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Potential Nutraceutical Use of *Tribulus terrestris* L. in Human Health

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ABSTRACT

Tribulus terrestris (*T. terrestris*) is an herb that has been used in various traditional medicine practices since ancient times. More recently, the pronounced health benefits of this herb have been evaluated within a wide scope, without properly acknowledging its nutraceutical value. Therefore, this article intends to provide an integrated overview on the nutraceutical potential of *T. terrestris* in the area of human health promotion. This review discusses the potential employability of *T. terrestris* and its derived products as nutraceuticals in prevention, treatment, and management of prevalent human diseases and associated conditions. The outcomes of several *in vitro* and *in vivo* studies elaborate on the ability of *T. terrestris* supplements and different fractions to act as antioxidant, anti-inflammatory, anticancer, antidiabetic, testosterone boosting, and cardio, renal and liver protective agents. Many studies reveal that *T. terrestris* would act as an excellent nutraceutical that prevents harmful impacts to the human body. Its bioactivities are driven by various factors, and it has been suggested to be used to replace certain pharmaceuticals and synthetic drugs. In-depth clinical studies on the herbal pharmacodynamics are needed and would broaden the scope of nutraceutical applications of *T. terrestris*.

KEYWORDS

T. terrestris; nutraceutical; testosterone; antioxidant; health protection

Introduction

Plants have a rich and diverse range of bioactive constituents that exert various bioactivities with promising health benefits on the human body. Generally, the consumption of plant-derived foods is reported to be associated with improved health status as it reduces the risk of non-communicable chronic diseases, such as type II diabetes, neurodegenerative diseases, cardiovascular diseases, and numerous types of cancers.[1] Therefore, the consumption of plant-originating nutraceuticals is encouraged in order to augment human health for optimal disease management and prevention.[2]

The concept of a "nutraceutical" was invented to make health-protective products readily available that did not require medical consultation. The term "nutraceutical" was created by combining components of "nutrition" and "pharmaceutics",[3] and is interpreted as "more than food but less

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than pharmaceuticals".[4] However, there is a lack of distinctive criteria in distinguishing the term nutraceuticals'.[5] as its properties are found to overlap with other foods in different categories. Such foods include: nutritional food, enriched food, dietary supplements, functional food, novel food, medicinal herbs, herbal products, and pre- and probiotics'.[2, 6, 7]

The intensified studies of different plants' bioactive constituents and their exertion of physiological effects has been carried out at a greater pace in recent years, which has seemingly been followed by an increasing interest in this area of research. Primary reasons for such interest include the rising trend of using plant-derived bioactive components in therapeutic and pharmacological aspects of health, emerging health promotion concepts, and increasing occurrences of the implementation of phytotherapy and nutritional therapy'.[2] In this setting of diverse plant-based health applications, *T. terrestris* has been subjected to various investigations aiming to determine its potential to perform various beneficial bioactivities.

T. terrestris is a dicotyledonous plant that comes under the family Zygophyllaceae, which is commonly known as puncture vine, land caltrops, or small caltrops'.[8] It grows abundantly in Asia, Africa, Australia, and Europe, and is most often found in regions with sandy soil and arid climate conditions'.[9] The plant is a small prostrate hirsute or silky hairy shrub, measuring 10–60 cm in height. It has opposite, unequal, paripinnate (5 to 8 pairs) leaves, with an oblong lanceolate or elliptical shape. The flowers are yellow in colour, while its fruits are ax-shaped and hard of texture, having a diameter of 7–12 mm at the "head", and a length of 3–6 mm for the "handle". The plant has cylindrical, slender, fibrous roots which are frequently branched, with many small rootlets (Fig. 1).

T. terrestris has been utilized since ancient times in traditional medicinal practices of various cultures; traditional Chinese medicine, traditional south-European medicine, and Indian Ayurvedic medicine have all benefited from the use of *T. terrestris*'.[9, 10] In traditional Chinese medicine, *T. terrestris* is considered an excellent medicine, with its roots and fruits having been used for over a thousand years to treat a number of diseases. Moreover, the effectiveness of roots and fruits of *T. terrestris* in treating a range of diseases are reported in countries such as India, Pakistan, and Sudan'.[10] There are various applications of *T. terrestris* in folk medicine, ranging in use as a tonic, lithotripsic, diuretic, stomachic, palliative, aphrodisiac, antihypertensive, astringent, and urinary disinfectant'.[8, 11, 12]

The *T. terrestris* herb has a rich range of bioactive constituents, such as: steroidal saponins, terpenoids, alkaloids, flavonoids, polyphenol carboxylic acids, tannins, phytosterols, amino acids, amide derivatives, and proteins. Among these constituents, steroidal saponins, alkaloids, and polyphenolic compounds are considered the key components which claim various bioactivities respectively'.[9, 10] The composition of these constituents is found to be varied in different parts of the plant'.[9] thus, almost all the parts of the plant, including its fruits, seeds, leaves and roots, have been utilized in treatments for different diseases'.[13]

As a whole, *T. terrestris* is reported to possess a range of various beneficial activities, including: antioxidant, anticancer, anti-inflammatory, antibacterial, anthelmintic, neurotonic, diuretic, immunomodulatory, antispasmodic, hypolipidaemic, anthelmintic, antitumor, aphrodisiac, analgesic, antidiabetic, larvicidal, anti-urolithic, hepatoprotective, cardiotonic, and anti-cariogenic agents'.[8, 10, 14–16] However, some claims were proved with little evidence'.[16] Nowadays, nutritional supplements made from *T. terrestris* are widely available in the pharmaceutical market'.[13] for instance, *T. terrestris* has become a popular dietary supplement among bodybuilders and male athletes due to its potential for enhancing serum testosterone levels'.[17]

Several studies have explored the bioactivities of different parts of *T. terrestris*, while numerous review reports emphasize its phytochemical and pharmacological characteristics. However, comprehensive discussions on *T. terrestris* which highlight its value under both aspects as a nutraceutical are yet to be done. Hence, the focus of this review is to elaborate on the collective importance of *T. terrestris* pertaining to its potential to act as a nutraceutical. In this review, the major findings of recent research on *T. terrestris* will be discussed thoroughly by explaining its underlying mechanisms in the human body. Thereby, this review will provide an overview of the broad applications of *T. terrestris* as a plant-based nutraceutical for improving the human health.

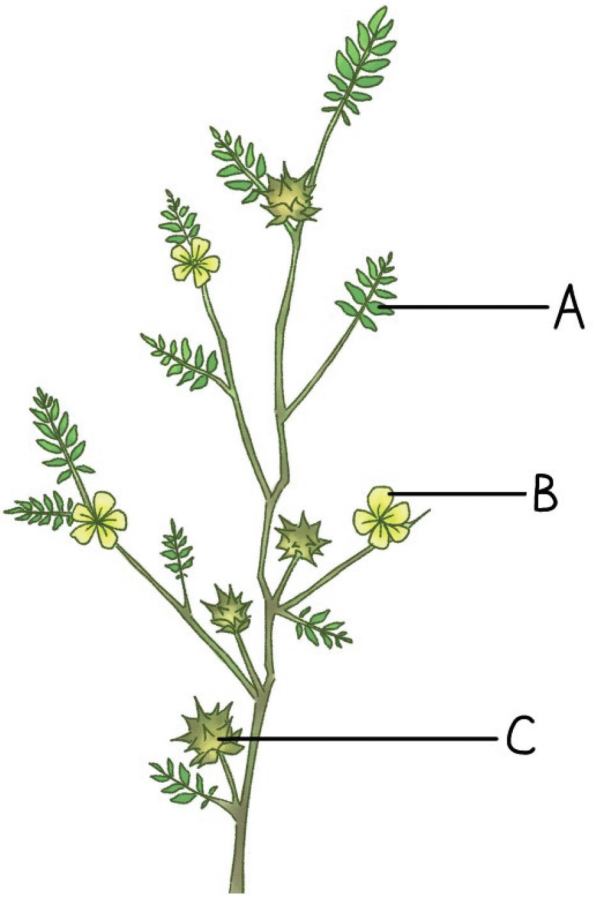

Figure 1. Illustration of *T. terrestris* plant and main parts (A – leaves, B – flowers and C – fruits).

Benefit on functions of human reproductive system

The treatment of *T. terrestris* is reputed for its beneficial influence on the human reproductive system. There is extensive literature on this aspect and most frequently, the pronounced role was attributed to the testosterone boosting ability of *T. terrestris* while other studies rendered its impact on other functions. It is found that *T. terrestris* is capable of influencing human sperm by improving viability, mobility, curvilinear velocity and the number of progressive motile spermatozoa.[18] In accordance with the previous finding, Asadmobini et al.[19] confirmed the proficiency of *T. terrestris* on viability and mobility of human sperms.

The protective role of *T. terrestris* on ovarian tissue against ischemia-reperfusion injuries has been explained based on a pre-clinical study where the treatment reversed the ovarian toxicity of female rats.[20] Another pre-clinical study proved the antiandrogenic activity of *T. terrestris* extract on rats with polycystic ovary syndrome.[21] Confirming the fact, a clinical study on obese women diagnosed with polycystic ovary syndrome showed that the *T. terrestris* treatment (MediHerb Tribulus Forte tablet) accompanied with lifestyle interventions can help to overcome this medical condition. Therefore, it is evident that *T. terrestris* may play a role in ameliorating the hyperandrogenism, menstrual irregularities and polycystic ovaries associate with polycystic ovary syndrome.[22]

Testosterone booster

Testosterone is a pleiotropic hormone that has a principal role in physiology and androgenesis in men or boys.[23] It is also naturally present in women and is subject to physiological decline as they age, beginning prior to natural menopause, with the late reproductive years are the stage with the highest decline in testosterone circulation.[24] The testosterone boosting ability and associated properties of *T. terrestris* have been reported in a number of studies, including *in vitro*, *in vivo* and clinical trials.[24–27]

Previous studies on *T. terrestris* suggested that the plant might have a favourable influence on testosterone regulations and sperm physiology. The steroidal saponins present in *T. terrestris* were identified as prominent constituents that possess the potential to produce high testosterone levels and boost the androgenic status.[25] Protodioscin derived from *T. terrestris* has been recognised as the main effective compound which triggers several attributes, such as sexual performance, hormone levels and muscle tonus.[28, 29] In the body, this chemical compound is reported to be responsible for converting testosterone into dihydrotestosterone,[28] which is known to have promising benefits over different sexual functionalities in males.[27]

