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Biological and pharmacological studies of *Tribulus terrestris* Linn: A review

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Abstract
Throughout history, many different cultures have recognized the potential use of *Tribulus terrestris* for prevention and treatment of various diseases. Recent studies support the effects of *Tribulus terrestris* and its extracts in a wide range of applications. These studies raised the possibility of revitalization of therapeutic values in different diseases. It has diuretic, aphrodisiac, Antiurolithic, immunomodulatory, anti-diabetic, absorption enhancing, hypolipidemic, cardio tonic, nervous system tonic, hepatoprotective, anti-inflammatory, analgesic, antispasmodic, anticancer, antibacterial, anthelmintic, parricidal, and anti-cariogenic activities. However, the exact mechanism of *Tribulus terrestris* and their long-term effects are not fully understood. Further studies are needed to elucidate the pathophysiological mechanisms of action of *Tribulus terrestris* as well as its efficacy and safety in treatment of various diseases.

Keywords: *Tribulus terrestris*, Pharmacology, Medicinal uses, Phytochemical, Saponin

1. Introduction

Tribulus terrestris (*T.terrestris*) is a ground hugging vine with tap rooted annual or perennial herb with many spreading slender branches, the immature portions covered in a fine silky hair. *T.terrestris* is a natural herb used for its medicinal effects around the world and it is a flowering plant in the family Zygophyllaceae, native to warm temperate and tropical regions such as southern Europe, Vietnam, Middle East, South Africa, India, China, Pakistan and Sri Lanka [1, 2].

It is common throughout Sri Lanka, growing as weed along roadside and waste places. The plant prefers light (sandy), medium (loamy) and heavy (clay) soils and requires well-drained soil. It cannot grow in the shade. This is a relatively fast-breeding species that may produce two or three generations in single season. Tribulus is Latin for "three-pointed a caltrop," the shape of which is suggested by the three-pronged *T.terrestris* fruit, and referring to the caltrop, a military weapon, an iron ball with projecting spikes. It can thrive even in desert climates and poor soil. *T.terrestris*, also called "puncture vine" is a plant used around the world for the treatment of various ailments [3].

T.terrestris is the plant of choice. It has a 5,000 year-old history of medicinal use in India. Traditionally it has been used for boosting hormone production in men and women. Its traditional usages are as rich and varied in different countries and cultures.

Parts Used In Medicine: Whole plant, Fruit, and Root [4, 5].

Medicinal Uses

It has diuretic, aphrodisiac, antiurolithic, immunomodulatory, antidiabetic, absorption enhancing, hypolipidemic, cardiotonic, nervous system tonic, hepatoprotective, anti-inflammatory, analgesic, antispasmodic, anticancer, antibacterial, anthelmintic, larvicidal, and anticariogenic activities [6].

It is also cooling, demulcent, aphrodisiac, tonic, promotes strength, increase digestive power and is also useful in cough, difficulty in breathing, impotence and heart diseases [7]. *T.terrestris* is an outstanding remedy in urogenital disease, promoting urine flow, soothing the mucosa, and aiding in the excretion of stones and calculi [8]. Nadkarni mentions that both the plant and fruits are used in decoction or infusion in the treatment of spermatorrhoea, impotence, infertility, phosphaturia, dysuria, gonorrhoea, gleet, chronic cystitis, renal calculi, incontinence, gout, menstrual disorders, and post-partum hemorrhage [4]. It is reported to be toxic against the causal organism of typhoid fever and hepatoprotective [9, 10]. Due to the diuretic action of the fruits, it is found to be highly beneficial for urolithiasis [11]

T.terrestris is indicated for Hemorrhoids, intestinal parasites, dyspnoea, asthma, dysuria, hematuria, urinary lithiasis, cystitis, nephritis, urinary tenesmus, spermatorrhoea, impotence, frigidity, infertility, venereal diseases, cardiovascular disease, gout, rheumatism, lumbago, sciatica, menorrhagia, postpartum hemorrhage, menopausal symptoms, anaemia, diabetes, ophthalmic headache, insufficient lactation [12]

There are indications that *T.terrestris* may have potential as a treatment for urinary stones [13], Parkinson's disease [14], malignant melanoma [15], liver and eye diseases [16] and benign prostatic hyperplasia [17]. There is some evidence that *T.terrestris* can improve male sexual function [18] and the performance of athletes [19].

The Chinese used it for liver, kidney, urinary tract disease and skin disorders and also used in the treatment of headache, vertigo and dizziness due to ascendant Liver yang and Wind-heat [20].

