sericea* root had a non-selective preventive action on both the COX isoenzymes [20-25, 40].
- Punicalagin at 10 mg/kg and punicalin at 5 mg/kg from *T. catappa* leaves reported anti-inflammation against carragenan-induced paw edema in rodents [25,27, 41].
- Ursolic acid and 2eα,3eβ,2e3-trihydroxyurs-12-en-28- oic acid from *T. catappa* ethanol extract of leaves reported anti-inflammatory potential, with a strong reduction (more than 50%) of edema on the mice ear pinna at 0.30 mg/ear [28, 29, 42].

3.3 Gastroprotective studies

- Chebulinic acid from fruit extract of *T. chebula* reported a gastroprotective action against duodenal ulcers caused by cold restraining (protection by 62.9%), aspirin- induced (protection by 55.3%), alcohol-induced (protection by 80.6%) and pyloric ligation-induced (protection by 66.6%) models. Chebulinic acid strongly decreases free acid levels by 49%, total acid levels by 38% and enhanced mucus production by 60%. Also, Chebulinic acid potentially suppressed H^+ K^+-Pump invitro with an IC_{50} of 65 μg/ml whereas, Omeprazole reported an IC_{50} of 30.24 μg/ml, showing its potent antisecretory power [30, 43].
- Methanolic *T. arjuna* extract resulted in a potent decrease in lesion-index in diclofenac-induced ulceration, and a strong raise in pH, non-protein suslfhydryls, decreased glutathione, protein-bound carbohydrate complexes, mucus content with a good decrease in

volume of gastric acid, free and total acid levels, pepsin levels, acid secretion, activity of lipid peroxidases and activity of myeloperoxidases [35, 44].

- Ethanolic *T. pallida* extract reported a potent anti-ulcer action against indomethacin, histamine and ethanol induced ulceration in rodents by increasing the antioxidant levels in mucosa, thus enhancing mucosal protection [36-45].

3.4 Antimicrobial and Antiviral studies

- *Terminalia* plant species were observed to possess a significant anti-microbial action on wide range of microbes. Water extract of *T. chebula* reported a strong antibacterial action on *H. pylori* with a MIC of 125 μg/ml and MBC of 150 μg/ml [46].
- Acetone *T. chebula* extract reported a significant antibacterial action on *Enterococcus faecalis, Bacillus sabtilis* and *Klebsiella pneuemoniae* [47].
- Casuarinin from *T. arjuna* bark extract, reported a strong antiviral action on *Herpes simplex* type II at 25 μM and prevented viral titers up to 1lakh-folds by preventing the attachment and penetration of virus [48].
- Fyhrquist reported that methanolic extracts of roots and bark of *T. sambsiaca* possessed lesser MIC values than aqueous, butanolic and chloroform extracts against mycobacterium [49].
- The significant antibacterial action of ethyl acetate leaves extract of *T. muelleri* was credited to gallic acid [50].
- Antifungal action of 6 *Terminalia* leaf extracts (*T. proteinoids, T. brachystemma, T. sericea, T. gazensis, T. mollis* and *T. sambsiaca)* were evaluated on various fungi. It was reported that extract of acetone had highest antifungal action. Extract of *T. sericea* was most active against wide spectrum of microorganisms [51].
- Anolignan B from ethyl acetate extracts of *T. sericea* roots had a potent action against microbes

with MIC 3.80 µg/ml with *Bacillus sabtilis* and 31 µg/ml with *Escherichia coli* [40].

- Gallic acid from *T. nigrovenulosa* bark extracts reported a significant antifungal action against *Fusarium solani* [52].

- *T. macroptera* ethanolic extract of roots had promising action against microbes, with the lowest MIC against *Shigella dysenteriae*, *Staphylococcus aureus* and *Vibrio cholera* with a strong action against *Campylobacter* [53]. Additionally, *T. macroptera root* ethanolic extract reported an antimicrobial action against *Neisseria gonorrhoeae* with a MIC range of 100 µg/ml to 200 µg/ml, diethyl ether extract had most active MIC value ranging from 25 µg/ml to 50 µg/ml [54]. Also, it was presumed that punicalagin and terchebulin, were the constituent responsible for activity against *Helicobacter pylori* [55-58].

3.5 Cytotoxicity studies

- Methanolic extract of *T. chebula* fruits reported a reduction in cell-viability, anti-cell proliferatory effects, and resulting in apoptosis as dose increased on cancer lines. Also, it resulted in cell death at reduced doses, and resulted in necrosis at increased doses. Chebulinic acid, tannic acid and ellagic acid, have IC_{50} of 53 µg/ml, 59 µg/ml and 78 µg/ml respectively, posed the highest cytotoxicity amongst the fruits of *T. chebula* [59]. Moreover, chebulagic acid from the fruits of *T. chebula* extract reported an antiproliferative effect against HCT-15, COLO-205, MDA-MB-231, DU-145 and K562 cell-lines [60].

- Water extract of *T.catappa* leaves and its constituents *punicalagin* were active against bleomycin- caused genotoxicity in Chinese hamster ovary cells. In addition, *T.catappa* leaves extract resulted in a inhibitory effect on invasion and motility of metastatic A549 and Lewis lung carcinoma cells. The leaf ethanolic extract of *T. catappa* strongly prevented migration of squamous cell carcinoma cells [61-63].