Haghmorad et al.[26] demonstrated the beneficial impact of root and flower extracts of *T. terrestris* on the sexual hormone levels and sexual performance of male rats, and emphasized its non-toxic attributes and absence of side effects. It was evident that *T. terrestris* possessed the ability to provide a protective role against testicular damage influenced by cyclophosphamide, an immunosuppressant and anticancer drug with negative side effects on fertility. Mice treated with dry extract of *T. terrestris* showed increased levels of curvilinear velocity, motility, the integrity of sperms, and exhibited protective action of *T. terrestris* against cyclophosphamide toxicity.[29] A study utilising the over-training rat model saw a noticeable increment in the rats' serum testosterone levels and increased exercise performance when treated with commercially available *T. terrestris* fruit extract (saponins >70%).[30] Moreover, the treatments of *T. terrestris* coupled with protodioscin were found to improve the testosterone levels of diabetic rats exhibiting the therapeutic impact of *T. terrestris* in diabetes complications.[31]

Many clinical studies have been carried out to evaluate the effectiveness of *T. terrestris* on the sexual functions of both men and women. As reported by Din et al.[25] *T. terrestris* showed its effectiveness in increasing the serum testosterone level and sexual function of aging men who were diagnosed with partial androgen deficiency and erectile dysfunction. Thus, the usefulness of *T. terrestris* capsules were discussed thoroughly within the study, and established appropriate measures which would ensure the safety of long-term prescriptions. Moreover, the plant has also been evaluated for its potential in treating infertile men within the age range of 18–50 years with oral treatments of commercial *T. terrestris* pills (Androsten). The treatments were found to be therapeutically beneficial on test populations with abnormal semen parameters and/or infertility.[27] Tribestan, an herbal medicine derived from *T. terrestris*, exhibited satisfactory results against male sexual dysfunction (particularly erectile dysfunction) in a clinical trial of males within the age range of 18–65 years.[16] It ameliorated the testosterone levels and erectile dysfunction of men who were suffering from spontaneous erectile dysfunction. However, contradictory results were found by Santos et al.[32] where the *T. terrestris* treatments within the tested doses exhibited non-significant results compared to placebo.

In addition to the beneficial effects on sexual disorders and improved sexual performance of men, *T. terrestris* is also widely used by bodybuilders and athletes in strength training, muscle mass gaining, and performance improving aspects.[30, 33] It is considered as a legal, safe, and natural testosterone booster that promotes the androgenic and anabolic mechanisms.[30] According to a previous clinical trial, *T. terrestris* supplement could be helpful in the recovery process of "CrossFit" athletes by diminishing the catabolism and fatigue which was attributed to the augmented testosterone levels.[34]

Interestingly, *T. terrestris* has been found to be beneficial to the sexual function of women, particularly those who are on the postmenopausal stage with sexual dysfunctions. Postigo et al.[35] reported the effectiveness of *T. terrestris* in boosting the sexual ability of menopausal women who have

troubled sexual functions. The synergic action of *T. terrestris* with other plants on women's improved sexual functions was highlighted in many studies. The Libicare®, an oral multi-ingredient food supplement that contains *T. terrestris* was found to exhibit a significantly beneficial effect on this aspect by improving the sexual function and hormone levels.[36] In consistence with the above findings, the attenuating effect on menopausal symptoms was found upon the treatment with an Aphrodit capsule containing a mixture of herbal extracts including *T. terrestris*.[37]

Vale et al.[38] stated that *T. terrestris* was found to benefit treatments for hypoactive sexual desire disorder (HSDD) of postmenopausal women. They believed that the effectiveness of *T. terrestris* over HSDD might be due to a potential association with a mechanism that increases free and bioavailable testosterone. This idea was further confirmed by a study carried out by De Souza, Vale, and Geber,[39] where commercially available *T. terrestris* pills (Androsten) were recognized as a safe alternative treatment for postmenopausal HSDD with minimum side effects.

Testosterone therapy is often prescribed to post-menopausal women in order to improve their sexual function, nevertheless, there is controversy in their approval concerning safety issues.[24] However, a recent study proposed that testosterone therapy was a safe treatment without side effects that could be used to attenuate the sexual dysfunction of women who were in both pre- and postmenopausal stages, acknowledging the ability of *T. terrestris* in regulating testosterone in women.[40] Thereby, it is evident that *T. terrestris*, in its various forms, can serve as one of the best nutraceuticals in improving human sexual and body functionalities in multiple aspects.

Antioxidant activity

The natural human defence system is responsible for acting against oxidative stress in the body. To a certain extent, the constant need for exogenous antioxidants is emphasized when considering the incapability of the innate human defence system to fight against severe oxidative stress. Thereby, the use of natural antioxidants has become popularized and gives prominent attention to plant-based sources and their wide range of active constituents and distinctive mechanisms.[41] The antioxidant potential of *T. terrestris* has been discussed in several studies over a wide range of applications.

Crude fractions obtained from different solvent extractions of the *T. terrestris* plant showed promising results for various *in vitro* antioxidant assays, such as DPPH, ABTS, superoxide hydroxyl radical scavenging assays, ferric reducing power, and β-carotene beaching assays.[9, 42–44] Additionally, commercially available products have also been utilized for their antioxidant activities.

Different products of *T. terrestris*, including Tribestan™ standardized dry extract (>112.5 mg furostanol saponins) and Tribestan™ film-coated tablets, have reported higher antioxidant activity and greater lipid peroxidation inhibition than butylated hydroxytoluene (BHT), highlighting its potential to be used in therapeutical implementations for free radical pathologies.[45] Furthermore, the standardized dry extract (containing 43.21% of total saponins) and saponin enriched extract of the commercially available dry extract of *T. terrestris*, were found to show potent antioxidant activity in comparison to gallic acid, which emphasizes a possible correlation between antioxidant activity and total saponin content of *T. terrestris*.[46]

Hammoda et al.[41] has reported that the presence of di-*p*-coumaroylquinic acid derivatives would play a major role in the antioxidant potential of the plant, while Ștefănescu et al.[9] has attributed its antioxidant potential to its polyphenols and flavanoids. A mild antioxidant activity was observed in the flavonoids fractionates obtained from *T. terrestris* leaves in comparison to BHT.[47] Meanwhile, the flavonoids and fatty acid fraction of the fruit have exhibited antioxidant activity for several antioxidant assays.[48] Therefore, it is clear that a range of constituents present in *T. terrestris* are contributing to its antioxidant potential.

These findings demonstrate the potential of *T. terrestris* and its products to be used for promoting health, as antioxidant activity is associated with ameliorating human chronic diseases.[9] This fact has been supported by findings of previous experiments.

According to a previous study, *T. terrestris* extract was found to possess the therapeutical potential to be used for the wellbeing of patients with age-related macular degeneration and other retinal disorders. *T. terrestris* treatments aided in reducing induced oxidative stress of ARPE-19 cells, exerting its antioxidant potential via regulating the PI3K/Akt-Nrf2 signalling pathway.[49] The oxidative stress in H9c2 cells was found to increase upon induced ischemic conditions. Due to the generation of superoxides, reactive oxygen species would impair the function of mitochondria. However, *T. terrestris* treatments could ameliorate these conditions simply by diminishing the cellular oxidative stress.[42, 50]

T.*terrestris* extracts have also been observed protecting the body from heavy metals such as cadmium and mercury, whose toxicity is generally associated with elevated free radical generation that could overwhelm the natural antioxidant system of the body.[51, 52] However, the antioxidant potential of *T. terrestris* was reported to have the ability to overcome kidney and liver damage of rats caused by cadmium toxicity.[51] Moreover, the renal protective activity against nephrotoxicity induced by mercury of a rat model can be assisted, in part, by the antioxidant activity of *T. terrestris*.[52] Taking *T. terrestris* along with regular aerobic exercise was found to possess a protective role on heart tissues against hydrogen peroxide poisoning of rats by attenuating the mitochondrial oxidative stress. This treatment was considered as the moderating factor in the biogenesis of mitochondria and found to be capable of reducing the DNA damage in the heart tissue of rat.[53]

These findings help to establish the promising potential of *T. terrestris* as an antioxidant, along with its role in alleviating disorders associated with different organs, such as the heart, kidney, liver, and eyes, among others. It appears that different fractions and commercial products of *T. terrestris* have the potential to act in such a way to protect the body from oxidative stress, and therefore, its utilization as a nutraceutical would provide vast health benefits in shielding against a range of disorders linked to oxidative stress of the body.

Anti-inflammatory activity

Several anti-inflammatory drugs, both steroidal and non-steroidal, are available to treat inflammation and related conditions but have a list of reported side effects.[54, 55] Research has shown the applicability of the *T. terrestris* herb as an alternative for synthetic drugs to prevent or cure inflammation-related complications. For instance, the herb was suggested for use in treating disorders and developing therapeutic substances.[54, 56]

A series of studies have explored the anti-inflammatory activity of *T. terrestris*, and more specifically, the activity on different fractions of chemical constituents. Different chemical constituents found in *T. terrestris*, such as flavonoids,[47] saponin,[54, 57] tribulusamide D,[56] flavonol glycosides, alkaloids and anti-inflammatory *N*-trans-ρ caffeoyl tyramine[55] are attributed to its anti-inflammatory activity.

RAW 264.7 cells have been prevalently employed in several studies that engaged in demonstrating the anti-inflammatory activity of *T. terrestris*. *In vitro* studies done on the anti-inflammatory activity of the flavonoid fraction of leaves demonstrated that it was safe for RAW 264.7 cells within the experimental concentration ranges. The effect of the flavonoid fraction on the phagocytosis of cells was attested to and proved that it held greater potential for phagocytic inhibition in preference to synthetic drugs such as dexamethasone.[47] Furthermore, previous studies have uncovered the anti-inflammatory potential of the saponin fraction of fruits[57] and leaves[58] upon RAW 264.7 cells by regulating cell deformation, NO, TNF-α content, and phagocytosis index.