Arcasoy *et al* stated that *T.terrestris* has been commonly used in folk medicine as diuretic and against colic pains, hypertension and hypercholesterolemia in Turkey [21]. The people of Bulgaria used *T.terrestris* as a sex enhancer and to treat infertility. The herb became widely known in the West when medal-winning Bulgarian Olympic athletes claimed that use of the plant had contributed to their success.

T.terrestris is now listed on the Australian Register of Therapeutic Goods. The listing is for the relief of menopausal and PMT (Pre-menstrual tension) symptoms. *T. terrestris*

provides a normal balance for the hormonal system resulting in optimum function [22].

Phytochemistry

T.terrestris is a rich source of numerous potentially significant biological substances including saponins, flavanoids, alkaloids and other nutrients. With all herbs, there is a variance in potency of the active ingredients from various areas of the plant; generally the above ground areas have higher concentrations such as the leaves and fruits. The major constituents of this plant fruits are steroidal saponins [23, 6] named terrestrosins A,B,C,D and E, desgalacto-tigonis, F-gitonis, desglucolanatigoneis, gitnin which on hydrolysis yield diosgenins, hecogenins and neotigogenin. Four pairs of sapogenins, tigogenin and neotigogenin, gitogenin and neogitogenin, hecogenin and neohecogenin, and manogenin and neomanogenin have been isolated through hydrolysis of the crude saponins of *T.terrestris* [24, 25].

Saponins

The steroidal saponins of *T. terrestris* L. (Zygophyllaceae) are considered to be the factor responsible for biological activity of products derived from this plant. The activity depends on the concentration and the composition of active saponins, which in turn is influenced by the geographical origin of plant material [26].

Variation in Saponin composition and content with geographical

T.terrestris saponins have been found to posses various pharmacological activities, based on which several sexual diseases in men and women are being cured and being used for cardiac treatment. Studies on *T.terrestris*, using HPLC-ELSD (High Performance Liquid Chromatography-Evaporative Light Scattering Detector) analytical technique [27] concluded with large variation in both saponin composition and saponin content, depending on the geographical regions of the world [28]. Most of the phytochemical investigations described in literature refer to *T.terrestris* from Chinese, Indian and of Bulgarian origin, while there are limited studies for saponins from the same herb of Turkey, Moldova, South Africa, Australia and Romania. Careful examination of data from literature reveals the difference in the saponins composition is a cause of different bioactivity of the herb at different regions [29, 30, 31].

Yan *et al* studies on the constituents of the fruits of *T. terrestris* led to the isolation of six new furostanol saponins, 26-O-β- -glucopyranosyl (25R)-furostane-2α,3β,22α, 26-tetrol-3-O-β- -glucopyranosyl (1–4)-β- -galactopyranoside, 26- O-β- -glucopyranosyl (25R,S) -5α-furostane 2α,3β,22α,26-tetrol-3-O-β--galactopyranosyl (1–2)-β—glucopranosyl(1–4)-β—galacto pyranoside, 26-O-β—glucopyranosyl (25R,S)-5α-furostane 3β,22α,26-triol-3- --O-β--galactopyranosyl(1–2)-β-glucopyran osyl (1–4)-β- -galactopyranoside, 26-O-β- -glucopyranosyl (25 R,S)-5α-furostan-12-one 3β,22α,26-triol-3-O-β- -galactopyranosyl(1–2)-β--glucopyranosyl(1–4)-β—galacto pyranoside, 26-O-β--glucopyranosyl (25R,S)-furost-5-ene-3β,22α,26-triol-3-O-β- -galactopyranosyl(1–2)-β—glucopyranosyl (1–4)-β-galactopyranoside, 26-O-β--glucopyranosyl (25R)-5α-furost-20(22)-en-12-one-3β,26-diol-3-O-β—galactopyranosyl (1–2)-β--glucopyranosyl(1–4)-β--galactopyranoside, named terrestrosin F—K, respectively. The structures were elucidated on the basis of spectroscopic studies of the isolated compounds and their hydrolysed products [32].

Different parts of the plant contain different constituents in varying ratios. Overall, the steroidal saponin content is considered the most important and includes constituents such as protodioscin, diosgenin, yamogenin, epismilagenin, tigogenin, neotigonin, gitogenin and neogitogenin. Two additional steroidal saponins, terrestrinins A (1) and B (2) have been isolated in 80% ethanol from the fruit [33].

