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Review Article

Tribulus terrestris-an Ethnomedical & Phytochemical Review

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Abstract

Tribulus terrestris has long been used for the treatment of various chronic and acute ailments. The aim of the current review is to compile literature encompassing all scientific aspects including: pharmacological properties, safety/toxicity studies, pharmacognostic studies and phytochemical investigation of this plant. The compiled data may be helpful for the researchers to focus on the priority areas of research yet to be discovered. Complete information about the plant has been collected from various books, journals and Ayurvedic classical texts.

Introduction

Herbal medicines (also known as traditional medicine and / or folk medicines) have been in use since ancient times for general health and for specific diseases. Despite great progress in allopathic medicine, use of herbal medicines is still popular [1]. Interestingly the use of herbal remedies has risen in the last decades in developing as well as some developed countries.

Plants have always been of considered a rich source of therapeutic agents; the active principles of many drugs are found in plants or are produced as secondary metabolites. Herbal remedies used in folk/traditional medicine provide an interesting and still largely unexplored area of medicine which if explored might come up with treatment of so far incurable diseases and/or to overcome problems of drug tolerance and toxicity associated with allopathic medicines. It is of therefore, great importance to scrutinize/screen the plants of medicinal importance in order to validate their use in folk medicine and to reveal the active principle.

The aim of this review is to compile literature available on *Tribulus terrestris* . The information included in this review has been carefully compiled to include knowledge from scientific research as well as that originating from pseudo-sciences.

Tribulus terrestris

Tribulus terrestris (aka goat's-head, bindii [2], bullhead, burragokharu, caltrop, small caltrops [3], cat's-head, [4] devil's eyelashes [5], devil's-weed, puncture vine [6], and tackweed[7], (Figure 1) is a member of the caltrop family (Zygophyllaceae) known for its diverse medicinal importance. Extracts from the full plants or fruits are now used for a large number of applications ranging from skin care to human hormones regulation [8-10], as anti-bacterial [11], antiinflammation [12], anti-virus and immunostimulant too. Biological activity (biocide and antioxidant) is clear in several studies but clinical, histologicaland cellular studies are rare [13-15].

Figure 1: Leaves, flower and fruit of *Tribulus terrestris* (image curtsey: Biomedica 2011.com).

Habit & Habitat

Tribulus terrestris is widely distributed around the world and is adapted to grow in dry and sandy climate; conditions only few other plants can survive. The habitat of this plant include dry and sandy districts of South Europe, Central & Southern Asia, Australia, tropical & South Africa [16,17] and Mediterranean region [18].

Plant Morphology

Tribulus terrestris is an annual (sometimes perennial in warm climates) herb with a long, slender, branched tap-root. The greenish-red stems are up to 2 m long, branched, radiating from a central axis and covered with fine hairs. Though usually prostrate, the stems become more erect in shade or when competing with other plants [19]. Leaves, 3-7 cm long, are in opposite pairs with one of the pair slightly smaller than the other. Each leaf consists of three to eight pairs of opposite, oblong-lanceolate bifacial leaflets, each leaflet being 5 to 15 mm long and 3 to 5 mm wide [20].

The flowers are 4-10 mm wide with 5 sepals, and 10 stamens and 5 yellow petals. The petals are 7-15 mm in diameter, solitary and borne on short stalks in the axils of the smaller leaves.

The fruits a woody burr, approximately 1 cm in diameter, which splits into 4 or 5 wedge-shaped segments (carpels), each with 2 unequal pairs of spines (aka nutlet). The nutlets strikingly resemble goats' or bulls' heads; the "Horns" are sharp enough to puncture bicycle tires and lawn mower tires. They can also cause painful injury to bare feet. Each nutlet contains 1-4 seeds stacked on top of each other and separated by a hard membrane. Seeds are yellow, variable in shape but more or less ovoid and 2-5 mm long. As an adaptation to dry climates, the largest seed germinates first, while the others may wait until more moisture is available before germinating [2].

