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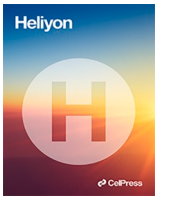

Review article

Promising phytopharmacology, nutritional potential, health benefits, and traditional usage of *Tribulus terrestris* L. herb

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ABSTRACT

Traditional medicines are becoming more popular as people become more aware of the dangers of synthetic pharmaceuticals. *Tribulus terrestris* L., (Gokharu) an annual herbaceous plant, has been extensively utilized by herbalists for numerous medicinal purposes. *T. terrestris* has been studied for its multiple therapeutic effects, including immunomodulatory, aphrodisiac, anti-urolithic, absorption enhancer, cardioprotective, antidiabetic, anti-inflammatory, hypolipidemic, neuroprotective, anticancer, and analgesic properties. Saponins and flavonoids are two examples of beneficial substances that have recently been found in *T. terrestris*. These chemicals are very important for a variety of therapeutic effects. Numerous studies have shown that *T. terrestris* products and various parts may have antioxidant, anti-inflammatory, anti-cancer, anti-diabetic, testosterone-boosting, and liver protective effects. According to the published evidence, *T. terrestris* boosts testosterone secretion, regulates blood pressure, and protects the human body against injuries. The cardiovascular, reproductive, and urinary systems are all severely impacted. Due to its potent bioactive compounds, the literature evaluated from a wide range of sources including books, reports, PubMed, ScienceDirect, Wiley, Springer, and other databases demonstrated the extraordinary potential to treat numerous human and animal ailments. Our review is different from other published articles because we explored its importance for humans and especially in veterinary like poultry health. It could also be used as an aphrodisiac to treat different fertility-related disorders in human and animal science. More research into the pharmacodynamics of herbs like *T. terrestris* is needed so that it can be used in a wider variety of nutraceutical products for humans and poultry.

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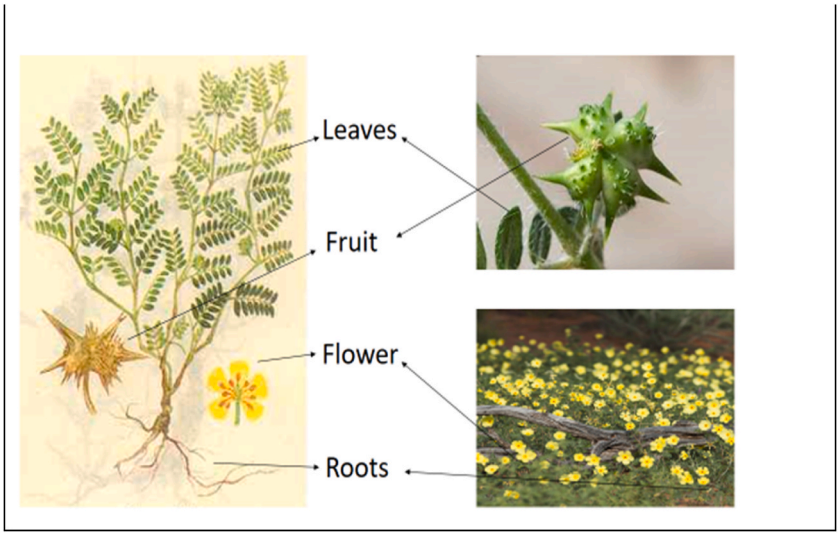

Fig. 1. *Tribulus terrestris* and its different parts.

1. Introduction

Nowadays, there is great concern about the use of herbal medicines worldwide. Additionally, laboratory studies have been conducted to explore the pharmacological characteristics of bioactive compounds and their potential to treat a range of illnesses in both animals and humans. The integration of traditional medicine and ethnopharmacology has facilitated the introduction of numerous novel drugs into the global market [1–4]. For several decades, herbal remedies have been used to treat and control a variety of diseases. Herbal medicines represent a potential substitute for traditional artificial treatments owing to the minimal side effects and are considered safe and effective in treating human ailments [5,6,152,153]. Synthetic medications can generate spectacular outcomes in most situations, but their adverse effects are a serious worry. Many chemicals employed in modern medicine have their origins in plants. Whether or not there is a scientific basis for the use of most herbal products, they are used because of their safety profile, easy availability, and low cost [7–9]. Both in the present and the future, phytochemicals will play a significant role. The side effects of synthetic medications are our primary concern, even though synthetic drugs can produce more dramatic results in most cases. Numerous compounds used in current medicine have a plant origin [10–12]. Every medicinal plant used in traditional medicine should be scientifically evaluated to reveal its active ingredient, which can be used as a phytomedicine [154]. Various herbs are claimed to improve human sexual dysfunction in this vast collection of phytoproducts [7,13].

Tribulus terrestris plant has been used as a cardiotonic, appetizer, aphrodisiac, anti-urolithiasis, diuretic, emollient, anti-helminthic, digestive, and antibacterial agent in traditional medicine. This herbal medicine has anti-hypertensive, *anti*-hyperlipidemic, and antioxidant properties [14]. *T. terrestris* is also used in traditional medicine in various countries to treat multiple disorders [15]. The entire *T. terrestris* plant's phytochemical, as well as phytopharmacological activities, have been intensively explored, including diuretic, anti-urolithiasis, anti-hypertensive, analgesic, *anti*-hyperlipidemic, immunomodulatory, antidiabetic, anticancer, anti-helminthic, aphrodisiac, antibacterial, hepatoprotective, and anti-inflammatory properties [16–18]. Because of its potassium-sparing, cardioprotective, and *anti*-hyperlipidemic properties, *T. terrestris* may have the potential of herbal therapy for successful blood pressure control, according to the literature [17,19]. *T. terrestris* is a plant that has been used in Chinese and Indian medicine for a long time. Other pharmacological characteristics of the plant have also been reported. Dietary supplements containing *T. terrestris* extracts are claimed to improve muscle tone, have a bio-stimulating action, and enhance spermatogenesis in many study publications [7].