Cai *et al* were isolated three new steroidal saponins from the fruits of T terrestris, and their structures were elucidated as (25R,S)-5 alphaspirostane-12-one-3 beta-ol-3-O-beta-xylopyranosyl(1-->2)- [betaxylopyranosyl (1-->3)]-beta-glucopyranosyl (1-->4)-[alpha-rhamnopyranosyl(1-->2)]-beta-galactopyranoside; 26-O-beta-glucopyranosy l-(25S)-5 alpha-furostane-12-one-3 beta,22 alpha,26-triol-3-O-betaglucopyranosyl (1-->2)-beta-galactopyranoside; 26-O-betaglucopyranosy l-(25S)-5 alpha-furostane-12-one-3 beta,22 alpha,26-triol-3-O-beta-glucopyranosyl (1-->4)-[alpha-rhamnopyranosyl(1-->2)] betagalactopyranoside, respectively, by spectroscopic analysis and color reaction [34].

Xu *et al* were isolated two new furostanol saponins from the fruits of *T.terrestris* L. Their structures were established as 26-O-beta-D-glucopyranosyl-(25S)-5alpha-furost-20(22)-en-3beta,26-diol-3-O-alpha-L-rhamnopyranosyl-(1 --> 2)-[beta-D-glucopyranosyl-(1 --> 4)]-beta-D-galactopyranoside (1) and 26-O-beta-D-glucopyranosyl-(25S)-5alpha-furost-20(22)-en-12-one-3beta,26-diol-3-O-beta-D-galactopyranosyl-(1 --> 2)-beta-D-glucopyranosyl-(1 --> 4)-beta-D-galactopyranoside (2) on the basis of spectroscopic data as well as chemical evidence [35].

Two new furostanol saponins, tribufurosides D (1) and E (2), were isolated from the fruits of *T.terrestris* L. With the help of chemical and spectral analyses (IR, MS, 1D, and 2D NMR), the structures of the two new furostanol saponins were established as 26-O-beta-d-glucopyranosyl-(25S)-5alpha-furost-12-one-2alpha,3beta,22alpha,26-tetraol-3-O-beta-d-glucopyranosyl-(1 --> 4)-beta-d-galactopyranoside (1) and 26-O-beta-d-glucopyranosyl-(25R)-5alpha-furost-12-one-2alpha,3beta,22alpha,26-tetraol-3-O-beta-d-glucopyranosyl-(1 --> 4)-beta-d-galactopyranoside (2) [36].

Su *et al* were isolated two new steroidal saponins and two known flavonoid glycosides from the fruits of T terrestris. Their structures were assigned by spectroscopic analysis and chemical reaction as 26-O-beta-D-glucopyranosyl-(25R)-5 alpha-furostan-12-one-3beta,22 alpha,26-triol-3-O-beta-D-glucopyranosyl (1 --> 2)-beta-D-glucopyranosyl(1 --> 4)-beta-D-galactopyranoside (1), 26-O-beta-D-glucopyranosyl-(25S)-5 alpha-furostan-22-methoxy-2 alpha,3beta,26-triol-3-O-beta-D-glucopyranosyl(1 --> 2)-beta-D-glucopyranosyl(1 --> 4)-beta-D-galactopyranoside (2), kaempferol-3-gentiobioside (3), and isorhamnetin-3-gentiobioside (4) [37].

Matin Yekta *et al*. isolated three flavonoid glycosides, viz. quercetin 3-O-glycoside, quercetin 3-O-rutinoside, and kaempferol 3-O-glycoside from the aerial parts of *T. terrestris* L. var. orientalis (Kerner) G. Beck in the northeast of Iran [38].

Xu *et al* investigated the chemical constituents of the fruit of *T.terrestris* L. various chromatographic techniques were used to separate the chemical constituents. ESIMS, IR, 1HNMR, 13CNMR and HMBC were used to determine the structures of the isolated constituents. Two new compounds were isolated

from the fruits of *T.terrestris* L and were identified as neohecogenin-3-O-beta-D-glucopyranosyl (1-->2)-beta-D-glucopyranosyl (1-->4)-beta-D-galactopyranoside (I); neohecogenin-3-O-beta-D-glucopyranosyl(1-->4)-beta-Dgalactopyranoside (II). Compounds I and II are new steroidal saponins [39].

Zhang *et al* isolated eight steroid saponins from T terrestris L., namely TTS-8, TTS-9, TTS-10, TTS-11, TTS-12, TTS-13, TTS-14 and TTS-15. The in vitro antifungal activities of the eight saponins against six fluconazole-resistant yeasts, Candida albicans, Candida glabrata, Candida parapsilosis, Candida tropicalis, Candida krusei, and Cryptococcus neoformans were studied using microbroth dilution assay and concluded that the steroid saponins TTS-12 and TTS-15 from T terrestris L. have significant in vitro antifungal activity against fluconazole-resistant fungi, especially TTS-12 also showed in vivo activity against fluconazole-resistant C. albicans [40].