- Luteolin, gallic acid and gallic acid ethyl ester from methanolic extract stems and leaf of *T.*

arjuna had a significant anti-neoplastic potential.

- Ivorenoside C from barks of *T. ivorensis* possessed an anti-proliferative action on MDA-MB-231 and HCT116 human cancer lines with IC_{50} of 3.96 μM and 3.43 μM respectively.
- Leaves acetone extract of *T. calamansanai* prevented viability of HL-60 cells.

3.6 Cardioprotective ~~studies~~activities

- *T. arjuna* bark had been in use as a folk medicine as cardiotonic. The ethanolic bark extract of *T. arjuna* increased cardiac intracellular antioxidant status in CCl_4-generated oxidation in rodents [57]. The antioxidant effect was similar to that of Vit C. Additionally, butanol fraction of *T. arjuna* bark extract possessed a protective effect on doxorubicin-generated cardiotoxicity by enhancing antioxidant enzymes, reducing serum creatine kinase levels and also by decreasing lipid peroxidation [61].
- Scientists reported that patients with refractory chronic congestive heart failure, on treatment with *T. arjuna* bark extract as an additive medicine, resulted in a long-term enhancement in the symptoms of cardiac failure with an enhancement in left ventricular ejection [62]. A clinical trial was conducted to estimate role of *T. arjuna* in ischemic mitral regurgitation (IMR) after myocardial infarction (MI). Patients on treatment with *T. arjuna* as an adjuvant resulted strong prevention in IMR and decrease in frequency of angina.
- Pre-treatment with fruit extract of *T. pallida* upgraded myocardial damage in isoproterenol-induced MI in rodents and resulted in protective actions on cardiac muscle.
- Pre-treatment with *T. chebula* extract upgraded effects of isoproterenol on lipid peroxide formation [51,52].

3.7 Anti-hypertensive study

- Bark extract of *T. superba* resulted a strong antihypertensive action in spontaneously

hypertensive rats, and also in glucose-induced hypertensive rats due to the withdrawal of sympathetic tone and enhancing antioxidant level [53,54].

3.8 Antiparasitic and molluscicidal studies

- *Invitro* nematicidal action of *T. nigrovenulosa* bark on *Meloidogyne incognita* was due to 3,4-dihydroxybenzoic acid [55].
- Ethyl acetate, acetone and methanol leaves and seeds extract of *T. chebula* resulted *invitro* ovicidal and larvicidal action on *Haemonchus contortus* [56]. Additionally, *T. chebula* fruit molluscicidal action was attributed for tannic acid which strongly prevented AChE, ACP and ALP action in the nervous system of *Lymnaea acuminate* [57].
- Ethanolic leaves extract of *T. catappa* had a molluscicidal action on snail intermediate hosts of schistosomiasis (*Biomphalaria pfeifferi* and *Bulinus globosus*) with *B. pfeifferi* being highly vulnerable.

3.9 Wound healing activity

- Topical application of *T. chebula* alcoholic leaves extract on rodents' wounds resulted a positive healing effect, by enhancing tensile strength of cells by around 41% and reducing epithelialization [59]. Additionally, tannin-rich fraction from *T. chebula* fruits were recognized for wound healing due to strong anti-bacterial and angiogenic activities [60].
- Topical administration of hydro-alcoholic extract of *T. arjuna* showed in a strong raise in tensile strength of wounds and epithelialization. This wound healing action was marked in tannin-rich portion compared to others.

3.10 Biological activities stated on *T. paniculata*

- Water extract of bark of *T. paniculata* decreased high blood glucose, HbA1c, creatinine, urea, ALT, AST levels and upturned the abnormal endogenic antioxidants and lipid levels to normal

in Steptazocin-generated diabetic rats in contrast with untreated diabetic rats.

- Ethanolic extract of *T. paniculate* bark reported hepato-protective action and decreased abnormal serum parameters and lipid peroxides in paracetamol- generated liver toxicity in rodents [30].
- Water extract of *T. paniculata* bark strongly decreased carrageenan-caused paw edema volume [37].

4 Conclusion

A wide-ranging literature on *Terminalia* genus has discovered a diversity of constituents formed by this genus. Tannins, flavonoids, phenolic acids, triterpenes, triterpenoid glycosides, lignan and lignan derivatives were found as the chief classes of secondary metabolites ~~phytochemicals~~ of this genus. Additionally, present report showed that many biological studies conducted on various extracts and isolated contents from various species of this genus were engrossed on the evaluation of antimicrobial, antioxidant, hepatoprotective, anti-inflammatory, hypoglycemic, hypolipidimic, cytotoxic and wound healing effect. The different biological studies authenticated folk medicinal use of various *Terminalia* species.

Though various phytoconstituents and biological findings were reported from *Terminalia,* the researches have attended on a few species, with *T. chebula*, *T. bellerica*, *T. arjuna*, *T. catappa*, *T. horrida*, *T. superba*, *T. macroptera*, *T. pallida*, *T. ivorensis*, *T. sericea and T. alata* being greatest phytochemically and biologically evaluated species, parting a lush area for further research on other species like *TP* that have not been fully explored yet.

This review delivers a complete understanding of the phytochemicals and biological activities of various *TP* which might benefit in the development of new alternate medicines for the therapy of various illnesses.

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