Phytochemistry

The chemistry of *Tribulus terrestris* has been extensively studied and the occurrence of saponins, flavonoids, alkaloids, lignanamides and cinammic acid amides has been reported in *Tribulus terrestris* [21-24]. This plant is extremely rich in substances having potential biological significance, including: saponins, flavonoids, alkaloids and other nutrients [25]. The quantities and presence of these important metabolites depend on the various parts of the plant used. The fruit and root of *T. terrestris* contains pharmacologically important metabolites such as phytosteroids, flavonoids, alkaloids and glycosides [26]. A good number of various saponins and their different derivatives have also been identified in *T. terrestris,* of which diosgenin, gitogenin and chlorogenin are in the leaf tissue. The presence of spirostanol and furostanol saponins is a characteristic feature of this plant, the latter being considered to be biogenetic precursors of their spiro analogs [27]. Various derivatives of tigogenin, neotigogenin, gitogenin, neogitogenin, hecogenin, neohecogenin, diosgenin, ruscogenin, chlorogenin and sarsasapogenin are found. Four sulphatedfuro and spiro saponins have been also isolated. In general saponins,

flavonoids, alkaloids, lignanamides and cinnamic acid amides are of therapeutic values, of which spirostanol and furostanol saponins are main ingredient [28].

Many pharmaceutical preparations/food supplements are on sale in market based on saponins content. The saponin composition has been correlated with the place of origin. This approach revealed interesting differences not only in the type of sapogenins, but also in the kind and the number of sugars of the saponins in plant samples collected from different geographical regions. The content of protodioscin also depends on the geographical region of collection. The freshly expressed juice of the aqueous extract of the whole plant contains inorganic nitrates, mostly potassium nitrate. The diuretic property of the plant is due to the nitrates. The fruit contains alkaloid, resin, fat, ascorbic acid, minerals (14%) and essential oils. Dried fruits contain semi drying oil, peroxides, diastase, traces of glucosides, resins, protein and large amount of inorganic matters.The amount of ascorbic acid increases from roots to fruits in *T. terrestris*. This plant isalso rich in iron[29,30].

Medicinal Uses of *T. terrestis*

*T. terrestris*has been in use for medicinal purposes since time immemorial. *T. terrestris* is used in Ayurvedic, Yunani as well as Chinese traditional medicines where this is known as gokshura (Sanskrit, meaning cow's hoof),Khar-e-KhasakKhurandbai ji lirespectively. In India and China, the medicinal use of this herb is traced 5,000 year back.

In Ayurvedicpharmacology, *Tribulus terrestris* (aka gokshura) is used as a powder form of the aerial parts, particularly the fruits for healthy flow of urine & helps in soothing the urinary membrane. It acts as tonic for the healthy production of sperm. It helps in rejuvenating the uterus & other organs responsible for pregnancy in females. Its saponins and flavonoid content helps in healthy production & maintain the level of hormones and calming the mind. It helps in purification of blood & helps to improve itching sensation of body. It helps to move flatulence downwards. It has been found to have diuretic properties as well [31]. In Ayurveda, this herb is known for its diuretic, aphrodisiac and anti-urolithiatic properties [32]. In the traditional Chinese medicine, its fruits have been used for treatment of eye trouble, abdominal distention, emission, edema, morbid leucorrhea, sexual dysfunction and veiling [33,34]. In South Africa, it is recommended in the form of a herbal tonic for diarrhea and diseases of the throat and the eyes [35]. In the Bulgarian folk medicine, *T. terrestris*is used for blood purification and in haemorrhoids [36]. It has been reported that the seeds or nutlets have been used in homicidal weapons smeared

with the juice of *Acokantheravenenata*in southern Africa [37].

Tribulus is used for kidney problems, including kidney stones, painful urination, a kidney disorder called Bright's disease, and as a "Water Pill" (diuretic) to increase urination; for skin disorders, including eczema (atopic dermatitis), psoriasis, and scabies; for male sexual problems, including Erectile Dysfunction (ED), involuntary release of semen without orgasm (spermatorrhea), and to increase sexual desire; for heart and circulatory system problems, including chest pain, high blood pressure, high cholesterol, and "Tired Blood" (anemia); for problems with digestion, including colic, intestinal gas (flatulence), constipation, and to expel intestinal parasitic worms; for pain and swelling (inflammation) of the tissue lining the mouth (stomatitis) and sore throat; and for cancer, especially nose tumors.