Xu *et al* isolated two new steroidal saponins and two known flavonoid glycosides were isolated from the fruits of T. terrestris. Their structures were assigned by spectroscopic analysis and chemical reaction as 26-O-beta-D-glucopyranosyl-(25R)-5 alpha-furostan-12-one-3beta,22 alpha,26-triol-3-O-beta-D-glucopyranosyl(1-->2)-beta-D-glucopyranosyl (1 --> 4)-beta-D-galactopyranoside (1), 26-O-beta-D-glucopyranosyl-(25S)-5 alpha-furostan-22-methoxy-2 alpha,3beta,26-triol-3-O-beta-D-glucopyranosyl(1-->2)-beta-D-glucopyranosyl(1 --> 4)-beta-D-galactopyranoside (2), kaempferol-3-gentiobioside (3), and isorhamnetin-3-gentiobioside (4) [41].

Gas chromatography-mass spectrometry analysis of methanolic extract of the whole plant of *T.terrestris* revealed the presence of α-Amyrin as the major constituent and seven minor constituents, which are 3,7,11,15-tetramethyl-2-hexadecen-1-ol, n-hexadecadienoic acid, hexadecadienoic acid ethyl ester, phytol, 9,12-octadecadienoic acid, 9,12,15-octadecatrienoic acid, and 1,2-benzenedicarboxylic acid disoctyl ester. Sterols such as β-sitosterols and stigmasterols were also found to be present [42].

Biological and Pharmacological Activities

Antispasmodic Activity

Arcasoy *et al* reported that the lyophilized saponin extract of dried and powdered *T.terrestris* caused a significant decrease on peristaltic movements of isolated sheep ureter and rabbit jejunum preparations in a dose-dependent manner ($p < 0.05$). However it has been observed no effect on isolated rabbit aorta and its contractile response to KCl or noradrenaline ($p > 0.05$). According to these results it has been suggested that *T.terrestris* L. or its saponin mixture may be useful on some smooth muscle spasms or colic pains [21].

Sandberg investigated the effects of lyophilized saponin mixture of this plant on several smooth muscle preparations in vitro. The LD_{50} of saponin mixture on albino mice were calculated. According to these results, it has been suggested that *T.terrestris* extract may be useful on some smooth muscle spasms or colic pains [43].

Sharifi *et al* & Arcasoy *et al* stated that biological properties of *T.terrestris* extracts include diuretic properties, increased endothelial nitric oxide, direct smooth muscle relaxant effects, and Angiotensin-converting enzyme (ACE) inhibition [44,21].

Spasmolytic Activity

Sri Ranjani studied an In-vitro Bioassay on aqueous extract of *T.terrestris* fruit on virgin rat uterine tissue and identified spasmolytic effect vs. acetylcholine induced contraction [45]. Ivan identified that the alkaloid fraction and water extract of the dried fruits of *T.terrestris* were active on the rat intestine vs. Ach- induced contraction [46].

Analgesic Activity

Heidari *et al* reported that the analgesic effect of methanolic extract of the fruit of *T.terrestris* on male albino mice was evaluated by formalin and tail flick test. Extraction of the fruits of the plant was done by two different methods (suxheletion and percolation) with methanol 80%. The percolated extract was injected intraperitoneally in mice at 50, 100, 200, 400, and 800 mg/kg. The results showed that a dose of 100 mg/kg of percolated extract had the highest significant analgesic effect compared to the control group ($P < 0.01$) in formalin and tail flick test [47].

Anti-Inflammatory Activity

Jaya and Raju were studied and identified that methanolic extract of *T. terrestris* possess anti-inflammatory and antibacterial activity [48].

Oh *et al* identified that the ethanolic extract of *T.terrestris* inhibited the expression of cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) in lipopolysaccharide-stimulated RAW264.7 cells. It also suppressed the expression of proinflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin (IL)-4 in macrophage cell line. Thus, the ethanolic extract of *T.terrestris* inhibits the expression of mediators related to inflammation and expression of inflammatory cytokines, which has a beneficial effect on various inflammatory conditions [49].

Baburao *et al* found that the methanolic extract of *T.terrestris* showed a dose-dependent inhibition of rat paw volume in carrageenan-induced inflammation in rats [50]. Rathi *et al* investigated that the Anti-inflammatory activity of steroidal saponins isolated from methanolic extract of fruits of *T. terrestris* [51].

Hong CH *et al* tested that the fruit of *T.terrestris* contains active principles such as phytoesteroides, flavanoids, alkaloids, glycosides, steroidal saponins of the furostanol type, which produce anti-inflammatory effects. The inhibitors of prostaglandin biosynthesis and nitric oxide production have been considered as potential anti-inflammatory agents and inhibition of COX-2 activity [52].