Protodioscin is the main saponin found in the extracts made from this *T. terrestris* plant's air-dried aerial portions, which mainly include steroidal glycosides [10]. *T. terrestris*, belonging to the Zygophyllaceae family, possesses aphrodisiac qualities as it can affect the levels of sex hormones. This perception has led to a rapid increase in the popularity of medicinal products derived from *T. terrestris* among consumers seeking to enhance their sexual well-being [20].

The aforementioned literature drafted on both animal and human experiments, *T. terrestris* increased the quality of sperm. In animal experiments, *T. terrestris* improved folliculogenesis and polycystic ovarian syndrome. Human clinical trials have shown that it is effective in treating female sexual problems. Various sources of literature on this topic have been examined. The objective of this review was to spread knowledge about *T. terrestris*'s health advantages to common people to benefit from their own and their animals' health issues and highlight this plant's potential to scientists and veterinarians for further research.

Table 1
Average proximate and mineral composition of Tribulus terrestris.

Item	Concentration
Moisture (% wet weight)	65.3
Fat (%)	1.1
Fiber (%)	0.5
Crude Protein (%)	21.33
Ash (%)	5.3
Carbohydrates (%)	55.6
Energy Value (Kcal/100g)	292.64
Calcium (mg/100g)	142 g
Potassium (mg/100g)	220 g
Iron (mg/100g)	2.8 g
Phosphorus (mg/100g)	23.04 g
Magnesium (mg/100g)	30.4 g
Sodium (mg/100g)	5.0 g
Zinc (mg/100g)	0.5 g
Copper (mg/100g)	1.28 g

Source (Gafar et al., 2011; Pokrywka et al., 2014): [24,136].

Table 2
Vernacular names of Tribulus terrestris.

Language	Name
English	Caltrops fruits and Land Caltrops
Hindi	Gokshri and Gokhru
Arabic	Khask, Hasak and Hamasulameer
Sanskrit	Traikantaka
Urdu	Gokharu
Marathi	Sarate, Lahanagokharu and Sarala
Persian	KhareKhask and Kharsagosha
Bengali	Gokshura, Gokhri, Gokhru, Gokhura and Gokshra
Tamil	Nerunjil, Yanai vanangi and thirikandam
Afghanistan	Krunda
Bengal	Gokshura and Gokhru,
Chinese	Ci ji li
Punjabi	Bhakra
Japanese	Byakushitsuri

2. Botanical description

T. terrestris is a creeping annual (occasionally perennial) herb, and the plant, especially the fruits, has traditionally been utilized for sexual health advantages. *T. terrestris* can flourish in various soil types, but it particularly prospers in loose, arid, sandy soils found near dunes or in loose, fertile soils along the borders of fields. Additionally, it thrives in dense soils, particularly when they are damp or rich in nutrients, and in compressed soils along highways [21]. Its' fruit is triangular, with spines on all four corners. It is greenish-yellow in color while the leaves are green [22]. Fig. 1 shows the various parts of *T. Terrestris.*

T. terrestris is a tiny prostrate herb with silky hairs. Pinnate leaves are small, opposite, and have 4–8 pairs of spear-shaped leaflets. Small yellow petal blooms and prickly fruits distinguish *T. terrestris*. The fruits have 1 cm diameter woody burr with sharp spines. A woody star-shaped structure encloses the seeds (carpels). The root is slender, fibrous, cylindrical, and light brown when young [23].

3. Proximate mineral content of *T. terrestris*

T. terrestris has a lot of protein in it (21.33 %), so it can be considered a good source of protein in addition to a rich mineral supply. *T. terrestris* is an effective provider of essential minerals such as potassium, calcium, and copper. The average proximate and mineral composition of *T. terrestris* is shown in Table 1.

4. Vernacular names

Tribulus gets its name from the Greek word "tribolos," which means "spike fruit" [24]. Puncture vine or Gokharu is also its common name [16]. Table 2 shows the vernacular names of *T. terrestris.*

5. Nutritional potential

The green leaves of *T. terrestris* (100 g) contain 79.09 % moisture, 7.22 % protein, 1.55 % calcium, 0.08 % phosphorus, 9.22 mg

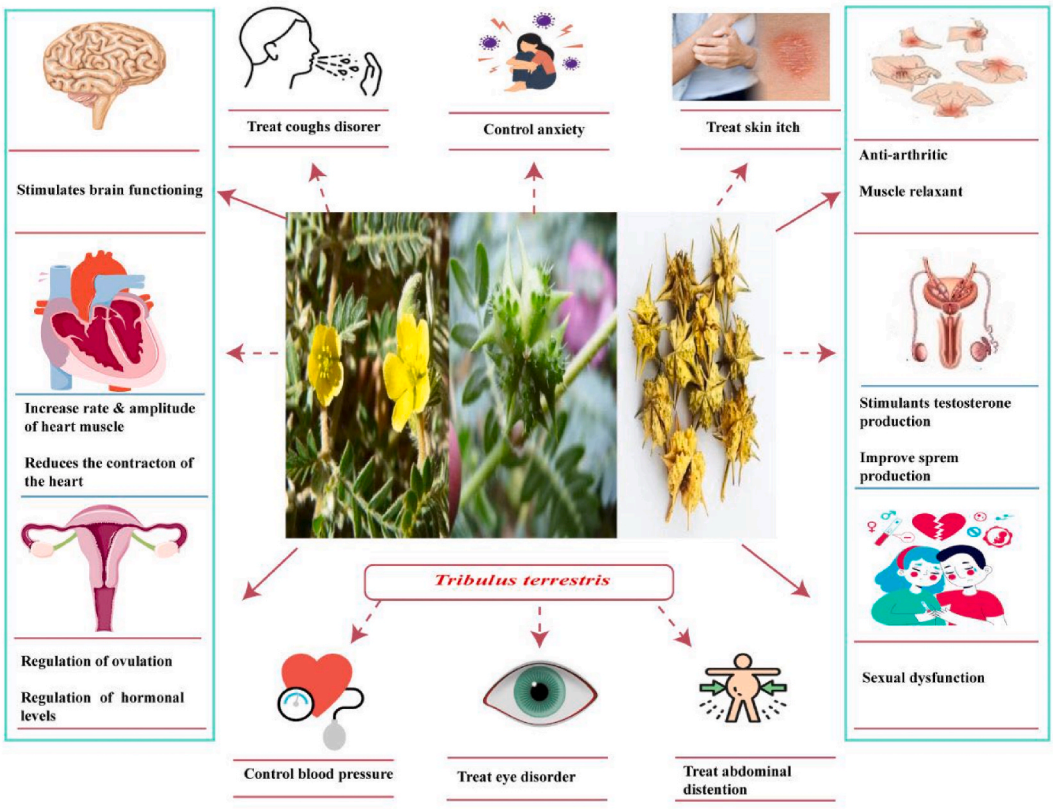

Fig. 2. The different promising traditional use of *Tribulus terrestris*.