Tian et al.[57] claimed that the compatibility of this fraction with an anti-inflammatory drug with high concentrations (200 μg/ml) of the saponin extract of fruit showed the same effectiveness as dexamethasone. Tribulusamide D fractions isolated from *T. terrestris* exhibited promising anti-inflammatory activity upon RAW 264.7 cells through suppressing cytokines and inflammatory mediators, downregulating the responsible enzymes for their production, and inhibiting the signalling pathways of NF-κB and p38 MAPK.[56] However, Zhao et al.[59] suggested that the underlying mechanism of the inflammatory activity of *T. terrestris* is more closely related to the inhibition of

NF-B/iNOS-NO and Akt/MAPKs signalling pathways. Furthermore, the phenolic amide fraction of the fruits contributed to its anti-inflammatory activity by inhibiting NO production in these cells that were induced by LPS.[60]

The anti-inflammatory potential of the saponin fraction of *T. terrestris* was reported to be effective in treating atherosclerosis, as it could reduce the gene expressions of adhesive molecules, such as vascular cell adhesion molecule-1, intracellular adhesion molecule-1, and E-selectin of LPS-induced HUVEC and HBMEC cells. These molecules play a critical role in the occurrence of atherosclerosis as they are involved in the adhesion process of monocytes to endothelial cells.[54, 55] In support of these findings, Zhao et al.[59] also highlighted the pronounced potential of *T. terrestris* in treating rheumatoid arthritis and atherosclerosis.

The therapeutical potential of *T. terrestris* fruits in the treatment of gut ailments is attributed to their anti-inflammatory ability. Gastrointestinal luminal environment impact from fruit-derived treatments targeting microbial peak populations and their imbalance is reported to have an influence on inflammatory molecules. In fact, *T. terrestris* treatments aided in maintaining the balance of gut microbial populations while also demonstrating a more pronounced *in vitro* anti-inflammatory activity than indomethacin, emphasizing its potential for protection against gut ailments.[61]

Flavonoid extract fractions of leaves were tested *in vivo* using an inflammatory rat model with induced ear swelling. The flavonoid fractions were effective against the degree of swelling and at times exhibited similar or stronger anti-inflammatory activities than aspirin.[47] Terrestrosin D (a steroid saponin) isolated from *T. terrestris* was confirmed to have potential as an anti-inflammatory agent by Qiu et al.[62] who found that Terrestrosin D was effective against pulmonary inflammation induced by bleomycin in rats by evaluating the changes in inflammatory markers of their bronchoalveolar lavage fluid.

The crude extracts of the areal parts of the plant were found to possess the hepatoprotective ability towards CYP, which could be partially explained by its anti-inflammatory activity. Mature rats pretreated with the extract were found to have attenuated levels of liver inflammation markers increased by CYP.[44] Additionally, the antiapoptotic potential of *T. terrestris* was found to contribute to the prevention and treatment of renal complications, such as drugs induced nephrotoxicity – further demonstrating its potent anti-inflammatory activity.[63]

The suitability of herbal extracts comprised with *T. terrestris* in treating acnes was clinically investigated.[64] Acne is the most frequently seen inflammatory skin disease. The *T. terrestris* treatment worked on the lesions of both inflammatory and non-inflammatory acnes successfully without causing significant side effects. Therefore, this treatment has been suggested to patients with mild to moderate acnes as a drug alternative.[64]

The findings of these studies highlight the employability of *T. terrestris* as an anti-inflammatory substance in comparison to common anti-inflammatory pharmaceuticals. Therefore, it is reasonable to state it can be used as an effective nutraceutical for the prevention and treatment of inflammation and related diseases.

Antidiabetic activity

Diabetes mellitus is a chronic disorder that can be characterized by changes in metabolic functions of carbohydrates, proteins, lipids, hyperglycaemia, and total or partial deficiency in insulin secretion or its functionalities.[65] Nowadays, the use of plant-based medicines in the treatment of diabetes has gained attention worldwide, as the secondary metabolites present in plants are known to possess the ability to inhibit these key carbohydrate hydrolysing enzymes.[66]

The anti-hyperglycaemic potential of *T. terrestris* was explained in previous studies by evaluating *in vitro* α-amylase and α-glucosidase activity.[66–68] exhibiting its promising antidiabetic potential. The plant's leaves, stems, roots, and seeds provoked potent inhibitory activity against both porcine and human pancreatic amylase. It was revealed that chemical constituents such as sorbinose and ethyl crotonate were found in organic extracts that inhibited human pancreatic amylase.[67]

An attempt was made to evaluate the anti-hyperglycaemic potential of the fruits of *T. terrestris* and to explore the active constituents responsible for observed activities. It was revealed that cinnamic acid amides present in the fruits had the ability to exhibit uncompetitive inhibitory activity of α-glucosidase, with *N-trans*-coumaroyltyramine being identified as the lead compound among other active cinnamic acid amide derivatives, including *N-trans*-Caffeoyltyramine and *N-trans*-Feruloyloctopamine. The A-ring hydroxyl and α, β-unsaturation carbonyl groups in cinnamic acid amide were found to display key functionalities for its α-glucosidase inhibitory activity.[68] Moreover, different extracts of its fruits have exhibited some inhibitory abilities for both α-amylase and α-glucosidase enzyme activity. It was found that the activity of different solvent fractions resulted in a varied capability in inhibition of these two enzymes, where hexane extract showed the highest inhibitory activity for α-glucosidase, while acetone extract showed the highest inhibition for α-amylase.[66]

An animal study was carried out to elaborate on the impact of *T. terrestris* on the fasting blood glucose levels of rabbits loaded with glucose. They ascertained that the treatment with methanol extract of *T. terrestris* (250 mg/kg) had the potential to reduce fasting blood sugar like glibenclamide (5 mg/kg).[65] Another study done on rats with diabetes induced by streptozotocin demonstrated that the treatments of hydroalcoholic extract of *T. terrestris*, with a dose of 50 mg/kg, were effective in reducing both fasting and postprandial blood glucose levels. The extent of its reductive effects on fasting and postprandial blood glucose levels was found to be equivalent to the effect of Olmesartan, and somewhat less than glimepiride. Furthermore, the treatments significantly increased the plasma insulin level that was suppressed in diabetic rats, and exhibited similar effects to glimepiride and olmesartan.[69]

The anti-hyperglycaemic potential of *T. terrestris* was employed in ameliorating the metabolic imbalance caused by polycystic ovary syndrome (PCOS). Women with PCOS are at high risk of developing non-insulin dependent diabetes mellitus. However, a study carried using a PCOS-induced rat model reported that the fruits of *T. terrestris* can restore the metabolic imbalance. These treatments decreased serum glucose and insulin levels while restoring glucose metabolism in the rat model, thereby proving its anti-hyperglycaemic potential.[70] Based on results attained using rat models, the streptozotocin-induced type 2 diabetes mellitus model and adrenaline hyperglycemia model, it became evident that *T. terrestris* has an efficacious impact on carbohydrate metabolism. The authors suggested that *T. terrestris* had the potential to be used in diabetic patients.[71] Furthermore, the saponins fraction of *T. terrestris* was reported to reduce the steatosis and improve the lipid profile in plasma of rats with induced diabetes.[72]

Clinical studies have been conducted to evaluate the antidiabetic properties of *T. terrestris*. Hydroalcoholic extract of *T. terrestris* showed a promising anti-hyperglycaemic effect on women diagnosed with type 2 diabetes.[73] Meanwhile, the Ayurvedic preparation of this herb was reported useful in managing microalbuminuria of patients with diabetes.[74] Such results demonstrate the potential applicability of *T. terrestris* as an herbal source in ameliorating diabetes and related complications, having shown effectiveness equal to its pharmaceutical counterparts.

Renal system protective activity

T.*terrestris* has been employed in treating renal diseases by Unani and Ayurvedic medicines.[52] There is a body of evidence which proves that *T. terrestris* can be applied safely in treatments based on toxicological studies on acute, subacute, and chronic toxicity.[15] Because of this, the nutraceutical applications of this herb have been widely evaluated regarding its renal protective aspects.

The properties of *T. terrestris* which exhibit protection of the renal system are ascribed to its compounds which possess antioxidant, anti-inflammation, and diuretic potential, such as oleic acid, octadecanoic, rhodoxanthin, cholestane, pyrimidine, pregnene, gamabufotalin and lanostane terpenoids.[75] Furthermore, the exhibited nephroprotective activity was suggested to be attributed to tigogenin, terrestrosid F, neotigogenin, gitonin and tribulusamides A and B presented in *T. terristris*.[15]

Treatments using *T. terrestris* have been shown to alleviate side effects caused by other medicines.[63, 76] The occurrence of kidney and urinary tract ailments in both developed and developing countries are seemingly associated with nephrotoxicity induced by medicines.[63] Gentamicin serves as a useful antibiotic against infections caused by gram-negative bacteria and is also used for allopathic purposes. However, the administration of this drug is ascribable to nephrotoxicity as it increases the serum uric acid, creatinine, and blood urea nitrogen. Promisingly, treatments coupled with *T. terrestris* have been shown to reverse the negative impacts caused by gentamicin,[76] with Kilany et al.[63] providing findings in support of this notion based on indicators of antioxidant parameters in kidney tissues, serum biochemical parameters and interleukins.