Effect on Female Reproductive System

T. terrestris is a plant that is most commonly used since ancient times in India as a treatment for both male and female sexual problems. An active preparation is obtained from the above-ground part fruit of the plant that contains steroid saponins of the furostanol type, with a predominant quantity of protodioscin (not less than 45%). Experimental and clinical studies in Eastern Europe have been conducted on the effects of this extract on the endocrine functions of pre-and postmenopausal women.

T.terrestris has been found to improve libido and alleviate the vasomotor and neuropsychic symptoms of menopause (hot flashes, depression and emotional instability). The regular use of *T.terrestris* for several months often significantly decreases

the intensity and occurrences of hot flashes, insomnia, general tenseness, sweating, insomnia, irritability, depression, apathy and loss of sexual interest. Two thirds of the women tested reported increased sex drive after treatment with *T. terrestris*. It is now listed on the Australian Register of Therapeutic Goods. The listing is for the relief of menopausal and PMT (Pre-menstrual tension) symptoms.

T. terrestris provides a normal balance for the hormonal system resulting in optimum function. The great benefit of assisting a return to balance for women with premenstrual or menopausal symptoms is that these symptoms are indicative of imbalance in the system. When the hormonal system is nourished to balance, symptoms of imbalance disappear [53].

John studied that a single herbal product of *T.terrestris* has recently become extremely popular in the natural health field. It has been found to benefit the sexual functions of both men and women. It is a libido enhancer. Clinical studies indicate that it helps with premenstrual syndrome (PMS) and with menopausal syndrome. It provides extra drive for body builders. It has been found to regulate hormone levels in both men and women. The result is increased sexual potency in men and improved hormonal balance in women. In a study conducted with 20 males and females, 75% of the participants had increased endurance, 80% had increased libido and sexual performance, and 95% of the females reported no PMS symptoms [54].

Effect on Male Reproductive System

Singh *et al*. evaluated the acute and repeated dose administration of lyophilized aqueous extract of the dried fruits of *T.terrestris* (LAET) at doses of 50 and 100 mg/kg of body weight as a sexual enhancer in the management of sexual dysfunction in male rat. A dose-dependent improvement in sexual behavior was observed with the LAET treatment, which was more prominent on chronic administration of LAET. A significant increase in serum testosterone levels too was observed. These findings confirm the traditional use of *T.terrestris* as a sexual enhancer in the management of sexual dysfunction in males [55].

Ethanolic extract of *T.terrestris* exhibited protective effect against cadmium-induced testicular damage. The protective effect appears to be mediated directly either through inhibition of testicular tissue peroxidation by antioxidant and metal chelating activity or by stimulating the testosterone production from Leydig cells [56]. Singh *et al*. found that the traditional use of *T.terrestris* as a sexual enhancer in the management of sexual dysfunction in males [55].

Brown *et al.* identified that the furastanolic type saponins (protodioscin and protogracilin etc.), from *T.terrestris* has stimulating effect on spermatogenesis by increase in the amount of Luteinizing Hormone (LH) produced by Pituitary gland, which stimulate the secretion of male hormone 'Testosterone', resulting in significant improvement in quality and quantity of sperm [56].

Adimoelja investigated *T.terrestris* in the treatment of male subfertility. The main active constituent identified was protodioscin, a nonhormonal agent having a steroidal chemical structure similar to dehydroepiandrosterone (DHEA). The dried powder extract was then experimentally administered in a double-blind study involving 45 sub fertile men with moderate idiopathic oligozoospermia. During the trial, 36 of the men were treated with *T.terrestris* dry powder extract and men were administered a placebo. After 3 months, 7 men were able to conceive with their wives. This was attributed to the enhancement of sperm function after *T.terrestris* consumption [57]

Effects on Urinary System

Diuretic Activity

Chhatre *et al* identified that the Comparative Evaluation of Diuretic Activity on Different extracts of *T.terrestris* Fruits in Experimental Animals [58]. An aqueous extract of *T.terrestris*, in oral dose of 5g/kg, elicited a positive diuresis in male rats, and evoked a contractile activity on Guinea pig ileum [13]. A recent in vitro study using human urine suggests that the diuretic properties of *T.terrestris* may be the most crucial mechanism for preventing urinary stone formation [59].

Antiurolithic Activity

Anand *et al*. identified that an ethanolic extract of the fruits of *T.terrestris* showed significant dose dependent protection against uroliths induced by glass bead implantation in albino rats. The extract provided significant protection against deposition of calculogenic material around the glass bead, and also protected leucocytosis and elevation in serum urea levels [60].

Aggarwal tested the activity of *T.terrestris* on the nucleation and growth of calcium oxalate (CaOx) crystals as well as on oxalate-induced cell injury of NRK 52E renal epithelial cells. The experiments revealed that *T.terrestris* extract not only has a potential to inhibit nucleation and growth of the CaOx crystals but also has a cytoprotective role [61].