Women use *Tribulus* to tone muscles before childbirth, to cause an abortion, and to stimulate milk flow.Some people use *Tribulus* for gonorrhea, liver disease (hepatitis), inflammation, joint pain (rheumatism), leprosy, coughs, headache, dizziness (vertigo), Chronic FatigueSyndrome (CFS), and enhancing athletic performance. It is also used for stimulating appetite and as an astringent, tonic, and mood enhancer. *Tribulus* has chemicals that might increase some hormones in animals. However, it doesn't appear to increase male hormones (testosterone) in human.

Some body builders use *T.terrestris* as Post Cycle Therapy or "PCT". After they have completed an anabolic-steroid cycle, they use it under the assumption that it will restore the body's natural testosterone levels.

The extract is claimed to increase the body's natural testosterone levels and thereby improve male sexual performance and help build muscle. Its purported muscle-building potential was popularized by American IFBB bodybuilding champion Jeffrey Petermann in the early 1970s. However, *T.terrestris* has failed to increase testosterone levels in controlled studies [38-40]. It has also failed to demonstrate strength-enhancing properties [41], a finding indicating that the purported anabolic steroid effects of *Tribulus terrestris* are untrue. Some users report an upset stomach, which can usually be counteracted by taking it with food

Sexual disorders

Procreation is essential for the propagation of race. Infertility is defined as the inability to conceive after 12 months of sexual practice without the use of contraception [42,43]. Approximately 15% of couples attempting their first pregnancy meet with failure and, in nearly 50% of all infertility cases, the cause is attributed to the male [44]. Although there has been considerable improvement in the understanding and treatment of female infertility, practically little advancement is seen in dealing with this problem in the male [45].

Traditional herbs have emerged in the past fewyears as an 'Instant' treatment for sexual and erectile dysfunctions [46]. *Tribulus terrestris* , is suggested to be effective in treatment of such dysfunctions by increasing serum LH and testosterone [42], and conversion of its phytochemical derivative, protodioscine to De Hydro Epi Androsterone(DHEA)[46]. The scientific proof regarding effectiveness of *T.terrestris* for the male impotace is rather ambiguous and is a matter of further exploration. A study conducted on males, with moderate idiopathic oligozoospermia, showed that protodioscin treatment of men resulted in increased level of testosterone [42]. Viktorov, et al.reported that administration of *Tribulus terrestris* preparation significantly increased the number of spermatogonia, spermatocytes and spermatids in the testes of adult rats. They suggested an intensified DNA synthesis under the effect of protodioscin [47]. Çek showed that spermatogenesis was accelerated among the *Tribulus terrestris* treated group of *Cichlasomanigrofasciatum* compared to the control group; further, it was observed that the histological response of the testes in *Tribulus terrestris* treated groups invariably included an increased number of spermatogenetic cysts and an excess of late stages of spermatogenesis [48]. A single study has shown that *T. terrestris* can alter sexual behavior in castrated rats [49].

It appears to do so by stimulating androgen receptors in the brain. Animal studies in rats, rabbits and primates have demonstrated ambiguous results.

One study found that administration of *Tribulus terrestris* extract can produce statistically significant increases in levelof testosterone, dihydrotestosterone and dehydroepiadrosterone [8], and produces effects suggestive of aphrodisiac activity [49]. Another study comprised of subjects with age between 21-50 years with oligozoospermia complaint; the test subjects were given Gokshura granules for 60 days (control group was given placebo). The results of the study indicated superior results in the management of oligozoospermia, as compared to the placebo granules [50].

Contrary to the above findings, in 2005, Neychev and Mitev reported that *Tribulus terrestris* did not induce an increase in testosterone or LH in young men [40] while Brown, et al. found that a commercial supplement containing androstenedione and herbal extracts including *Tribulus terrestris* , was not effective in raising serum concentrations of free or total testosterone. *T. terrestris* has also been reported to improve libido and sexual activity in patients with Klinefelter's syndrome, Noonan syndrome, and simple undescended testes [51]. A research review conducted in 2000 stated that the lack of data outside of this study prevents generalizing the results to humans, particularly healthy individuals [52].

Although the debate is still continuing and it is yet to be decided whether *T. terrestris* is capable of curing the male impotence, strong evidence suggests that *T. terrestris* can improve male

sexual function [49] and the performance of athletes [53]; the note of caution being that care should be exercised in the use of *T. terrestris* because it contains poisons that can harm man.