Nephrotoxicity induced by heavy metals is considered one of the key contributors to the onset of acute kidney injuries.[52] Research has shown *T. terrestris* having a beneficial role against nephrotoxicity of rats, which can be partially attributed to its antioxidant potential against free radicals and oxidative stress induced by mercury[52] and cadmium.[51] Furthermore, the renal protective role of *T. terrestris* was related to its ability to retard heavy metal accumulation in the renal system. Therefore, the pronounced therapeutic value of *T. terrestris* was suggested to be useful in protecting against possible heavy metal-induced renal damage.[52]

Aluminium toxicity has become an alarming human health issue due to regular contact with aluminium that comes from medicinal treatments, food additives and environmental conditions. Administration of *T. terrestris* was found to be effective in restoring the markers of kidneys of mice that were altered by $AlCl_3$ administration.[77] Utilising the CCl_4 induced rat model, different extract fractions of *T. terrestris* can ameliorate the impaired kidney functions resulting from CCl_4. Thus, the protective attributes of the plant against these scenarios were identified as its antioxidant potential, since CCl_4 and Al were greatly associated with the generation of highly reactive free radicals, lipid peroxidation, and induction of oxidative stress.[15, 77]

Historical concerns surrounding the side effects caused by plant-based medications treating nephrolithiasis are known, hence, the promising therapeutic antiurolithic potential of *T. terrestris* with its preclinical safety has been investigated. According to previous toxicity studies on a hyperoxaluria induced rat model, safe preventive and curative aspects of *T. terrestris* were produced at the dose of 750 mg/kg of optimized aqueous extract per body weight.[78] Moreover, the antilithiatic potential of *T. terrestris* was studied using renal tubular epithelial cell lines of different mammalian populations. This cell line study found that *T. terrestris* was able to protect renal cells by reducing oxalate induced injuries irrespective of the origin of the cells,[75] and that these pronounced potentials were partly due to the antioxidant and anti-inflammatory molecules present in *T. terristris*.[75, 78]

Reperfusion injuries are considered a common causative condition for the occurrence of acute kidney injuries. *T. terrestris* administration, however, provides a solution for this, as the herb has exhibited effectiveness in reducing ischemia-reperfusion induced acute kidney injuries in rats. The treatments aided in diminishing cellular damage and oxidative stress, which helped to improve the functions of kidneys.[79] A study assessed the use of isolated antilithiatic protein biomolecules from *T. terristris* in treatments associated with urolithiasis. This purified protein, with a weight of ~ 60 kDa, showed that its effectiveness on renal epithelial cells injured by oxalate induction was comparable to cystone, an herbal treatment practiced on sufferers of kidney stones. This protein increased the cell viability and decreased the LDH release, normalizing the effect induced by oxalate.[80] Therefore, the *T. terrestris* shows potential as an herbal treatment for kidney stones, further emphasizing its applicability as a nutraceutical.

A preliminary clinical trial highlighted the possible use of *T. terrestris* against urolithiasis. This study reported that *T. terrestris* was found to be responsible for altering the risk factors of urinary stones.[81] Nevertheless, more clinical studies on the renal protective potential of *T. terrestris* would be useful to realise its potential.

Hepatoprotective activity

The liver is the primary organ engaged in metabolism and detoxification of the body.[82] Elevated free radical generation takes place during metabolism, and oxidative stress can trigger liver damage and lead to liver ailments.[82, 83] Unfortunately, drugs with promising liver protective potential are scantly found, and therefore, drugs inspired by natural sources have gained attention for this purpose.[83, 84]

Drugs such as methotrexate, statins, and paracetamol that are being used in treating clinical conditions display hepatotoxic behaviour as they can trigger liver damage.[82] Paracetamol (acetaminophen, APAP) is an antipyretic and analgesic drug that can cause hepatotoxicity when it is either used taken at too high a dosage or used for a long period of time,[83, 85] but according to the findings of Al-Doaiss,[85] *T. terrestris* is capable of alleviating APAP induced-hepatotoxicity. Additionally, the effectiveness of *T. terrestris* on a rat hepatotoxicity model was highlighted when it is co-administrated with selenium, proving its suitability to be used for hepatoprotective purposes. The findings of Dar and Kaloo[83] further elaborated on the proficiency of *T. terrestris* in paracetamol-induced liver toxicity when used as synergistic extracts with medicinal plant sources. They proposed that the liver activity exhibited against paracetamol toxicity was due to its ability to maintain the integrity of tissues and its capability to act as an antioxidant.[83, 85]

The liver is an organ which could suffer greatly from the impacts of toxic compounds from the environment such as heavy metals.[84] Therefore, many studies have investigated the effectiveness of *T. terrestris* against these toxic compounds. This plant has shown to be effective at restoring liver markers negatively manipulated by toxic substances such as aluminium,[77] cadmium,[51] mercury,[84] arsenic,[86] CYP[44] and CCl_4.[15, 82]

Kilany et al.[82] demonstrated the potential of *T. terrestris* in alleviating oxidative stress, inflammation, and apoptosis in the liver by highlighting its protective activity against hepatic damage in comparison to silymarin using a CCl_4 induced rat model (as shown in Fig. 2). Additional studies *in vivo* confirmed that the oral administration of fruit extracts of *T. terrestris* had the ability to alleviate mercury-induced liver damage. This was achieved by observing the enzymological parameters of liver cells, where treatments were competent in restoring alterations in liver enzymes.[84] It was revealed that the liver tissues would drastically consume their bio-chemical constituents upon toxic stress in order to compensate for energy. However, the biochemical constituent levels in mercury-induced liver tissues were found to be restored upon both the pre- and post-treatments of *T. terrestris*.[87] Arsenic is infamous for causing cancers in different tissues, including the liver, however, endurance training combined with *T. terrestris* administration was proven to produce protective attributes against arsenic poisoning liver tissue. The underlying mechanism of this synergistic approach was ascribed to the inhibition of apoptosis and oxidative stress.[86]

The therapeutic role of *T. terrestris* in terms of liver protection is also proven by its ability to improve non-alcoholic fatty livers. This was demonstrated in a rat model where treatments were found to restore serum markers in the liver, and characteristics that were altered by non-alcoholic fatty liver induction. Thereby, *T. terrestris* demonstrated its potential to ease liver complications associated with a non-alcoholic fatty liver, such as cirrhosis, fibrosis, hepatocarcinoma and liver failure.[88]

Altay et al.[89] reported on the effectiveness of *T. terristris*' hepatoprotective ability on CCl_4 induced liver fibrosis. The occurrence of liver fibrosis is caused by chronic liver injuries, and the development of fibrosis could worsen liver conditions and lead to liver failure, cirrhosis, and liver transplants. However, the results of this study demonstrated the efficacy of herbal treatments, like *T. terrestris*, in reversing fibrosis to improve the liver's condition at a level comparable to drugs such as *N*-acetylcysteine. *T. terrestris* extract has shown its ability in liver protection by acting as an anticancer agent and has thereby been suggested for use in patients with hepatocellular carcinoma. There has been a marked increase in the occurrence of liver cancers in recent times due to increased exposure to hepatocarcinogens, including aflatoxin, nitrosamine, alcohol, and persistent virus infections such as hepatitis B.[90]

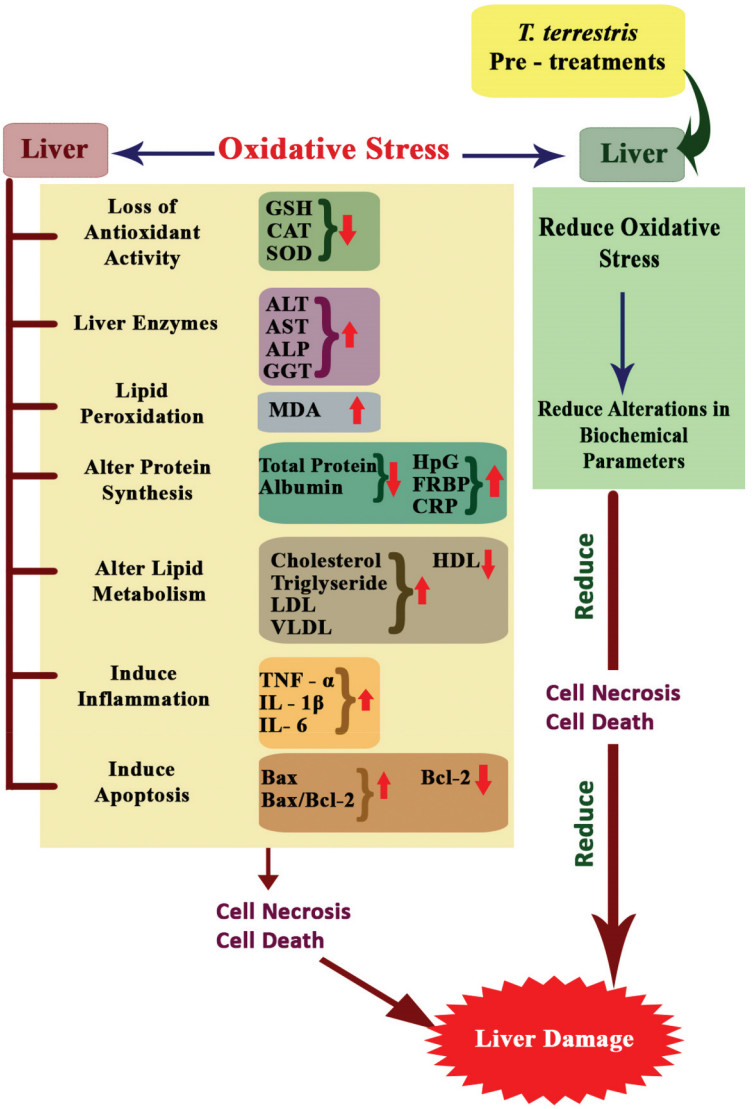

Figure 2. Liver protective activity of *T. terrestris* against oxidative stress. the oxidative stress impacts on liver functions of rats leading to liver damage through cell necrosis and death. the alteration of liver and serum biochemical parameters; antioxidant enzymes, liver enzymes, peroxidation markers, interleukin, protein expression, protein and lipid profile indicate impaired liver functions. Pre-treatments with *T. terrestris* attenuate the alterations of liver and serum biochemical parameters, thereby indicating its alleviating effect upon liver damage over oxidative stress.

When examining the data further, it became evident that *T. terrestris* has the potential to protect the liver from various internal and external harmful causes of injury. Most of the liver ailments previously discussed are related to oxidative stress, thus, it is fair to say that *T. terristris*' role as an antioxidant is a significant contributor to its ability in improving conditions associated with liver toxicity.