iron, and 41.5 mg vitamin C. Resins, alkaloids, nitrates, and oils are all found in the powdered root extract [10]. *T. terrestris* leaves had an 84.67 percent moisture content and 19.0 percent fiber content, according to another study. On a dry weight basis, the percentages of crude protein, carbohydrate, and fat contents were found to be 13.21 percent, 46.79 percent, and 1.0 percent, respectively [25].

6. Traditional uses

T. Terrestris has been used to treat many diseases in China, India, and Greece, according to ancient documents. The plant is utilized as an herb and as a primary component in manufacturing numerous medications and nutritional supplements, including for physical rejuvenation for liver, cardiovascular, kidney, and immune system disorders. It is used as a folk remedy to improve muscle strength and sexual potency, as well as to treat urinary tract infections, heart problems, and coughs. It is also an aphrodisiac, stimulant, and nutritious herb [18].

T. terrestris is a traditional plant with medicinal properties, commonly employed in the treatment of various ailments such as gonorrhea, liver diseases, urinary tract infections, heart issues, eye problems, edema, high blood pressure, skin itch, and cardiovascular diseases [26,27]. The fruit of *T. terrestris* is known for its diuretic properties and is used for addressing sexual dysfunction and veiling [26,28]. Additionally, the *T. terrestris* plant is utilized to promote liver healing, improve eye color, enhance blood circulation, and alleviate abdominal distention, edema, and cardiovascular problems [29]. Rheumatism, vesical calculi, piles, premature ejaculation, menorrhagia, and impotence might all benefit from the roots and fruits. This plant treats premature ejaculation, headaches, dizziness, and spermatorrhoea [30]. Gokhru (the Indian name of *T. terrestris*) is a diuretic, demulcent, antibacterial, anti-inflammatory, and aphrodisiac, according to Indian Ayurvedic practitioners. The ancient Greeks employed the *T. terrestris* to promote urine production and mood enhancer. In ancient Chinese medicine, it was employed to treat various kidney, liver, and cardiovascular ailments. More recently, athletes from Eastern Europe have utilized it to enhance their strength and endurance [10].

The dried fruits of herbs are particularly beneficial for most genito-urinary tract diseases. It contains crucial elements that play a significant role in supporting the proper functioning of the genitourinary tract and removing urinary stones. This potent Ayurvedic medicine has been utilized for centuries in Ayurveda to address venereal disorders and sexual debility. Additionally, in Bulgaria, the plant is used as a traditional remedy for treating impotence. Furthermore, the root and fruit of this plant are recognized in the Ayurvedic Pharmacopoeia of India for their cardiotonic properties. The fruits treated eye issues, edema, stomach distension, morbid leukorrhea, and sexual dysfunction in traditional Chinese medicine [17]. Fig. 2 shows the different promising traditional uses of *T. terrestris.*

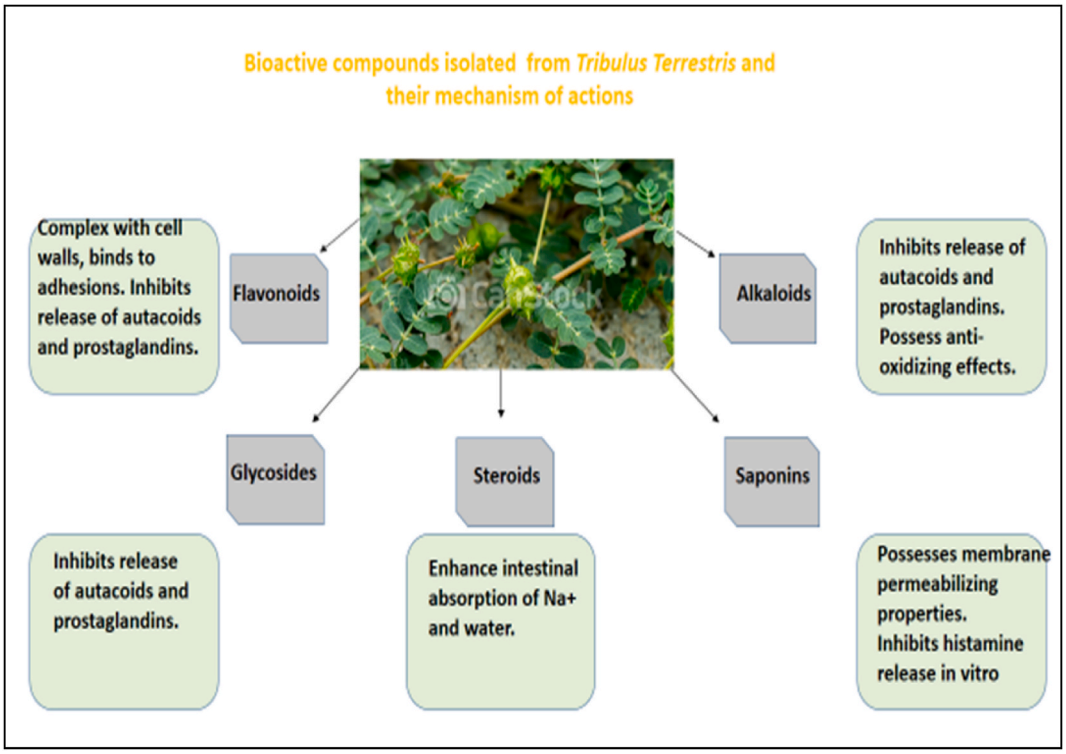

Fig. 3. Bioactive compounds isolated from *Tribulus terrestris* with their mechanism of actions.