Shirfule *et al* stated that Glycolate oxidase (GOX) is one of the principal enzymes involved in the pathway of oxalate synthesis converting glycolate to glyoxylate by oxidation and finally to oxalate. The antiurolithic activity of *T.terrestris* is attributed to its GOX inhibition. Quercetin and kaempherol, the active components of *T.terrestris*, were found to be non-competitive and competitive inhibitors of GOX, respectively [62].

Chaudhuri *et al* identified that Nephroprotective action of *T.terrestris* by the renal damage produced by gentamicin was decreased when given simultaneously with T terrestris extract to albino rats [63]. Nagarkatti stated that the simultaneous administration of 200mg/kg/day of *T.terrestris* and Gentamycine to female rat's decreased gentamycine induced renal damage in both structural and functional terms. The effect was comparable to verpamil [64].

Kavitha and Jagadeesan investigated that the influence of methanolic fraction of *T.terrestris* fruit extract on the kidney tissues of mercury intoxicated mice, Mus musculus. The results suggested that the oral administration of methanolic fraction of *T.terrestris* fruit extract provided protection against the mercuric chloride induced toxicity in the mice [65].

Effects on Cardiovascular System

Wang *et al* investigated that in a clinical trial 406 patients with coronary heart disease were treated with saponins of *T.terrestris*. The results showed that the total efficacious rate of remission angina pectoris was 82.3 percent. The total efficacious rate of ECG improvement (52.7 %) was even higher than that of control group (35.8 %). It is shown that saponin of *T. terrestris* has the action of dilating coronary artery and improving coronary circulation and thus has better effects on

improving ECG of myocardial ischemia. No adverse effects were noted [31].

Anti-Hypertensive Activity

Sharifi *et al.* found that 10 mg/kg/day of the aqueous extract of the *T.terrestris* fruit have shown antihypertensive effects in an animal trial [44].

Activity in cardiac disorders

Cai *et al.* identified that the clinical trial shows that a soponin of *T.terrestris* have action of dilating coronary artery and improving coronary circulation, so recommended for treating angina pectoris. Chinese drug named 'Xinnao Shutong' is made of crude saponins of Chinese T. terrestris, which has significant effect in the treatment of coronary disease, myocardial infarction and cerebral diseases [34].

Zhang *et al*. evaluated that the protective effect of tribulosin from *T.terrestris* against cardiac ischemia/reperfusion injury to study the underlying mechanism in rats. Tribulosin protected myocardium against ischemia/reperfusion injury through protein kinase C epsilon activation [66]. *T.terrestris* also appears to protect the heart cells and may even improve the heart function following a heart attack [67].

Triglyceride and Total Cholesterol Reduction Activity

Experiments with the healthy mice have found *T.terrestris* significantly reduces triglyceride and total cholesterol levels [68]. Water extract of the fruit was active on cat papillary muscle, frog and rabbit hearts [46]. Khan *et al* identified that Anti-hyperlipidemic potential of fruits of *T. terrestris* [69].

Tuncer *et al* identified that Influence of *T.terrestris* extract on lipid profile and endothelial structure in developing atherosclerotic lesions in the aorta of rabbits on a high-cholesterol diet [70].

The aqueous extract of the fruits of *T.terrestris* was evaluated for their hypolipidemic activity in Wistar albino rats. A dose of 580 mg/kg of the extract was found to decrease cholesterol-induced hyperlipidemia, with a decrease in cholesterol, triglycerides, low density lipoprotein (LDL), very low density lipoprotein (VLDL), and atherogenic index (AI), and an increase in high density lipoprotein (HDL) levels in the blood. Hypolipidemic activity may be due to the presence of phenolic compounds leading to increased lipoprotein lipases in the muscles and decreased activity in the adipose tissues, thus indicating that plasma triglycerides are utilized for energy production by the muscle and not for energy storage by the adipose tissue [69].

Effect on Diabetic Mellitus

Lamba identified that *T.terrestris* ethanolic extract at 2 g/kg body weight produced protective effect in streptozotocin-induced diabetic rats by inhibiting oxidative stress. Ethanolic extract of *T.terrestris* exhibited 70% inhibition of α-glucosidase at 500 µg/ml using maltose as the substrate and 100% inhibition of aldose reductase at a dose of 30 µg/ml using dl-glyceraldehyde as the substrate [71]. Experiments with the healthy mice have found *T.terrestris* significantly inhibits gluconeogenisis and influence glycometabolism and reduces triglyceride and total cholesterol levels [68]. The saponin fraction from *T.terrestris* was demonstrated to exhibit a hypoglycemic effect in alloxan-diabetic rats, with a commensurate reduction in serum triglycerides and cholesterol, and a rise in serum super oxide dismutase [72].