Cardiovascular protective activity

Cardiovascular diseases (CVDs) are prominent among worldwide non-communicable diseases, with CVD deaths being associated with: hypertension, stroke, ischaemic heart disease, rheumatic heart disease, atrial fibrillation and cardiomyopathy.[91] Among these, stroke and hypertension are identified

as one of the world's leading health issues.[92, 93] The risk of cardiovascular complications is greatly associated with hypertension, and its prevalence is drastically increasing over time,[92] while strokes are prominent causes of global deaths and long-term disabilities.[93]

The cardioprotective role of *T. terrestris* has been demonstrated in traditional medicinal practices, successfully treating heart palpitations, hypertension, and other CVDs.[92] Contemporary studies have also recognized the therapeutic and nutraceutical value of *T. terrestris*, finding that its cardioprotective activity can be attributed to its potential to serve as an antioxidant, anti-inflammatory and anti-apoptotic agent, and its capability to stabilize membranes of cardiac tissues.[12, 94]

The intestinal microbiota is found to have a great impact on overall human health as it is associated with the onset of chronic diseases including hypertension. There is a relationship between the imbalance of gut microbes and hypertension, where one can influence the other,[95] but it has also been found that *T. territris* is capable of improving the gut microbiota.[61, 95] Traditional Chinese medicine has historically used a combination of *T. terrestris* and *Eucommia ulmoides* in treating hypertension, and its effectiveness has been scientifically proven in recent studies. It was found that this combination can reduce blood pressure as well as increase the gut's microbiota diversity,[95] with *T. terrestris* specifically promoting selective gut microbial activity by retarding *Escherichia coli* and promoting *Lactobacillus rhamnosus* proliferation, respectively.[61]

"Thraatchathi Chooranam" is a cardioprotective medicine used in Indian Siddha medicinal practices, consisting of a combination of herbs which includes *T. terrestris*. This medicine was found to have a profound protective ability in an *in vivo* study with isoproterenol-induced myocardial necrosis.[94]

It is reported that ischemic events or conditions are responsible for 80% of all strokes. Ischemic conditions can obstruct the blood supply to the brain and result in neurological damage.[93] Pre-treatment of *T. terrestris* extracts were reported to have a significant effect in preventing apoptosis, alterations in mitochondria of H9c2 cells, and other cell changes caused by ischemia.[42] These findings were further supported in results reported by Reshma et al.[50] who studied the effectiveness of *T. terrestris* fruit extracts mitigating the ischemia induced mitochondrial dysfunction of H9c2 cells. This protective role was examined further in *in vitro* and *in vivo* studies on H9c2 cells and rat models, respectively. The results of these studies demonstrated the cardioprotective ability of *T. terrestris* against cardiac ischemia.[12]

Another study utilizing rat models focused on the positive impact of tribulosin, an active component of gross saponins from *T. terrestris* which prevents myocardial ischemia/reperfusion injury. The abilities of tribulosin in alleviating myocardial apoptosis and oxidative stress were demonstrated, and the underlying effects were attributed to the activation of the protein kinase C pathway.[96]

The protective role of the fruit-derived gross saponins against ischemic stroke was further researched using the ischemic rat model induced by middle cerebral artery occlusion (MCAO). Treatments with gross saponins of fruits reversed the deviations of urine metabolism and neurological defects altered by MCAO, suggesting that this fraction possessed the potential to be used in treatments for ischemic stroke.[93] This fact was further confirmed by Guo et al.[97] who investigated the mechanism of fruit-derived gross saponins in alleviating MCAO-induced ischemic stroke. LC-MS-based metabolomics integrated with network pharmacology was used in the mechanism analysis. The tested saponin fraction was found to reverse the MCAO-induced alterations in serum metabolism.

A subsequent study further elaborated on the effectiveness of these gross saponins by tying them to the underlying mechanisms of an ischemic stroke, finding that it was capable of reversing the serum metabolic alterations induced by MCAO in rats by regulating several metabolic pathways, such as carbohydrate, fatty acid, and amino acid metabolisms.[98] Furthermore, the gross saponins modulated several proteins in rat brain tissues, and among those, protein F2 was found to play a prominent role in the protective activity.[99]

Nowadays, the habit of using anabolic-androgenic steroids has increased among athletes, and thereby, the awareness of medical defects associated with abusive use of these drugs has been raised. Stanozolol, for example, is a widely used drug with a harmful impact on heart tissues. *T. terrestris*

treatments were observed protecting the cardiac tissues in rats induced with stanozolol toxicity, demonstrating its anti-apoptotic capabilities. Moreover, *T. terrestris* treatment involving high dosages and resistance training were found to produce impressive results in attenuating stanozolol-induced cardiac impairments.[100] Furthermore, *T. terrestris* supplementation along with resistance training was found to reduce the gene expression of Bax and caspase 3 and increase Bcl-2 in rats, thereby exhibiting its protective role against cardiac apoptosis.[101]

The cardio protective effect of *T. terrestris* was investigated in a number of clinical studies. For instance, a clinical trial on patients newly diagnosed with grade I essential hypertension used a commercially available extract of *T. terrestris* in combination with *Convolvulus pluricaulis Chois*. The results of this combination were promising as it was successful in controlling hypertension without producing any significant adverse effects. Treatment for 28 days showed a significant effect on blood pressure reduction, which produced results similar to drugs such as Triamterene and Benzthiazide while not exhibiting the side effects of those allopathic drugs.[92]

T.*terrestris* extract has exhibited systolic and diastolic antihypertensive properties on patients diagnosed with hypertension in mild to moderate levels and prehypertension.[102, 103] In an attempt to find the underlying mechanism of this pronounced antihypertensive potential, Wang et al.[104] explored the presence of a number of active constituents, potential targets and pathway characteristics of *T. terrestris* that were associated with treating hypertensive vascular remodelling, using a protein-protein interaction network, analyzing Gene Ontology and Kyoto Encyclopedia of Genes and Genomes pathways.

Neuroprotective activity

Neurodegenerative disorders is a big concern in the health sector. Utilization of herbal sources that provide neuroprotective materials has drawn much attention, concerning the shortfall in some treatments, expensiveness of the medications and high morbidity rates associated with neurodegenerative disorders.[105]

Many *in-vitro* studies have acknowledged the neuroprotective activity of *T. terrestris* based on its potency in acetylcholinesterase (AChE) inhibition. The extract obtained from the roots of this plant was found to exhibit dose-responsive anti-acetylcholinesterase (AChE) activity.[106]

The use of *T. terrestris* in relieving neurodegenerative diseases such as Parkinson's disease[107, 108] and Alzheimer's disease[105] were explored in rat models. Saleem et al.[107] proved the potent neuroprotective activity of *T. terrestris* in ameliorating the symptoms associated with Parkinson's disease. The neuroprotective fact was confirmed by Alzahrani et al.[108] based on an investigation carried out for testing standardized extract of *T. terrestris* against neurodegenerative ailments. The activity was partly attributed to the antioxidant and anti-inflammatory activities of the plant extract by the authors.

The protective role of *T. terrestris* extract on Alzheimer's disease was evaluated previously.[105] The behavioral and biochemical parameters of a rat model were found to be beneficially influenced by the treatments without exhibiting any acute toxicities. Furthermore, $AlCl_3$ induction was found to decrease the AChE activity and interestingly *T. terrestris* treatments improved this activity dose-dependently.[105] In this instance, the improved AChE activity was rendered as a positive point by the authors.

The saponins of *T. terrestris* seems to have drawn attention with regards to its neuroprotective activity. For instance, the neuroprotective potential of the gross saponins on a rat model was described by Zhai et al.[109] and Jiang et al.[110] highlighting its effectiveness over cerebral ischemia. According to Zhai et al.[109] the underlying mechanism was associated with its ability in suppressing the inflammatory reactions and hindering the blood-brain barrier permeability. However, based on the findings of Jiang et al.[110] the saponins exhibited the protective effect via suppressing the inflammatory cytokines production and activating the NF-κB pathway.

The saponins treatment tested on rabbits fed with cholesterol-rich diet rendered an affirmative effect on cerebral architecture.[111] On this account, the saponins were reported to impact neurons directly or by converting to steroidal saponins.[111] Another study on rabbit with high intraocular

pressure proved that the gross saponins fraction of *T. terrestris* possesses a significant protective effect on optic nerve damages.[112] Furthermore, *T. terrestris* treatment was also found to exhibit a protective role on retinal ganglion cells in rabbits with hyper-intraocular pressure.[113]

Abusive utilization of androgenic-anabolic steroids was reported to cause harmful results on cognitive functions. A study conducted on rats exposed to stanozolol showed that *T. terrestris* synergistically improved memory in combination with resistant training. This favorable impact of *T. terrestris* on impaired cognitive function was dose dependent.[114] Considering the cognitive function, the aqueous extract of fruit of *T. terrestris* was reported to improve the learning ability and memory of rats. This effect was also found to be dose-responsive where 200 mg/kg dose was identified as the most beneficial.[115]

Anticancer activity

Cancer is identified as a prominent global health issue, and it is the second most common cause of death worldwide. The replacement of synthetic drugs with plant-derived sources in treating cancers has become a novel trend, considering the side effects of more prevalent cancer treatments. There is an expanded potential for natural plant-derived sources to be employed as anticancer drugs. *T. terrestris* is reported to exert cytotoxic, pro-apoptotic and anti-proliferative activities, meaning that the use of the extracts and components of this plant as anticancer supplements has great potential.[116]

The anticancer properties of *T. terrestris* have been utilized on several types of cancer cells. In comparison to doxorubicin, the commercially available *T. terrestris* dry extract has shown promising potential in anti-tumoral activity with its strength in inhibiting the proliferative activity of human tumour cell lines, including: melanoma (UACC-62), glioblastoma (U251), renal cell carcinoma (786–0), high-grade ovarian serous adenocarcinoma (OVCAR-03), chronic myelogenous leukaemia (K562), breast cancer (MCF7), large cell lung carcinoma (NCI-H460), doxorubicin-resistant high-grade ovarian serous adenocarcinoma (NCI-ADR/RES) and rectosigmoid adenocarcinoma (HT-29).[46] Treatments utilizing *T. terrestris* have been observed to have a negative impact on the colorectal carcinoma cell line (HCT-15),[61] human liver cancer cells (HepG2),[90] human colon adenocarcinoma cells (HT-29),[116] and prostate carcinoma cells.[116, 117]

The findings of previous studies on *T. terrestris* focused on the significant role of saponin fractions in treating several types of cancers, suggesting that the anticancer properties could be attributed to the saponin components present in *T. terrestris*.[116–118] The effectiveness of its purified steroidal saponins and the potential to exert a wide range of anticancer properties were observed over several types of cancer cells.[116]

Breast cancer is considered the most prevalent type of cancer among women. Previous studies revealed that saponin and methanolic fractions of the leaves and seeds of *T. terrestris* exerted anticancer properties against human breast cancer cells by inducing both intrinsic and extrinsic apoptotic pathways.[119] Based on the findings of in-depth studies, nautigenin types of steroidal saponin were found in the active fraction of saponin extracts procured from seeds. Thus, the findings of this study exhibited the anticancer potential of saponin fractions of *T. terrestris*, and demonstrated how the nautigenin saponins can be used as a therapeutic drug in treating breast cancers.[118] The marked protective activity against breast cancer was further supported by Goranova et al.[120] who studied the impact of saponin extract over selected gene expression of breast carcinoma cells. 32 genes associated with the formation and development of breast cancers were analyzed, and they found that only 3 genes (CCR7, CXCR4 and BCL2) were impacted by the saponin. The three genes' expressions were downregulated upon *T. terrestris* saponin treatments as it diminished the cancer cells' potential to metastasize, and activated apoptosis by CXCR4 and BCL2, respectively.