7. Phytochemistry

T. terrestris contains various compounds including steroids, vitamins, alkaloids, unsaturated fatty acids, aspartic acid, saponins, tannins, flavonoids, resins, potassium nitrate, and glutamic acid [27]. Diosgenin and steroidal saponins are present in this plant. It contains a lot of proteins and calcium levels. Dried fruits contain semi-drying oil, peroxides, diastase, small amounts of glucosides, protein, and a considerable variety of inorganic components [21]. Fruits with nitrates contain a tiny amount of essential oil, resin, and traces of alkaloids (0.001 %) [31]. An alcoholic extract of fruits produces a crystalline residue in water that contains an alkaloid-like material precipitated from its solution by ammonia and linked with alkaline chlorides or hydrochloric acid. The fruits also contain fat and resin, the latter of which is most likely the source of drug scent because it emits a sweet smell when burned. Mineral stuff is found in abundance in the fruits [32].

The chemical components of *T. terrestris* fruits include flavonoids, flavonol glycosides, steroidal glycosides, steroidal saponins, saponins, furostanol, furosteroidal saponins, sapogenins, furostanol glycosides, and alkaloids [16]. Secondary metabolites found in *T. terrestris* fruits include saponins, polyphenolic chemicals, and alkaloids. Furostanol and spirostanol are the most common steroidal saponins. The spiro analogs' biogenetic antecedents are thought to be the furostanol saponins. *T. terrestris* has been shown to have about 70 distinct chemicals [33]. This plant is known for its high concentration of steroidal saponins. In various parts of this herb, gitogenin, tigogenin, hecogenin, diosgenin, neohecogenin, chlorogenin, ruscogenin, neotigogenin, and sarsasapogenin derivatives were obtained.

Depending on the plant origin, the sugar moieties of separated furostanol, and saponins are oligosaccharides, which contain 2 to 4 different types of sugars, including galactose, xylose, glucose, and rhamnose [18]. Fig. 3 shows the bioactive compounds isolated from *T. terrestris* with their mechanism of action. *T. terrestris* is an important plant that is utilized in natural medicine and may be found all over the world. *T. terrestris* is mainly composed of spirostanol and furostanol saponins of the chlorogenin, hecogenin, diosgenin, tigogenin, gitogenin, neogitogenin, ruscogenin, neohecogenin and sarsasapogenin. *T. terrestris* also yields four different forms of sulfated saponins [34].

7.1. GC-MS of T. terrestris

Studies using Gas Chromatography-Mass Spectroscopy (GC-MS) analysis for *T. terrestris* extract revealed that it contains many compounds, most of which have been recognized for their biologically active functions like hexadecanoic acid, octadecanoic acid, phytol, rhodoxanthin, α-Amyrin, cholestane, etc [35]. Sitosterol-D-glucoside and tribulosin belong to spirostanol-type saponin and has also been characterized in *T. terrestris* extract and these exhibited anti-parasitic properties [21]. The extract of Iraqi *T. terrestris* shows forty-six compounds including some novel compounds like thiazole, terpineol, myristic acid, and coumarin. Moreover, the study also

Table 3
Phytochemistry of *Tribulus terrestris* (Phytochemical, Their prevalence, and their effect).

Sr. No.	Phytochemical of Tribulus Terrestris	Present in	Major Effect	References
1	Furostanol and Spirostanol saponins (Tigogenin, Chlorogenin, Neotigogenin, Neogitogenin, Hecogenin, Neohecogenin, Diosgenin, Gitogenin, Ruscogenin, and Sarsasapogenin)	The aerial part of Leaf	Diuretic Anti-hypertensive, Aphrodisiac and Anti-diabetic,	[16,137]
2	Flavonoids (Kaempferol, Kaempferol-3-glucoside, and Tribuloside)	Leaf	Analgesic, Aphrodisiac and Anti-diabetic	[33]
3	Alkaloids (β-carboline Alkaloid, Tribulusterine, Terrestribisamide, Tribulusin A, Harmine, Tribulusamide, Harman, Terrestriamide, and N-trans-coumaroyltyramine.	Leaf	Anticancer, Aphrodisiac, prevent Cardiac diseases.	[27]
4	Furostanol and Spirostanol saponins (Chlorogenin, Ruscogenin, Gitogenin, Neotigogenin, Hecogenin, Diosgenin, Neohecogenin, and Sarsasapogenin)	Fruit	Anti-helmintic Diuretic, Aphrodisiac Anti-spasmodic and Anti-oxidant.	[7,35]
5	Flavonoids (Kaempferol-3-glucoside Tribuloside, Kaempferol, and Kaempferol-3-rutinoside	Fruit	Aphrodisiac Diuretic, Anti-spasmodic and Antioxidant	[99,138]
6	Alkaloids (Tribulusterine, Tribulusamide, Tribulusin, Harmine, Harmmol, Terrestriamide and Terrestribisamide,	Fruit	Antibacterial Antioxidant and Aphrodisiac.	[84,139]
7	Saponins, Phytosterols, Rutin, Tannins, Protodioscin, Tannins, Arginine, Carbohydrates, β-carboline Alkaloid and Tribulusin,	Stem	Immunomodulatory effects, Anti-Spasmodic and Antioxidant,	[7]
8	Tribulus Terrestris roots have entirely reducing sugar properties; Flavonoids, Saponins, alkaloids, Triterpenoids, Xanthoprotein, and Unique phenolic compounds are phenol 2-(5,6-dimthyl pyrazinyl), and Histidine.	Root	Aphrodisiac, Ant- bilious, and Antidiabetic.	[34,140]

observed the antioxidant potential of these compounds by enhanced levels of ascorbic acid, superoxide dismutase activity, and serum glutathione levels in rats [22]. The phytochemistry of *T. terrestris* (phytochemicals, their prevalence, and their effect) has been presented in Table 3.