In both normal and diabetic mice, *T.terrestris* decreases serum glucose, perhaps by inhibiting gluconeogenesis [72, 68]. Amin *et al* investigated that the protective effects of *T.terrestris* in diabetes mellitus. Diabetes is known to increase reactive oxygen species level that subsequently contributes to the pathogenesis of diabetes. This investigation suggests that the protective effect of *T.terrestris* for streptozotocin-induced diabetes rats may be mediated by inhibiting oxidative stress [73].

Zhang *et al* investigated that the *T.terrestris* extract consisting of saponins appear to decrease blood sugar increase after a meal inhibitory effects of saponins from *T. terrestris* on alpha-glucosidase in small intestines of rats [74].

Hepatoprotective activity

Kavitha *et al* identified that the *T.terrestris* extract (250 mg/kg) showed a remarkable hepatoprotective activity against acetaminophen-induced hepatotoxicity in Oreochromis mossambicus fish. The elevated biochemical parameters and decreased level of reduced glutathione enzymes were normalized by treatment with *T.terrestris* extract (250 mg/kg) for acetaminophen-induced toxicity in freshwater fish [75].

The result suggested that the oral administration of Methanolic fraction of *T. terrestris* fruit extract has provided protection against the mercuric chloride induced hepatic damage in the mice [76]. The methanolic extract of the fruits was fractionated using column chromatography. The four fractions obtained were evaluated for their hepatoprotective activities on albino rats, using carbon tetrachloride induced and paracetamol induced hepatotoxicity respectively. Results of HPTLC showed that out of the four fractions, acetone fraction was found to contain flavonoid. The liver function was assessed on the basis of biochemical tests (such as SGOT, SGPT, Alkaline phosphates and total bilirubin) and histopathological profile. The acetone fraction of methanolic extract was found to exhibit statistically significant reduction in biochemical parameters [77].

Tribulusamides A and B isolated from the fruits of *T.terrestris* prevented cell death in cultured mouse hepatocytes induced by D-galactosamine (D-GalN) /tumor necrosis factor a [16].

Action on Central Nervous System

Deole *et al* found that Swiss Albino mice demonstrated antidepressant and anxiolytic activity on administration of 260 mg/kg dose of Rasayana Ghana tablet comprising three potent well-established rejuvenator herbs, viz. Tinospora cordifolia (stem), Emblica officinalis (fruit), and *T.terrestris* (fruit and root), present in equal quantities in the tablet. It was suggested that harmine, a β-carboline alkaloid present in *T.terrestris*, is one of the main active constituents that contributes to the above-mentioned activities. Harmine is an inhibitor of monoamine oxidase which helps to increase level of dopamine in the brain [78].

Immunomodulatory activity

Tilwari *et al* stated that Saponins isolated from the fruits of *T.terrestris* demonstrated dose-dependent increase in phagocytosis, indicating stimulation of nonspecific immune response. An alcoholic extract of the whole plant of *T.terrestris* exhibited a significant dose-dependent increase in humoral antibody titer and delayed type hypersensitivity response, indicating increased specific immune response [79].

Anthelmintic Activity
Two isolated constituent's tribulosin and beta sitosterol d-glucoside have shown anthelmintic activity [80].

Antifungal Activity
Zhang *et al* identified that of eight saponins tested, two showed potent antifungal activity against Candida albicans, with one, demonstrating its ability to decrease virulence and destroy the cell membrane. The anti-fungal activity of saponins isolated from T.terristris was studied against fluconazole resistant yeasts, candida albicans. The results showed that saponins from Tribulus terristris have significant in-vitro and in-vivo anti-fungal activity by weakening the virulence of candidia albicans and killing fungi through destroying the cell membrane [81]

Antibacterial Activity
Aqueous extract from *T.terrestris* fruits showed good activity against the tested bacteria and the strongest activity was seen against C**.** diphtheriae MIC=0.62 mg/ml), which was similar to what was achieved by the standard drug Maxipime; meanwhile, S**.** typhimurium was inhibited using the highest extract concentration (MIC=5.00 mg/ml). In addition, S. marcescens and P**.** aeruginosa resisted all aqueous extracts of various concentrations. Ethanol and chloroform extracts of *T. terrestris* fruits demonstrated very close activities against all reference bacteria. Very strong activity was seen against S**.** aureus**,** B**.** subtilis**,** B**.** cereus**,** C**.** diphtheriae**,** E**.** coli and P**.** vulgaris using both extracts. The highest antibacterial activity was seen against B**.** subtilis**,** B**.** cereus**,** C**.** diphtheriae and P**.** vulgaris in the ethanol extract (MIC=0.15 mg/ml), while B**.** subtilis**,** B**.** cereus and C**.** diphtheriae were the most sensitive bacteria to the chloroform extract (MIC=0.31 mg/ml). S. marcescens, S. typhimurium, K**.** pneumoniae and P**.** aeruginosa were inhibited by high concentrations of ethanol and chloroform extracts (MIC=2.50 and 1.25 mg/ml) [82].