Women are not excluded from the benefits of *Tribulus*. *W*omen suffering from nonovular menstrual cycles were given *Tribulus* in the range of 750-1500 mg/day for a duration of 5 daysthrough 14 of their menstrual cycle. The results of this open study were overwhelming that resulted in normalized ovulation in 67% of the women, with successful pregnancies occurring in 6%. In a parallel group of 62 women using a drug targeting the same problem of nonovulation, 39% had normalized ovulation with pregnancy, and 35% had normalized ovulation without pregnancy. From these results, it is clear that *Tribulus* possessed a considerably more moderate effect than the drug: 24 of the 36 women had normal ovulation restored, but only two of them became pregnant, and no effect was recorded in 12 of them. On the other hand, the women taking *Tribulus* had no side effects, compared to 38% of the women in the group treated with the ovulation-stimulating drug.*Tribulus* has also been observed to alleviate menopausal symptoms (e.g., hot flashes, sweating, depression, insomnia, and anxiety) in 98% of subjects experiencing natural as well as post-operative menopause. The most important aspect of treatment with this herb is that no significant changes in any measured hormone level, including Follicle-Stimulating Hormone (FSH), Luteinizing Hormone (LH), prolactin, estradiol, progesterone, and testosterone were observed also use of *Tribulus* was without significant side effects [54].

Anti-Cancerous Activity

Among the different saponins analyzed from different parts (stem & fruit) of *T. terrestris* collected from different regions (Bulgaria, China & India), only spiro compounds exhibited remarkable activity [55]. The most active spirostanol glycoside (Hecogenin) exhibited a broad range of anticancer activity against cell lines SKMEL, KB, BT 549 and SKOV- 3 [56,57]. Dioscin& also prosapogenin A of dioscin showed *in vitro*anti-cancerous activity against the cancer cell line K562[58].Protodioscin proved to be cytotoxic against cell lines from leukemia and solid tumors and particularly against one leukemia line (MOLT-4), one NSCLC line (A549/ATCC), two colon cancer lines (HCT-116 and SW-620), one CNS cancer line (SNB-75), one melanoma line (LOX IMVI), and one renal cancer line (Hu & Yao, 2002). Based on computer analysis of methylprotodioscin as a seedcompound, a potential novel mechanism was suggested for its anti-cancer action [58].The saponin mixture from Chinese origin on Bcap37 breast cancer cells had potent inhibitory effects in a concentration dependent manner [59].In addition, it has been reported that the extract of *T.macropterus*, which is in the same family as *T. terrestris*, has cytotoxic activity against a human liver cancer cell line. Since long, *T. terrestris*extracts have been used as anticancer therapy in oriental medicine, however the mechanisms of these effects have not been well elucidated.

Trouillas, et al. 2005 found that other saponins, structurally similar todiosgenin, present in *T. terrestris*extracts, may block cell cycle, suppress proliferation and induce apoptosis in human sarcoma cell lines [60]. Sisto, et al. in their study showed experimental evidence that TT has a preventive efficacy against UVB-induced carcinogenesis and the molecular knowledge on the mechanisms through which TT saponins regulate cell death suggests great potential for TT to be developed into a new medicine for cancer patients [61].

Cardiac Dysfunction

Cardiovascular Diseases (CVDs) remain the principle cause of death in both developed and developing countries, accounting roughly 20 % of all deaths worldwide annually. Among various CVDs, Myocardial Infarction (MI) or heart attack is the leading cause of morbidity and mortality and major cause of death by the year 2020 worldwide. MI occurs when the blood supply to a part of the heart is interrupted, causing death of heart tissue. It means necrosis of a region of myocardium, usually as a result of occlusion of a coronary artery [62]. It is most probably induced by catecholamine metabolism in particular redox reactions that results in aminochromes and adrenochromes [63] These oxidative reactions produce free radical [64].

Over the years, people have taken *Tribulus*in an attempt to enhance athletic performance and for a wide range of health issues that may include heart and circulatory conditions and sexual issues. Limited studies show it might be helpful in lessening symptoms of angina and in enhancing athletic performance. Biochemical findings of the present study indicate that aqueous fruit extract of *Tribulus terrestris* possesses antioxidant properties in myocardium and protects against Isoproterenol (ISO) induced MI. The most important protective mechanism offered by extract of *Tribulus terrestris* is through its ability to decrease lipid profile, lipid peroxidation and increased levels of antioxidant enzymes [65].