7.2. Pharmacokinetics of the major compounds derived from T. terrestris

The possible therapeutic benefits of the herb *T. terrestris* have led to its widespread usage in traditional medicine. Saponin is thought to have multiple pharmacological effects and is one of the primary active chemicals in *T. terrestris* [34]. Understanding the absorption, distribution, metabolism, and excretion of saponins from *T. terrestris* is crucial because it can affect the efficacy and safety of treatment [33]. *T. terrestris* saponin has the following pharmacokinetic properties:

Absorption: Saponins from *T. terrestris* are not absorbed well in the digestive tract because their molecules are big, and they are like water. But they can be taken in through the intestinal mucosa through a process called passive diffusion, especially when given with a lipid-based carrier.

Distribution: *T. terrestris* saponins are present throughout the body, with large amounts in the liver, kidney, and lungs.

Metabolism: *T. terrestris* saponins are extensively metabolized in the liver and changed into their aglycone forms. The cytochrome P450 enzymes control this process.

Excretion: Saponins from *T. terrestris* are mostly eliminated through the feces, with a negligible amount also leaving the body through the urine [36].

8. Phytopharmacological activities/medicinal properties

It possesses a diversity of beneficial effects on the body, including diuretic, immunomodulatory, anticancer, antidiabetic, anti-urolithic, absorption enhancer, larvicidal, anti-inflammatory, antispasmodic, cardiotonic, aphrodisiac, hepatoprotective, central nervous system modulator, analgesic, antibacterial, anthelmintic, immunomodulatory and anticarcinogenic [16,17]. Modern research has revealed that the chemical components viz., steroidal saponins and flavonoids, which have potent anti-inflammatory and antiaging characteristics, are the primary contributors to the traditional therapeutic activity of *T. terrestris* [27]. *T. terrestris*, sometimes known as puncturevine, is a widespread weed that grows in many countries and is classified as a toxic weed in some places. One of the most well-known aphrodisiacs today, the herb is mainly used in Chinese and Indian medicine. In both people and animals, it has been used to treat hormonal imbalance, impotence, and sexual problems. It is also used as a stimulant for sexual activity [7]. There is some evidence that *T. terrestris* could be used to treat urinary stones, intestinal parasites, menorrhagia, infertility, urinary tenesmus, dyspnea, venereal disorders, urinary lithiasis, nephritis, gout, rheumatism, lumbago, impotence, frigidity, asthma, dysuria, hematuria, and cystitis [37]. It is also tonic to improve digestive ability, boosts strength, and is beneficial for difficulties of breathing, cough, impotence, and heart disorders [38].

T. terrestris has been employed for various purposes such as a diuretic, tonic, aphrodisiac, pain reliever, astringent, stomach aid, and urinary antiseptic. It is believed that *T. terrestris* can enhance testosterone levels by stimulating the release of gonadotropin-releasing hormone (GnRH), which in turn triggers the production of follicle-stimulating hormone (FSH) and luteinizing hormone (LH). In addition to boosting sex drive and fertility, testosterone is recognized for its ability to enhance the immune system and promote bone marrow activity, both of which are crucial for the production of red blood cells [39]. *T. terrestris* is used in various traditional medical practices, i.e., Ayurveda, Traditional Chinese Medicine, and Siddha, as a diuretic, aphrodisiac, immunomodulatory, anti-urolithic,

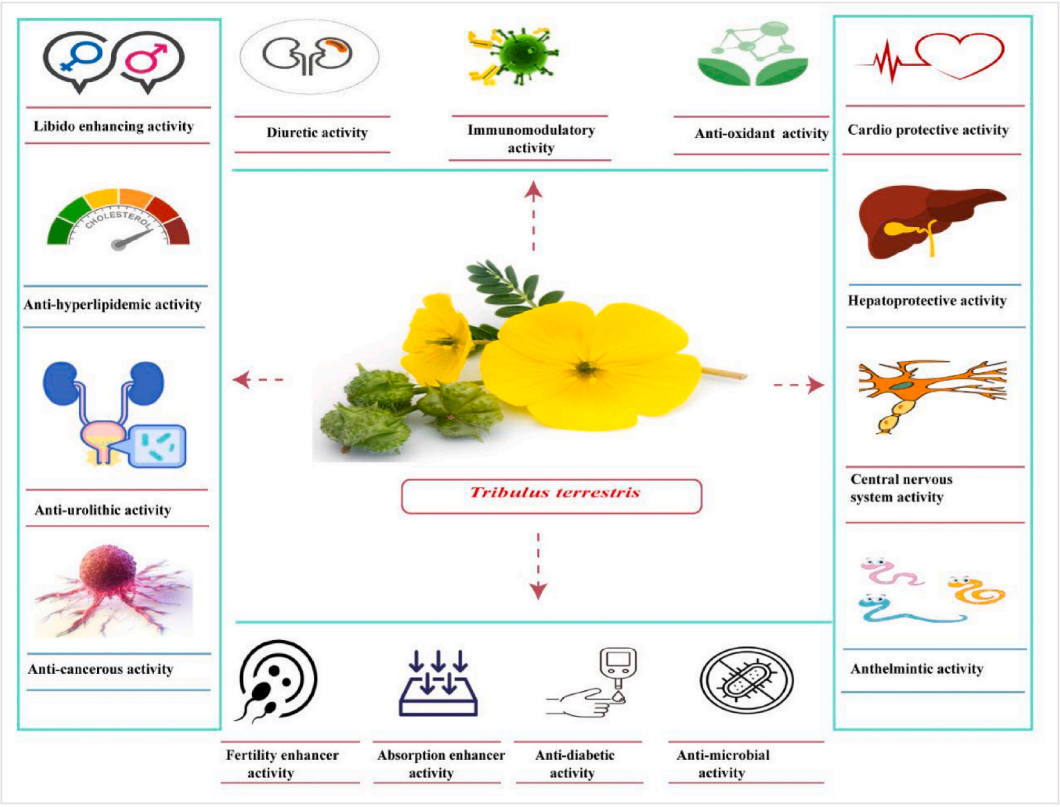

Fig. 4. Important Pharmacological effects of *Tribulus terrestris*.

Table 4
Medicinal properties of *Tribulus terrestris*.