Larvicidal activity
The petroleum ether extract of the leaves of *T.terrestris* exhibited better larvicidal activity against the third instar larvae and adults of the mosquito, Aedes aegypti, which is the vector of dengue fever, with LC_{50} of 64.6 ppm as compared to the crude ethanol and acetone extracts [83, 84, 85].
Anticancer activity
Steroidal saponin constituents obtained from *T.terrestris* demonstrated significant cytotoxic effects upon human cancer cell lines [86]
Kim *et al* found that the aqueous extract of *T.terrestris* blocked proliferation in HepG2 cells and could also induce apoptosis through the inhibition of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling. *T.terrestris* Thus has clinical therapeutic effects against liver cancer cells [87].

Radioprotection action
Kumar *et al* identified that the aqueous root extract of *T.terrestris* produced significant radioprotection when given orally (800mg/kg) for seven consecutive days prior to gamma irradiation. *T.terrestris* extract pretreatment protected against radiation damage by inhibiting radiation-induced glutathione depletion and decreasing lipoperoxidation level in the liver of mice [88].

Anticariogenic activity
Oh *et al* identified that the ethanolic extract of fruits of *T. terrestris* (0.1-0.5mg/ml) possesses significant anticariogenic activity against S treptococcus mutans, the pathogen responsible for dental caries. The growth, acid production, adhesion, and water insoluble glucan synthesis of S.mutans were significantly inhibited in the presence of the ethanol extract of *T. terrestris* [89].

Antioxidant Activity
Pandey *et al* investigated that the antioxidant activity of the aqueous extract of *T.terrestris* fruit in spleen cells [90].

Nutritional Source
Beta-sitosterol, vitamin C Potassium and calcium are found in the tribulus terrestris. [16]. Duhan *et al* found that *T.terrestris* was found to be a rich source of calcium [91].
Recently *T.terrestris* has gained a reputation amongst body builders as an alternative to anabolic steroids [92].

Lethal Dose
The liophilized material was obtained from dried and powdered *T.terrestris* L. by specific extraction method for saponins. Median lethal dose (LD50) of saponin mixture on Swiss albino mice was calculated according to Litchfield-Wilcoxon method via i.p. route. LD_{50} and its 95% confidence limits were 813 and 739-894 mg.kg-1 respectively. The LD_{50} of Tribulus-derived saponins in mice is 813 mg/kg, which is considerably higher than the commonly used dose (which rarely exceeds more than a gram daily of saponins) [21].

Adverse Reactions
No adverse effects to the central nervous or cardiovascular systems were noted in any of the clinical studies; no toxicity and no deviations in blood count occurred. No known negative effects presently exist when *T. terrestris* is used. Taking food with it can minimize these effects. Adverse effects from supplementation with *T.terrestris* are rare and tend to be insignificant. However, some users report an upset stomach. About one in ten people have associated some gastrointestinal upset with taking *T.terrestris*. Gastrointestinal disturbance may occur in sensitive individuals due to the herb's saponin content which can usually be counteracted by taking it with food. Another rare side effect which has been reported is gynaecomastia [93].

Contraindications
Dehydration [8], pregnancy [20]

Conclusion
Tribulus terrestris Linn, one of the popular and important medicinal plants of tropical and moderate areas of the world specially India and Sri Lanka. Many different cultures have used it for a number of conditions. For example, the Greeks used *T. terrestris* L as a diuretic and a mood-enhancer. Indians used it as a diuretic, antiseptic, and anti-inflammatory, and anti-spasmodic. The Chinese used it for a variety of liver, kidney, and cardiovascular diseases. The people of Bulgaria used *T.terrestris* L as a sex enhancer and to treat infertility. Recently, eastern European athletes and strength champions have used it as well. The whole plant of *T.terrestris* has been analyzed thoroughly for its biochemical and pharmacological activities

such as diuretic, anti-hypertensive, anti-hyperlipidemic, cardioprotective, antidiabetic, anticancer, hepatoprotective, anthelmintic, antibacterial, analgesic, and anti-inflammatory, anti -oxident, anticariogenic, lavicidal anticariogenic activity, radioprotective activity. Further study should be carried out to identify the mechanism of the pharmacological action of T. terrestris.

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