Water extract of fruit showed cardiotonic activity on cat papillary muscle, frog and rabbit hearts. Ethanol (95%) extract of the entire plant caused increase in the rate and amplitude of frog heart [65]. Ethanol (95%) extract of dried plant decreased the force of contraction of rabbit heart [66].

Nervous System

The pharmacological screening of the *T. terrestris* extract showed marked CNS stimulant activity. Chloroform extract of the dried entire plant, administered intra peritoneally to mice showed analgesic effect. The dried fruit, administered by gastric intubation to mice in a preparation containing *Bombyx mori, Aconitum*

*sinense, Alpinia*species, *Menthaarvensis*, and*Sophoraflavescens*, was active versus acetic acid induced writhing [66]. The dried fruit, administered by gastric intubation to mice in a preparation containing *Bombyx mori*, *Aconitum sinese*, *Alpinia*species, *Menthaarvensis*, and*Sophoraflavescens*showed anticholinergic effect [66].

Many research studies revealed that aqueous extract of *T. terrestris*fruits have some antihypertensive effect [67-69]. These beneficial effects have partly been attributed to its ability to increase Nitric Oxide (NO) release from the endothelium and nitrergic nerve endings [70]. Antihypertensive mechanism of *T. terrestris*was studied in 2K1C hypertensive rats by measurement of circulatory and local ACE activity in aorta, heart, kidney and lung. The systolic blood pressure and ACE of *T. terrestris*fed hypertensive rats was significantly decreased compared to hypertensive rats indicating a negative correlation between consumption of *T. terrestris*and ACE activity in serum and different tissues in 2K1C rats [71].

Immunologic Effect

The powdered plant, taken orally in combination with*Ledebouriellaseseloides, Potentillachinesis, Clematis armandii, Rehmanniaglutinosa, Paeoniaalbiflora, Lophaterum gracile, Dictamnusdasycarpus, Glycyrrhaziaglabra* and *Schizonepetatenufolia,* showed immunologic effect in atopic eczema patients and interleukin 4 induced CD23 expression in atopic eczema patients [66].

Musculo-Skeletal Activity

The methanolic extract of *Tribulus terrestris* fruit has been found to exhibit for anti-arthritic activity againstFrund's complete adjuvant (FCA) induced arthritis in rats.The anti-arthritic activity has been associated with the presence of flavonoids which are well known for their surface charge neutralizing effects; it is this property which is responsible for modulating membrane stability and hence the anti-arthritic activity.It was also found that the administration of*T.terristris* (200 and 300 mg/kg bodyweight) leads to inhibition of leukocyte migration which may have beneficial effect for joint preservation. The activity may be due to presence of steroidal glycoside [72]. The dry extract of *T. terrestris*have been reported to cause anincreased calcium level in the blood serum of broilers [19] whereas the Ethanolicextract of the dried entire plant, administered intraperitoneally to mice showed skeletal muscle relaxant activity and the Ethanol (95%) extract of the dried aerial plant, showed smooth muscle relaxant activity on rabbit duodenum [66].

Physical Strength and Endurance

Traditionally, a tonic is something that produces physical, mental, or emotional vigor. *Tribulus* has a tonic reputation that has been verified in the lab by increased endurance in rats [73]. In humans, *Tribulus* has been shown to be a general stimulator, enhancing activity across a wide spectrum. In addition to improving motor activity and muscle tone, it helps restore vigor, vitality, and stamina [74].

It has also been shown to intensify protein synthesis, particularly in the liver, kidney, and heart tissue of animals [75], while it enhances energy metabolism [76]. The best explanation of the tonic effects of *Tribulus* is that its steroidal properties may enable it to regulate the secretion of antistress hormones such as cortisol, produced by the adrenal cortex [77].