Sr. no	Medicinal properties of Tribulus Terrestris	References
1	Diuretic, anti-urolithic, cardiotonic, aphrodisiac, antispasmodic, antibacterial, anthelmintic, larvicidal, and anticarcinogenic properties	[16–18]
2	Anti-inflammatory and antiaging	[27]
3	Sexual issues, sexual stimulants, impotence, and hormonal imbalance	[7,37]
4	Treating urinary stones, lithiasis, cystitis, nephritis, urinary tenesmus, hemorrhoids, intestinal parasites, dyspnea, asthma, dysuria, hematuria, and dysuria and hematuria	[37]
5	Cooling, demulcent, aphrodisiac, tonic, boosts strength, cough, difficulties breathing, impotence, and heart disorders	[38]
6	Bone marrow activity, immune system, and gonadotropin-releasing hormone	[39]
7	Diuretic, aphrodisiac, antiurolithic, anticancer, anthelmintic, antibacterial, and analgesic	[15]
8	Renal difficulties, liver problems, and cardiovascular system problems	[40,45, 46]
9	Aesthetic stimulants, increased physical vigor, sexual power, and aphrodisiac	[41,42]
10	Antispasmodic, anticancer, antibacterial	[47]

antibacterial, *anti*-hyperlipidemic, antidiabetic, hepatoprotective, anticancer, anti-hypertensive, anthelmintic, analgesic and anti-inflammatory drug [15]. Fig. 4 shown the pharmacological effects of *T. terrestris*.

T. terrestris is used as an herb or as a critical component in the production of numerous pharmaceuticals and consumable supplements for physical rejuvenation, renal difficulties, liver problems, immune system problems, and cardiovascular system problems [40]. Because of the diverse chemical composition of this plant, its applications range from local to systemic illnesses. It refers to greater physical vitality and sexual power [41,42], nutrition, and the treatment of urinary ailments, cough, and cardiac disorders [18]. In addition, it also has diuretic [42], immunomodulatory effect [40], antidiabetic, absorption enhancing, anti-urolithic [43], hypolipidemic [44], central nervous system, hepatoprotective, cardiotonic, analgesic, anti-inflammatory [45,46], antispasmodic, antibacterial, anticancer [47], anthelmintic, larvicidal, and anticarcinogenic activities [17]. Tables 4 and 5 summarize the medicinal/pharmacological properties of *T. terrestris*.

Table 5
Summarized the Pharmacological properties of *Tribulus terrestris*.

Phytochemical	Activity	References
Saponin	Anti-cancerous	[42,48]
Terrestrosin D (TED)	Anti-cancerous	[50]
Spirostanol-type saponin, tribulosin, and sitosterol-D-glucoside	anthelmintic	[21]
Saponin	improve coronary circulation and dilate coronary arteries	[60]
Tribulusterine	neuroprotective	[69]
Saponins	neuroprotective	[70–72]
Oleic acid, octadecanoic acid, rhodoxanthin, cholestane, pyrimidine, pregnene, gamabufotalin,	nephroprotective	[83]
Tigogenin, terrestrosid F, neotigogenin, gitonin	nephroprotective	[82]
liophilized saponin mixture	Antispasmodic activity	[89]
Saponin	smooth muscle spasms or colic pains	[89]
T. terrestris saponins	antidiabetic	[93]

8.1. Anticancerous

In a Bulgarian study, *T. terrestris* L. saponin fraction and the entire extract were investigated against the survival ability of human breast cancer cells and apoptosis (MCF7). The whole section of *T. terrestris* obtained from Bulgaria showed a significant dose-dependent inhibitory effect on the viability of cancerous breast cells. When compared to the whole extract, the saponin fraction exhibits a more substantial inhibitory impact. Apoptotic processes are implicated in the mechanisms of *T. terrestris* anticancer action. After therapy, morphological alterations and DNA fragmentation were found to be indicators for early and late apoptosis in tumor cells. The findings are the first to reveal that *T. terrestris* has anticancer action in human cancerous cells [42]. When tested on peripheral blood mononuclear cells, *T. terrestris* extracts were found to have no harmful effects on non-cancerous cells. To examine its impact on breast cancer cells, MCF-7 cells were treated with methanol extracts from *T. terrestris* leaves and seeds, as well as saponin extracts. These treatments resulted in DNA fragmentation and apoptosis in the cancer cells. The activity of caspase 3, a protein involved in cell death, significantly increased in MCF-7 cells exposed to *T. terrestris* extracts. Furthermore, the expression of Bax and p53 genes, known to promote apoptosis, was upregulated, while the expression of the Bcl-2 gene, which inhibits apoptosis, was downregulated. These findings suggest that *T. terrestris* extracts induce an intrinsic apoptotic pathway. Additionally, elevated genes for FADD, AIF, and caspase 8 suggest the activation of an extrinsic apoptotic pathway. As a result, our findings show that *T. terrestris* extracts may have anticancer action via both intrinsic and extrinsic apoptotic mechanisms [48].

A study was conducted to determine whether Terrestrosin D (TED) inhibits the development of castration-resistant prostate cancer. It was found that TED suppresses angiogenesis and cancer growth by arresting the cell cycle and triggering apoptosis in PCa and endothelial cells [49]. The effects of *T. terrestris* fruit on prostate and cancer cell lines of the colon were studied. *T. terrestris* was less hazardous to colon cancerous cell lines and fibroblast-like cells than the prostate cancerous cell lines [50].

Another study sought to investigate the anticancerous activities of *T. terrestris* in liver cancer cells. *T. terrestris* extract inhibited the proliferation and clonogenicity, which caused apoptosis and increased growth of liver cancerous cells in the G0/G1 phase. It was also demonstrated that *T. terrestris* extract increased the cellular amount of IB by preventing its' phosphorylation and degradation while decreasing the expression of NF–B-dependent reporter genes and NF–B subunit p50. Furthermore, the extract of *T. terrestris* inhibited the expression of genes related to the regulation of the cell cycle, invasion, and prevention of cell death. Additionally, the activity of IKK (IκB kinase) was reduced in a manner that depended on the dosage used [51].