Terrestrosin D is a prominent steroidal saponin found in *T. terrestris*, which has been observed demonstrating antiangiogenic and antitumor properties in its suppression of the occurrence of prostate cancer. Based on these promising results, researchers have suggested that Terrestrosin D be used as a first-line therapy for young patients with prostate cancer.[117]

Clinical practices have begun adopting tiliroside, a major compound in steroidal saponins found in *T. terrestris*, as an alternative therapy for liver cancer. Liver cancer is responsible for a great sum of global cancer-related deaths due to its truculent nature, and the dearth of therapies with any significant effectiveness. However, tiliroside was found to be effective against the progression of liver cancers because of its inhibition of carbonic anhydrase XII, a zinc metalloenzyme associated with the progression of cancer.[121] The NF-κB transcription factor is an important mediator of carcinogenesis-associated inflammation, cell proliferation and survival. The underlying mechanism of the protective action of *T. terrestris* against liver cancer was attributed to its ability in suppressing NF-κB signalling, and thereby, the promotion of apoptosis and inhibition of the proliferation of human liver cancer cells.[90]

T.*terrestris*' effectiveness in combatting oral cancer cells was demonstrated by its ability to inhibit autophagic flux in cancer cells (as increased autophagy being related to the progression of cancers), because its extracts were capable of inhibiting the expression of ATG4B, a prominent autophagy protease.[122] The application of compounds coming from natural sources in treating leukaemia and lymphoma has recently become an area of focus. Use of *T. terrestris* in the treatment of leukaemia found that the alkaloid extract of fruits could induce apoptosis activity of acute T cell leukemic cells. Furthermore, the *N*-feruloyltyramine derivatives found in this alkaloid fraction were found to possess anti-leukemic potential.[123]

Upon closer examination of these findings, it became evident that *T. terrestris* plays a significant role as a therapeutic agent for cancers in various aspects. The potential of *T. terrestris* to enhance human health by employing it as a nutraceutical in the prevention and management of a number of diseases has been researched thoroughly and demonstrated both *in vivo*, *in vitro* studies (summarised in Table 1) and clinical studies (summarised in Table 2)

Toxicological studies

Possible toxicities of *T. terrestris* have been investigated in the literature. The safeness of *T. terrestris* was reported at clinical dose ranges.[15, 30, 40, 47, 78, 102, 103, 124]

However, some studies have alarmed on the possible toxicities of *T. terrestris*.[125] A recent study on Terrestrosin D isolated from *T. terrestris* found hepatorenal toxicity in Sprague-Dawley rats. The induced toxicity was reversible after 14 days of treatment withdrawal.[126] However, an ayurvedic compound called "Gokshuradi guggulu" which contains *T. terrestris* extract was tested for oral toxicity in Wistar rats and it was found to be safe up to 2700 mg/kg/day for 28 days continuously.[124]

T.*terrestris* was found to cause motor neuron disease in sheep.[127, 128] Furthermore, *T. terrestris* related hepatogenous photosensitisation was reported in both sheep and goats.[129] Aslani et al.[130] and McDonough et al.[131] reported supporting evidence of sheep poisoning which is in consistence with that of Jacob and Peet.[129]

Some clinical incidences were reported on the aspect of *T. terrestris* toxicities. According to a recent clinical study, the onset of ventricular fibrillation arrest of male patients with aborted sudden cardiac death was suspected to be associated with the *T. terrestris* induced dihydrotestosterone and testosterone increase.[132] Furthermore, a priapism incident that occurred upon *T. terrestris* supplementation was reported.[133] Another case study reported the probability of *T. terrestris* in increasing transaminases via rhabdomyolysis.[134] The consumption of *T. terrestris* was also reported to cause severe nephrotoxicity in a young healthy man.[135] A clinical study further investigated this aspect and found that *T. terrestris* might promote toxicity in kidney by causing acute kidney injury and hyperbilirubinemia.[136]

Table 1. Nutraceutical potential of *T. terrestris* screened from *in vivo* and *in vitro* studies.

plant type or product type/origin of the plant	Study design and treatments	Observations upon *T. terrestris* treatment	Studied nutraceutical property	Reference
Methanol extract of whole plant excluding fruit/India	Male albino Wistar rats with myocardial ischemia induced by isoproterenol pre-treated with extract	Decreased serum CK, LDH, serum GOT, CK myocardial B fraction, serum GPT: reduced the expression of TNF-α, IL-6: decreased MPC-1, IL-1β and increased IL-10	Protective activity against cardiac ischemia	Reshma et al.[12]
Methanol extract of dried fruits/India	H9c2 cells. pre-treated with extract for 24 h before the induction of ischemia	Significantly reduced LDH: significantly increased antioxidant potential, GSH, SOD, CAT: protected mitochondrial transmembrane: improved respiratory complexes activities, ATP consumption, mitochondrial protein expression and managed mitochondrial gene expression	Cardioprotective potential against myocardial ischemia claimed by antioxidant and cytoprotective potential	Reshma et al.[50]
Flavonoid fraction of leaves obtained from Ethanol extract/China	Mice with xylene-induced ear oedema. Pre-treated with flavonoids extract, aspirin (positive control)	Reduced the degree of swelling in dose responsively. The doses of 25 and 50 g RMM/kg exhibited equal and significantly stronger anti-inflammatory activities than aspirin respectively.	anti-inflammatory activity	Tian et al.[47]
Ethanol extract of whole plant/India	Adult Wistar albino male rats Administrated with $CdCl_2$, $CdCl_2$ with extract	Significantly increased the antioxidant levels in liver and kidneys; CAT, SOD, GSH: reduced the peroxidation markers; protein carbonyls, thiobarbituric acid reacting substances: increased the functional markers of liver; albumin, total protein: decreased kidney functional markers; BUN, serum creatinine: reduced the alterations of hepatocytes caused by Cd and significantly reduced the Cd levels of kidney and liver	Kidney and liver protection against Cd toxicity	Lakshmi et al.[51]
Ethanol (70%) extract of fruits/China	Human retinal pigment epithelial cells; ARPE-19 with induced oxidative stress and treated with the extract	Obstruct the apoptosis of H_2O_2 treated cells by regulating Bcl2, Bax, cleaved caspase-3, and caspase-9: decrease ROS: increase SOD activities and their mRNA expression	Antioxidant potential	Yuan et al.[49]
Tribulusamide D fraction of fruits/ South Korea	LPS induced RAW 264.7 cells treated with tribulusamide D fraction	Reduced the cyclooxygenase-2 and inducible NOS2 expression, decreased the prostaglandin E2 and NO production respectively: diminished the expression of TNF-α, IL-6, IL-10	Anti-inflammatory activity	Lee et al.[56]
Terrestrosin D	Male KM mice administrated with bleomycin, Terrestrosin D and co-administration of Terrestrosin D and bleomycin	Significantly decreased neutrophils, macrophages number, macrophages percentage in monocyte-macrophage system, lymphocytes, TNF-α, TGF-β1, PDGF-AB, IL-6, IL-8: reduced the deterioration in the lung	Anti-inflammatory activity and anti-fibrotic potential in lungs	Qiu et al.[62]
Water extract of plant/China	LPS induced RAW 264.7 treated with the extract	Decreased NO production, TNF-α, IL-1β, IL-6, NF-κB, NOS2, phosphorylation of Akt and MAPKs (ERK, MEK, JNK, p38)	Anti-inflammatory activity	Zhao et al.[59]

(*Continued*)

Table 1. (Continued).

plant type or product type/origin of the plant	Study design and treatments	Observations upon *T. terrestris* treatment	Studied nutraceutical property	Reference
Commercially available fruit powder liquid extract	Male Wistar rats Gentamicin induced nephrotoxicity, pre-treated and administrated with *T. terrestris*	Increased serum albumin and total protein, SOD, CAT, GST: decreased BUN, uric acid, creatinine, MDA in kidney, NO, serum levels of β2 M, KIM-1, caspase-3 expression and histopathology in kidney tissues	Nephroprotective activity	Kilany et al.[63]
Commercially available hydroalcoholic extract/India	Male Wistar rats With mercury chloride-induced nephrotoxicity, pre-treated and administrated with *T. terrestris* together with other plant extracts	Significantly decreased BUN, MDA, serum creatinine: increased GPx, GSH, SOD: diminished KIM-1 level, liver FABP level, accumulation of mercury in kidney tissues	Renal protective activity against heavy metal-induced toxicity	Yadav et al.[52]
Ethanol extract of the whole plant subsequently extracted with petroleum ether, aqueous methanol, dichloromethane/Saudi Arabia	Male Wistar albino rats with CCl_4 induced toxicity, pre-treated and administered with different extract fractions, silymarin	Reduced AST, ALT, GGT, ALP, bilirubin, LDH, CK, uric acid, urea, creatinine, sodium, calcium, potassium, histopathological changes in kidney cells, MDA: increased non-protein sulfhydryl groups, total protein in liver and kidney tissues, dichloromethane fraction: significantly reduced urea, serum creatinine, uric acid compared to silymarin	Nephroprotective activity and mild hepatoprotective activity	Kader et al.[15]
Aqueous extract of mature fruits/India	Hyperoxaluria induced male Wistar rats treated with the extract	Increased urinary Mg and decreased Ca, P, uric acid: decreased serum urea, creatinine, uric acid restoring electrolyte balance: increased GSH: decreased lipid peroxidation in curative and prophylactic regimen: reduced the size and number of urinary crystals, inflammation, downregulate p38MAPK (at protein and gene level) expression	Anti-urolithiatic Potential	Kaushik et al.[78]
70% Ethanol extract of fruits/India	Male mice of Swiss strain with aluminium chloride-induced toxicity treated with the extract	Restored MDA and antioxidant enzyme activities in kidney, liver, testis, brain by reducing MDA and increasing GPx, CAT, SOD: restored kidney and liver markers; reduced the AST, ALT, urea, creatinine: increased albumin of serum: restored brain markers: reduced the activity of LDH and CK in brain: restored testicular markers by reducing LDH and ALP activities in testis	Activity against aluminium toxicity	Kumar and Singh[77]
Aqueous extract of commercially available mature fruits/India	Renal epithelial cells; MDCK, PK 15, NRK-52E exposed to oxalate and co-treated with extract	Hindered the nucleation and aggregation of oxalate crystals on cell surface: reduced the oxidative stress by decreasing H_2O_2 levels, apoptosis and necrosis in oxalate injured cells: increased the cell viability.	Antilithiatic potential	Kaushik et al.[75]