Diuretic Effects

The diuretic properties of TT are due to large quantities of nitrates and essential oil present in its fruits and seeds. The diuretic activity can also be attributed to the presence of potassium salts in high concentration.Jabbar et al., studied the effects of herbal extract of *T.terristris*on the urine output and electrolytes in rabbits and noted significant increase in urine volume over a period. Additionally, they also noted that it significantly decreased the sodium level and serum potassium level throughout the study period. Hence, they recommended that the use of this herb may be promoted as diuretic agent which will be helpful in hypertensive and renal disease patients [78,79]. Diuretic potential of *T. terrestris*has been evaluated in albino rats. The diuretic effect was credited to the presence of potassium salts in high concentration and this action was confirmed of *T. terrestris*with minimal side effect in albino rats [80]. Ali, *et al.* tested the aqueous extract of TT prepared from its fruit and leaves in rat diuretic model and strips of isolated Guinea pig ileum were used for the contractility test. The aqueous extract of TT, in oral dose of 5 g/kg, elicited a positive diuresis, which was slightly more than that of furosemide. Sodium and chloride concentrations in the urine were increased. The increased tonicity of the smooth muscles, which was produced by TT extract, together with its diuretic activity helped in the propulsion of stones along the urinary tract [81].

Anti-inflammatoryActivity

The ethanolic extract of TT inhibited the expression of cyclooxygenase-2 (COX-2)[82]. 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 TT inhibits the expression of mediators related to inflammation and expression of inflammatory cytokines, which has a beneficial effect on various inflammatory conditions [11]. The methanolic extract of TT showed a dose-dependent inhibition of rat paw volume in carrageenan-induced inflammation in rats [83]. The anti-inflammatory activity of TT is attributed to the presence of Protodioscin (PTN) [84].

Antioxidant Property

The many number of medicinal plants are used in the cellular and metabolic disease treatment such as diabetes, obesity and cancer etc. There are some speculations that the generation of free radicals inside the body in some physiological conditions is resulted in the cellular changes and development of cancer etc. and this could be neutralized by the antioxidants from different medicinal plants. Several studies have shown that plant derived antioxidant nutraceuticals scavenge free radicals and modulate oxidative stress-related degenerative effects [85,86]. Free radicals have been implicated in many diseases such as cancer, atherosclerosis, diabetes, neurodegenerative disorders and aging [87,88].

*T. terrestris*also has antioxidant properties and it has been found the extract from *T. terrestris*significantly reduce the formation of hydroperoxide, thus implying that this species is powerful natural antioxidants [89]. TT has been shown to have significant antioxidant activity when measured using various in vitro assays such as scavenging of DPPH, superoxide radicals, reducing power and inhibition of microsomal lipid peroxidation [90].

Dermatology

A number of creams have been developed using *T. terrestris* extracts with anti-bacterial, anti-inflammatory, anti-viral activities, and other activities for topical use on skin and mucosal tissues. It has also been suggested to combine *T. terrestris* extracts with metals for preparing anti-viral pharmaceutical compositions [91,92]. Several examples of plant extracts combinations including *T. terrestris* extracts are found in Asian patent literature. Some of such patent documents specifically refer to the usage involving topical administration such as pruritus and skin disorders [93], increasing the skin permeability and stimulating the generation of melanophore [94] and improving skin tenderness or other cosmetic applications [95,96].

Antimicrobial Activity

Antimicrobial activities of *T. terrestris*are reported to vary with the origin of the plant and the part of the plant used. The ethanolic extracts of Yemeni *T. terrestris*has demonstrated no detectable antibacterial activity against any of the reference bacteria [97]. whereas the methanolic/ethanolic extracts of different parts (fruits, roots and stems with leaves) of Iranian, Indian or Turkish *T. terrestris*inhibited the growth of different microorganisms tested. Antimicrobial activity has been found against Staphylococcus aureus, Escherichia coli and Candida albicans [98]. The ethanolic extracts of all parts (fruits, stems plus leaves and roots) of Turkish *T. terrestris*showed activity against all reference bacteria [99]. Moreover, ethanolic extracts of the fruit and leaf of Indian *T. terrestris*were active against *Escherichia coli*and *Staphylococcusaureus* [100]. Iranian *T. terrestris* demonstrates activity against the most prevalent gram-negative bacteria in urinary infections namely *E.coli* [101]. The mode of action of antibacterial effects of saponins seems to involve membranolytic properties, rather than simply altering the surface tension of the extracellular medium, thus being influenced by microbial population density. Flavonoids have been found in vitro to be effective antimicrobial substances against a wide array of microorganisms. Their activity is probably due to their ability to complex with extracellular and soluble proteins and to complex with bacterial cell walls. More lipophilic flavonoids may also disrupt microbial membranes.