8.2. Anthelmintic

The utilization of medicinal plants such as *T. terrestris* in chickens has demonstrated promising anthelmintic effects. These plants can potentially serve as alternatives to commonly used synthetic medications. By incorporating them into treatment regimens, the reliance on synthetic drugs may decrease. This, in turn, can help reduce drug resistance among populations affected by endemic pathogens, as well as minimize the presence of drug residues in poultry meat [52].

Previously researchers employed the microscopic worm *Caenorhabditis elegans* to examine the effectiveness of *T. terrestris* extract against parasitic worms in a controlled laboratory environment. Based on the investigations involved in separating and extracting specific bioactive compounds from the 50 % methanol extract using chromatography, it was found that only two substances, namely tribulosin and sitosterol-D-glucoside, belonging to a type of chemical called spirostanol-type saponin, exhibited anti-parasitic properties. Therefore, both tribulosin and sitosterol-D-glucoside can be considered as effective anthelmintic drugs [21,53].

8.3. Antibacterial

The efficacy of *T. terrestris* L., a plant known for its urinary anti-infective properties in traditional medicine, was assessed against 11 different bacteria, both pathogenic and non-pathogenic. These bacteria included *Proteus vulgaris, Staphylococcus aureus, Bacillus subtilis, Bacillus cereus, Corynebacterium diphtheriae,* and *Bacillus subtilis*. Extracts derived from different parts of the plant exhibited antibacterial activity against most of the tested microbes. Among the extracts, the ethanol extract from the fruit demonstrated the highest level

of activity against both Gram-negative and Gram-positive bacteria, with minimum inhibitory concentration (MIC) values of 0.15 mg/mL for *B. cereus, P. vulgaris, B. subtilis,* and *C. diphtheriae* [54].

The effectiveness of *T. terrestris* water-based extract in killing bacteria was examined using the plate agar diffusion technique. The extract's antibacterial properties were tested against both Gram-positive bacteria, specifically *Bacillus subtilis* and *Staphylococcus aureus*, and Gram-negative bacteria, namely *E. coli* and *Pseudomonas aeruginosa*. These various bacterial species' susceptibilities to the plant's extracts were compared to those of other bacterial species and a positive control antibiotic, i.e., streptomycin. The aqueous extract of *T. terrestris* was found to have antibacterial properties [26]. Mojdeh et al. [55] investigated the antibacterial action of a whole extract of *T. terrestris* L. using the method called Disc diffusion. On *Pseudomonas aeruginosa, Escherichia coli*, and *Bacillus subtilis*, the entire extract had an antimicrobial effect.

8.4. Urinary system

The antibacterial effectiveness of a methanol extract from *T. terrestris* was examined against *E. coli* strains isolated from urinary tract infections. The saponins containing methanol extract of *T. terrestris* underwent testing through a micro-broth dilution assay. The findings indicated that *T. terrestris* has the potential to serve as an alternative treatment for urinary tract infections [56].

Previously it was investigated the impact of *T. terrestris* on the creation and growth of calcium oxalate (CaOx) crystals and the resulting cell damage in NRK-52E renal epithelial cells. The extract of *T. terrestris* hindered the formation and progression of CaOx crystals in a manner that depended on their concentration. Additionally, the *T. terrestris* extract protected the NRK-52E cells from oxalate-induced damage for 72 h in a dose-dependent manner. Lactate dehydrogenase release decreased, and cell viability increased in a concentration-dependent way after treatment with varied concentrations of the plant. The current evidence demonstrates that *T. terrestris* extract has not only the ability to suppress CaOx crystal nucleation and growth but also has a cytoprotective effect. These findings suggest it could be a viable choice for urolithiasis phytotherapy [57].

According to a study, using *T. terrestris* extract causes alterations that cause or trigger the development of urinary stones. The levels of oxalate, uric calcium acid, proteins, and glycosaminoglycans in blood and urine altered considerably after administration of *T. terrestris* extract. In contrast, inorganic phosphate, citrate, and urine volume were unaffected. *T. terrestris* extract may have beneficial effects in treating urolithiasis [58]. Another study discovered that a carefully designed liquid extract of *T. terrestris*, when used in an optimized manner, can prevent and treat experimentally induced kidney stone formation. It achieves this by employing various mechanisms to restrict the complex process of stone formation [59].

8.5. Cardiac system

T. terrestris saponin was used to treat coronary heart disease (CHD). The total effective reduction rate in angina pectoris was 82.3 %, based on cross-test and 406 cases of clinical observation instances (67 patients treated with "Yufen Ningxin Pian" as a control). The total effective rate was 67.2 %, more significant than the control group ($P < 0.05$). The overall effective rate of ECG improvement was 52.7 %, more critical than in the control group (35.8 %). *T. terrestris* saponin has been demonstrated to improve coronary circulation and dilate coronary arteries, which is more advantageous for enhancing the ECG of myocardial ischemia. It has no adverse effects on the circulatory system, hepatic, or renal functions when used for a long time. It also has no negative consequences. It is one of the most effective treatments for angina pectoris [60].

It was reported that *T. terrestris* effectively prevented weight gain without causing any changes in the energy balance of the diet, testosterone production, or the histo-morphometry of the heart in rats [61]. The objective of this research aimed to examine the impact of *T. terrestris* extracts dissolved in water on endothelial injury in spontaneously hypertensive rats (SHR) and their protective effects on human umbilical vein endothelial cells (HUVECs) against damage induced by Angiotensin II (Ang II). Various parameters were assessed, including blood pressure (BP), heart rate, the structure of the endothelial thoracic aorta, levels of Ang II, endothelin 1 (ET 1), superoxide dismutase (SOD), and malonaldehyde (MDA) in the blood. The growth and survival of HUVEC cells induced by Ang II were suppressed by *T. terrestris*. Additionally, *T. terrestris* improved the movement of cells and extended their lifespan. It also lowered the levels of Akt 1, Fak, Jak 2, Erk2, PI3K, and NFKB p65 mRNA and reduced the expression of Fak, Erk2, and NF-KB p65 proteins. Ultimately, through its effects on Erk2, FAK, and NF–B p65, *T. terrestris* demonstrated its ability to lower blood pressure and protect endothelial cells [62].