(*Continued*)

Table 1. (Continued).

plant type or product type/origin of the plant	Study design and treatments	Observations upon *T. terrestris* treatment	Studied nutraceutical property	Reference
70% Ethanol extract of aerial parts/ Iran	Ischemia and reperfusion-induced male Sprague-Dawley rats pre-treated with extract	Reduced creatinine and urea nitrogen in plasma: high urine osmolarity and creatinine clearance: low absolute excretion of sodium and fractional potassium excretion: reduced oxidative stress and cellular damage	Protection against acute kidney injury	Najafi et al.[79]
Methanol extract of the whole plant (excluding fruits)/Saudi Arabia	Adult male albino rats with APAP toxicity co-administrated with extract/selenium	Reduced; ALP, AST, ALT, Total bilirubin: increased total protein: reduced histopathological lesions, glycogen depletion of hepatocytes	Hepatoprotective activity against APAP (drugs)	Al-Doaiss[85]
70% methanol extract of seeds	Male Wistar rats fed with high fructose diet, co-fed with extract	Reduced ALT, AST, ALP, bilirubin, total cholesterol, LDL, VLDL: increased albumin: ameliorated histopathological alterations in liver tissues	Protective activity against non-alcoholic fatty liver	Almasi et al.[88]
Methanol-water extract of fruit extract powder (minimum 40% saponin)	Male Wistar rats induced with CCl_4 and treated with the extract	Reduced ALT, AST, GGT, liver and serum MDA, liver fibrosis, steatosis, inflammation, necrosis levels, collagen 1, NF-κB, TNF*α*: increased Nrf2	Protection against liver fibrosis	Altay et al.[89]
Commercially available aqueous extract of fruit/USA	Male Sprague Dawley rats induced with CCl_4 and pre-treated with extract	Increased serum total protein, HDL, serum albumin: decreased direct bilirubin, total bilirubin, cholesterol, lipoproteins (LDL and VLDL), triglycerides, AST, serum ALT, GGT, ALP: decreased inflammatory biomarkers; FABP, C-reactive protein, haptoglobin: decreased serum interleukins TNF-*α*, IL-1*β*, IL-6: reduced the expression of Bax: increased Bcl-2 expression: preserved the liver architecture	Liver protective activity	Kilany, El-Beltagy, and El-Sherbeeny[82]
Aqueous extract of dried fruits/Korea	Human cancer cell line; HepG2 treated with the extract	Hindered the proliferation, clonogenicity, induced apoptosis of cells: suppressed the expression of NF-κB dependent reporter gene, phosphorylation and degradation of IκB*α*, IKK activity: inhibited the transcription of genes engaged in anti-apoptosis, invasion, cell cycle regulation	Protective activity against hepatocellular carcinoma	Kim et al.[90]
Country: Iran Type: Ethanol extract of fruits	Male Wistar rats induced with arsenic and treatments with extract and endurance training	Synergistic treatments reduced the MGMT, MDA, cytochrome C, prooxidant-antioxidant balance: increased hepatic ATP	Liver protection activity against arsenic poisoning	Farokhi et al.[86]
Commercially available formula granules	spontaneously hypertensive male rats treated with ET (*Eucommia ulmoides* and *T. terrestris* combination)	Steady declined in blood pressure: improved intestinal microbiota by changing the composition and structure of the imbalanced microbiota, ameliorating the morphology of colonic tissues and increasing *Eubacterium* count	Anti-hypertensive activity	Qi et al.[95]

(*Continued*)

Table 1. (Continued).

plant type or product type/origin of the plant	Study design and treatments	Observations upon *T. terrestris* treatment	Studied nutraceutical property	Reference
Tribulosin from *T. terrestris*	Ischemia, reperfusion-induced Wistar rats (male/female) treated with tribulosin	Increased SOD: significantly decreased AST, malondialdehyde MDA, LDH, CK: reduced the size of infarct, rate of myocardial apoptosis: increased the PKCε, Bcl-2 expression and diminished caspase-3 and Bax expression	Cardioprotective activity against ischemia, reperfusion	Zhang, Li, and Yang[96]
Alcohol extract of the fruit	Stanozolol administrated Sprague Dawley male rats, resistant training and treated with the extract	Significantly reduced P53, Bcl-2, Bax, caspase 3, Bax/Bcl-2 ratio	Cardioprotective activity pertaining to antiapoptotic effects	Arjmand, Abedi, and Hosseini[100]
Commercially available the gross saponins of *T. terrestris* (GSTT) fruit, purity of saponins >60%/China	Sprague Dawley male rats injected with GSTT before and after middle cerebral artery occlusion (MCAO)-induced ischemic stroke	Reversed the downregulated protein expression including F2, Fga, Fgb, Fgg, C3, Plg in brain tissues indicating the ability in regulating complement and coagulation cascade	Protective activity against ischemic stroke	Wang et al.[99]
Methanol extract and saponin fraction from dried leaf, seed collected in the fruiting period/India	Human breast cancer cell line; MCF-7	Cytotoxicity against MCF-7 cells: DNA fragmentation, apoptosis induction, significantly upgrade the activity of caspase 3 in cells: induced intrinsic apoptotic pathway by increasing p53, Bax gene expression: induced extrinsic apoptotic pathway by decreasing Bcl-2, AIF, FADD and increasing caspase 8 gene expressions of cells	Anticancer properties against breast cancers	Patel et al.[119]
hydroalcoholic extract of dried fruits/Iran	Prostate carcinoma cell line (LNCap-FGC-10), Human colon adenocarcinoma cell line (HT29) treated with the extract	Induced apoptosis in cells: exhibited cytotoxic activity with significant-high toxicity on prostate cancer cells	Anticancer properties against human prostate and colon cancer	Pourali, Yaghoobi, and Sormaghi[116]
Terrestrosin D isolated from *T. terrestris*	Male nude mice xenografted with PC-3 cells subsequently treated with terrestrosin D	Hindered the growth of tumour: promoted apoptotic cell death: suppressed angiogenesis	Anticancer properties against prostate cancer	Wei et al.[117]
Tiliroside/USA	Human hepatocellular carcinoma cell; Hep3B, SNU-449 treated with Tiliroside	Inhibited arcbonic anhydrases XII (CAXII) expression, formation of 3D spheroid, CD133 expression, E2F1 and E2F3 expression, cell proliferation, migration, invasion increased caspase-3 activity	Inhibitory potential against the development of liver cancer	Han et al.[121]
Standardized dry extract (total saponin content, 43.21%) and saponin enriched extract of commercially available dry extract/Brazil	Human tumour cells: U251, UACC-62, MCF7, NCI-ADR/RES, 786–0, NCI-H460, OVCAR-03, HT-29, K562 treated with the extract	Saponin enriched extract showed a high anti-proliferative activity against 786-O cells with moderate activity for other cell lines. Standardized dry extract showed moderate activity for cell lines.	Anti-proliferative activity for tumour cell lines	Figueiredo et al.[46]
Alkaloid extract of dried extract/India	Acute T cell leukemic cell line; Jurkat E6–1 treated with alkaloid fraction	Induced cytotoxicity in cells dose responsively: promoted fragmentation of DNA, phosphatidylserine translocation, caspase-3 activity: significantly impacted on the expression of critical genes; NFKB1, DFFA, TP53, CASP8, AIFM, FADD, TNFR1	Anti-leukemic potential	Basaiyye et al.[123]

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Table 1. (Continued).

plant type or product type/origin of the plant	Study design and treatments	Observations upon *T. terrestris* treatment	Studied nutraceutical property	Reference
70% ethanol extract of dried flowers/ Iran	Male Wistar rats administrated with extract	Significantly increased testosterone level; increased sperm count, LDH; spermatogonia, leydig, spermatid cells	Activity in Improving fertility	Haghmorad et al.[26]
Commercially available dry extract/ China	Adult male Swiss albino mice pre-treated with extract and then treat with Cyclophosphamide	Ameliorated the adverse effect of cyclophosphamide by reducing reactive species, lipid peroxidation, protein carbonylation, reversed the alterations in antioxidant enzymes (CAT, SOD, GPx, GR, GST): increased 17β-Hydroxysteroid Dehydrogenase activity	Protective activity on the male reproductive system against side effects of drugs	Pavin et al.[29]
Saponin fraction	Male Sprague–Dawley rats with streptozotocin-induced diabetes mellitus type 2 treated with saponin	Reduced the deposition of lipid droplets in hepatocytes: improved the lipid profile of plasma; reduced triglycerides, cholesterol, increased HDL and reduced the total cholesterol/HDL ratio	Liver protective activity against type 2 diabetes mellitus	Misiakiewicz-Has et al.[72]
Methanol extract of dried fruit/ Pakistan	Male Wistar rats with haloperidol-induced Parkinson's disease, treated with the extract	Significantly impacted on the behavioral performance by enhancing the muscular strength, stride strength, locomotor functions, reversion of catatonia: Significantly increased the levels of CAT, SOD, GSH, GPx: reduced MDA, acetylcholinesterase levels: demoted the expression of TNF-α, AChE, α -synuclein, IL-1β	Neuroprotective activity against Parkinson's disease.	Saleem et al.[107]
Commercially available standardized extract (minimum 45% saponins)	Male Swiss albino mice with rotenone-induced Parkinson's disease, treated with the extract	Reduced rotenone-induced motor dysfunction; reduced the expression of markers of DNA damage and inflammation; MTH1, 8-OHdG, iNOS, COX-2: Higher doses (10 mg/kg) suppressed $CD_{11}b$, MDA activity and enhanced SOD, GSH, CAT activity	Neuroprotective activity against Parkinson's disease.	Alzahrani et al.[108]
Methanol extract of fruits/Pakistan	Male Wistar rats with aluminium chloride-induced Alzheimer's disease, treated with the extract	Ameliorated the impact of Alzheimer's disease. Significantly improved the behavioral performance, neurofibrillary tangles, AChE activity, CAT, SOD, GSH, GPx: decreased MDA	Neuroprotective activity against Alzheimer's disease	Chauhdary et al.[105]
Gross saponins of *T. terrestris* (purity >96%)	Male Wistar rats subjected to MCAO, pre-treated with extract	Significantly decreased the brain edema, infarct volume, abnormalities in neuro-behavior: reduced the brains' pathological changes: decreased the serum TNF-α and IL-1β: increased NF-κB levels in brain	Protection against cerebral ischemic injury	Jiang et al.[110]