Among the seven different saponins tested from *T. terrestris*, only the spirostanol saponins showed antifungal activity against *C.albicans*and *Cryptococcus neoformans*, while none of the furostanol derivatives exhibited inhibitory activity. Further, these compounds were not effective against *S.aureus*, *Aspergillus fumigatus*, *P.aeruginosa* and *Mycobacterium intracellulare* [56]. Antimicrobial activity of organic and aqueous extracts from fruits, leaves and roots of *T. terrestris*from Iraq was examined against 11 species of pathogenic and non-pathogenic microorganisms. All the extracts from the different parts of the plant showed antimicrobial activity against most tested microorganisms. The most active extract was ethanol extract from the fruits with a minimal inhibitory concentration of 0.15 mg/ml against different bacteria and fungi [102].

Insecticidal Activity

Extracts of *T. terrestris* have been found to control or suppress the growth of *Spodopteralitura* [103], *Dysdercuscingulatus* [104], *Meloidogynejavanica* [105], *Meloidogyne incognita* [106], *Bulinustruncates* [107], groundnut leaf miner [108], *Macrophominaphaseolina* [98], and Rice tungro virus (Rice tungro bacilliform virus / Rice tungro spherical virus) [109]. Leaf treatment of mulberry with aqueous extracts of*T. terrestris* and *Psoraleacorylifolia* during the third larval instar of silkmoth (*Bombyx mori*) suppressed grasserie, caused by a nuclear polyhedrosis virus, by 60%[110]. Oil extracted from the seeds of *T. terrestris* has a synergistic effect when mixed with deltamethrin [111].

Miscellaneous Activities

Theuse of *T. terrestris* has been found to be effective for the cure of Parkinson's disease [112], malignant melanoma [57], liver and eye diseases [113], and benign prostatic hyperplasia [114]. Recent research has also confirmed that dietary intake of *T. terrestris*can significantly lower serum lipid profiles, decrease endothelial cellular surface damage and rupture and may partially repair the endothelial dysfunction resulting from hyperlipidemia in New Zealand rabbits fed a cholesterol-rich diet[115].

Speaking of agricultural importance, despite being a parasite, *T. terrestris* has been cultivated in India to reduce soil erosion by wind and water and loss of soil moisture. It has also been used to improve soil texture and water holding capacity in wastelands [116].

Toxicology& Side Effects

T. terrestris is toxic to animals, mainly sheep, but also to goats and cattle. At least three forms of poisoning are involved: (a) nitrate poisoning occurs when sheep gorge themselves on the fresh lush growth. The nitrate is converted to nitrite in the rumen, leading to death; (b) photosensitization results after animals consume *T. terrestris* and a fungus on pasture litter, making sheep listless and sometimes causing death; (c) staggers (ataxia) arises after prolonged grazing. An irreversible weakness develops in the hind legs of sheep leading to paralysis and death. An estimated 20,000 sheep died of this disease in New South Wales, Australia during and after a prolonged drought in 1981-1983 [117]. An investigation of poisoning of sheep and goats by *T. terrestris* in Western Australia found symptoms which included anorexia, photophobia, dehydration, icterus, swollen and green kidneys, orange livers, and serious exudation around eyes, ears and tails [118].

T. terrestris is reported as an alternative host of root-knot nematode (*Meloidogyne* spp.)[119], Bean leaf roll virus which causes stunt in chickpea [120], Tomato spotted wilt virus [121], silverleaf whitefly (*Bemisiatabaci* B biotype) of cantaloupe melons [122], and sugarcane weevil (*Nicentrussaccharinus*)[123]. Sheep that eat *T. terrestris* have been found to suffer staggers (limp paresis) which is caused to the presence of two beta-carboline alkaloids: harman (harmane) and norharman (norharmane) [124,125].

In humans, the use of *T. terrestris* as a supplement for short time is mostly safe given the conditions that subject is healthy, non-pregnant and is not involved in breastfeeding. Experiments on lab animals has indicated that intake of *T. terrestris* may cause problem with fetal development. Common side effects observed among women include insomnia and irregular menstrual cycle. Use of this herb may cause prostrate problems in male subjects.

The use of *Tribulus* in combination with certain heart and blood pressure medicines must be avoided since this herb has been found to interact with such medicines esp. beta-blockers, calcium channel blockers, digoxin, and/or diuretics.

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