Abbreviations: MDA,Malondialdehyde; NO, Nitric oxide; β2 M, Beta 2 microglobulin; KIM-1, Kidney injury molecule-1; GST,Glutathione S transferase; BUN, Blood urea nitrogen; FABP, Fatty acid binding protein; AST, Aspartate aminotransferase; ALT, Alanine aminotransferase; LDH,Lactate dehydrogenase; ALP,Alkaline phosphatase; ACP, Acid phosphatase; MGMT, O-6-methylguanine-DNA methyltransferase; GPx, Glutathione peroxidase; GR,Glutathione reductase; GST,Glutathione S-transferase; GSH, Glutathione; CAT,Catalase; SOD, Superoxide dismutase; HDL, High-density lipoprotein; LDL, Low density lipoprotein; VLDL, Very low density lipoprotein; GGT, Gamma-glutamyltranspeptidase; TNF-α, Tumor necrosis factor-α; IL, Interleukin; GPT, Glutamate pyruvate transaminase; GOT, Glutamate oxaloacetate transaminase; CK, Creatine kinase; NF-κb, Nuclear factor kappa B; Nrf2, Nuclear factor erythroid-2-related factor 2; MAPKs, Mitogen-activated protein kinases; NOS2, Inducible nitric oxide synthase; CAXII, Carbonic anhydrases XII; GSK3B, Glycogen synthase kinase-3 beta; HpG, Haptoglobin; CRP, C-reactive protein; ROS,Reactive oxygen species; LPS, Lipopolysaccharides; 8-OHdG, 8-hydroxy-deoxyguanosine; AChE, acetylcholinesterase.

Table 2. Nutraceutical potential of *T. terrestris* screened from clinical studies.

Form of *T. terrestris*	Design of the clinical study	Dose	Observations upon *T. terrestris* treatment	Studied nutraceutical property	Reference
T. terrestris tablet	A randomized, single-blind, placebo-controlled trial employing CrossFit® athletes within 18 and 50 years	770 mg of the supplement daily for 6 weeks	Significantly increased testosterone levels, however, did not impact anaerobic performance, the composition of the body and total strength	Ability in testosterone boosting	Lázaro et al.[34]
T. terrestris tablet (250 mg)	A prospective, randomized, double-blind, placebo-controlled clinical trial employing women in the postmenopausal stage observed with sexual dysfunction	Three times daily for 90 days.	Improved the sexual desire and the interest, foreplay, interaction with partner, intercourse, vaginal lubrication, sensation in the genital region, capability of having an orgasm	Ameliorating activity in sexual dysfunction of menopausal women	Postigo et al.[35]
Aphrodit capsule contain *T. terrestris* (40 mg), *Zingiber officinale* (12.27 mg), *Crocus sativus* (3 mg), *Cinnamomum zeylanicum* (11 mg)	A randomized, triple-blind, controlled trial employing women within 50–60 years, in the postmenopausal stage	Two times per day for 4 weeks	Reduced the genitourinary, physical and mental related symptoms of menopause	Potent activity in decreasing the symptoms of menopause	Taavoni, Ekbatani, and Haghani[37]
Libicare®	Exploratory, prospective, non-controlled, observational trial employing women within 45–65 years, in postmenopausal stage and risk of having sexual dysfunction	2 tablets daily for 2 months	Increased the sexual excitement, desire, lubrication, orgasm, satisfaction, testosterone, sex hormone-binding globulin	The ability to improve the sexual function of postmenopausal women	Palacios et al.[36]
Tribestan/Sopharma AD, Bulgaria (250 mg)	A prospective, randomized, double-blind, placebo-controlled clinical trial employing Males;18 and 65 years with mild or moderate erectile dysfunction and with or without HSDD	3 × 2 tablets daily for 12 weeks	Significantly improved the international index of erectile function, orgasmic function, sexual desire, intercourse and overall satisfaction	Activity against male sexual dysfunction	Kamenov et al.[16]
Androsten (250 mg of *T. terrestris* dried extract per capsule)/Brazil	Men, within 18–50 years, with altered semen evaluation	One pill in every 8 hr for 84 days	Significant reduction in body fat: increment in lean mass and levels of dihydrotestosterone: significantly improved sperm concentration, liquefaction time and motility	Activity in improving the quality of semen	Salgado et al.[27]
Capsules (250 mg) of *T. terrestris* extract with ≤45% steroidal saponins/Trib Gold	A placebo-controlled trial employing aging men with partial androgen deficiency with erectile dysfunction	Three times daily for 3 months	Increased AST, total prostate-specific antigen: significant increment in total testosterone: validated Arabic index of erectile function score,	Potential against erectile dysfunction with partial androgen deficiency	Din et al.[25]

(*Continued*)

Table 2. (Continued).

Form of *T. terrestris*	Design of the clinical study	Dose	Observations upon *T. terrestris* treatment	Studied nutraceutical property	Reference
T. terrestris	A randomized Study employing women in premenopausal and postmenopausal stages	94 mg, three times per day or 280 mg once per day for 90 days	Increased total, free and bioavailable testosterone levels	Effectiveness on female sexual dysfunction.	Vale et al.[40]
Herbal extracts comprised with *T. terrestris* along with Mangosteen, *Lithospermum officinale*, *Houttuynia cordata* Thunb	Randomized, double-blinded, controlled trial employing patients with mild to moderate acne within 20–40 years.	Two times per day (morning and evening) for 8 weeks	Significantly decreased the lesion count of both inflammatory and non-inflammatory acne and the expression of keratin 16, IL-1α, IL-8: downregulated the TNF-α expression	Anti-inflammatory activity against acne	Yang et al.[64]
Decoction enema and unctuous enema	A randomized study employing diabetic patients with microalbuminuria (30 and 300 mg of urine albumin excretion in 24 hour)	Treatment for 8 days; unctuous enema on1st and 8th, decoction enema on 2nd to 7th days	Decreased urine albumin, blood sugar, blood pressure	Anti-diabetic activity	Ramteke et al.[74]
Hydroalcoholic extract	A double-blind randomized placebo-controlled trial employing women of 40 to 60 years with type 2 diabetes	Capsules (containing 500 mg of extract powder) two times per day for 3 months	Significantly decreased blood sugar level, total cholesterol, LDL: significant impact on triglyceride and HDL	Hypoglycemic potential on type 2 diabetes	Samani et al.[73]
Water extract of leaves, flowers and fruits	Patients with renal stones within 22–60 years	10 mL of extract per day for 7 days	Significantly decreased uric acid in urine and serum: significantly decreased the oxalate, citrate, glycosaminoglycan, proteins in urine	Anti- urolithiasis potential	Arasaratnam et al.[81]
Solid water extract of whole plant and fruits	Patients with non-complicated, mild to moderate hypertension with headache, insomnia and giddiness, palpitation etc.	3 g/day given in 3 divided doses	Reduced the symptoms of headache, insomnia, giddiness, palpitation: decreased systolic, diastolic, mean blood pressure and pulse rate: increased 24-hour urinary volume	Antihypertensive potential on mild to moderate hypertension	Murthy, Dubey, and Tripathi[102]
Dried, powder of fruits	Randomized, double-blind, placebo-controlled, clinical trial employing pre-hypertensive patients over 18 years	6 g/day given in 3 divided doses for 2 months	Decreased systolic, diastolic blood pressure	Effectiveness against pre-hypertension	Siddiqui et al.[103]

Conclusion

This review discussed the potential of *T. terrestris* in promoting human health as a nutraceutical, based on evidence found in *in vitro*, pre-clinical, and clinical studies. Previous findings on the phytochemical and pharmacological properties of *T. terrestris* have greatly contributed to exemplifying its value as a nutraceutical. The whole plant of *T. terrestris*, including its leaves, fruits, seeds, and flowers, possess the ability to be used in health promotion. Currently, *T. terrestris* extracts and other derived products are available in the market and are commonly served as supplements for various aspects of health. This review examined various physiological mechanisms of the human body, and how they interacted with both the administration of different parts of the *T. terrestris* plant, or commercially available products. By presenting physiological responses to *T. terrestris* treatment at a cellular level, these in-depth reviews were carried out to fully elucidate these treatments' effectiveness as antidiabetic, anticancer, and testosterone boosting agents, and their roles as cardiovascular, renal system, and liver protective agents.

The antioxidant and anti-inflammatory activity of *T. terrestris* show that it has great potential in the management of numerous acute and chronic diseases. According to various publications of *in vivo* and *in vitro* studies, *T. terrestris* and its products can be used as supplements in first-line therapies in place of specific pharmaceuticals, and have also demonstrated their capacity to ameliorate side effects of pharmaceuticals and negative impacts of environmental pollutants. *T. terrestris* could be applied as an herbal extract or a dietary supplement as a nutraceutical, as evidence for applications of *T. terrestris* as a food source is scantly found. Notably, while the role of *T. terrestris* as a nutraceutical in human health promotion is evident in various aspects of health, there is still a need for further clinical studies to produce more in-depth evidence of its capabilities and applications.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Author contribution

J.Lu. conceived the idea, R.G. & H.N. performed the review and wrote the initial draft, A.L. drew and prepared the graphs, J.Li, T.Y., B.Z. and J.Lu edited the draft.

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