It was reported that *T. terrestris* works as an antihypertensive agent in rats with 2k1C-induced hypertension. The author evaluated the activity of ACE (Angiotensin converting enzyme) in various organs such as the heart, aorta, lung, and kidney, as well as in the circulatory system. The systolic blood pressure (SBP) of the 2k1C rats was notably higher, however when the hypertensive rats were fed with *T. terrestris*, their SBP significantly decreased. The ACE activity in all organs, including the aorta, lungs, heart, kidney, and serum, was significantly elevated in the 2k1C rats compared to the normal rats. These findings revealed a negative relationship between Tribulus ingestion and ACE activity in serum and several organs in 2k1C rats. This data shows that *T. terrestris* reduces blood pressure by inhibiting the ACE activity in treating renovascular hypertension [63].

8.6. Reproductive system/aphrodisiac activity

The reproductive system of albino female mice was tested using an aqueous extract of *T. terrestris*. During the estrus phase, many ovarian and uterine characteristics were investigated, as well as the levels of FSH, LH, and estradiol hormones. Both dose levels (100 and 200 mg per kg daily) increased the significant number of developing follicles, the diameter of the mature follicle, endometrial

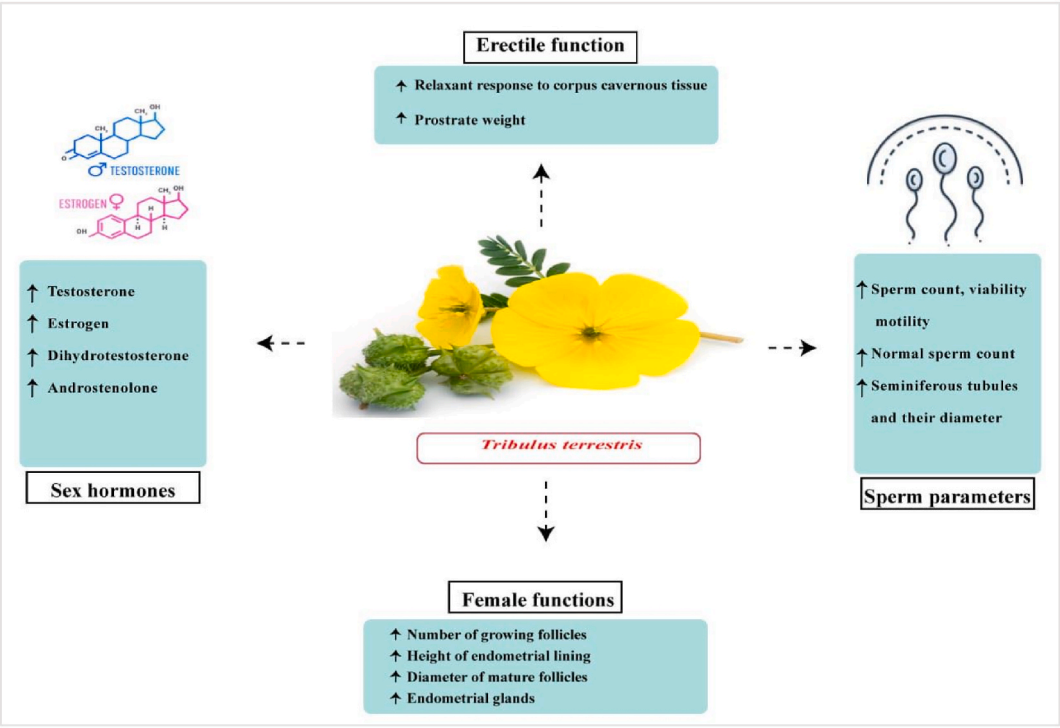

Fig. 5. The key function of *T. terrestris* on both sexes.

gland diameter, and endometrial lining cell height. Although the changes in reproductive hormone levels were insignificant, both dose levels showed an increase in LH and FSH and a decrease in estradiol levels. Despite some variation, a dose-dependent activity was found, with the two-week period being more beneficial on both ovarian and uterine parameters. In contrast, the four-week period was more effective on uterine parameters [64]. The key function of *T. terrestris* on both sexes is expressed in Fig. 5. The effectiveness of a dry extract of *T. terrestris* in protecting against cyclophosphamide (CP)-induced testicular injury was studied. Mice were gavaged with *T. terrestris* dry extract (11 mg per kg) or vehicle for fourteen days. On the 14th day, a single dosage of saline or CP was given intraperitoneally (100 mg per kg). Epididymis and testes were extracted for the histological and biochemical investigation, as well as sperm evaluation, 24 h following CP delivery. Protodioscin (1.48 % w/w) presence was detected in the dry extract of *T. terrestris* by using the HPLC analysis. CP exposure changed antioxidant enzymes i.e., SOD, CAT, GST, GPx, and GR, and enhanced lipid peroxidation, reactive species, and protein carbonylation. Furthermore, acute CP exposure resulted in a decrease in 17β-HSD (17β-hydroxysteroid dehydrogenase) activity, this may be associated with decreased serum testosterone levels and histological alterations in the semen quality and testes. This study emphasized the significance of *T. terrestris* dry extract in reducing the effects of CP injection in mice testes, which was probably due to the presence of protodioscin [65].

In the absence of reproductive manipulation, the effect of *T. terrestris* on the activities of testicular enzymes in "*Poecilia latipinna*" was investigated. For two months, different concentrations of *T. terrestris* extract (100, 150, 200, 250, and 300 mg) and control were tested for the testicular activity of enzymes in male "*Poecilia latipinna*," revealing that *T. terrestris* is an aphrodisiac herb capable of inducing testicular function in male "*Poecilia latipinna*" as the enzyme activities of Sorbitol dehydrogenase were improved [66]. The effects of *T. terrestris* on endocrine-sensitive organs were studied in castrated and intact male rats, as well as in a post-menopausal rat model using ovariectomized females. *T. terrestris* could not trigger androgen-sensitive organs, including the seminal vesicle and prostate gland, in both castrated and intact male rats. *T. terrestris* failed to stimulate sensitive endocrine organs in species of rats called "Wistar rats," including the prostate gland, seminal vesicles, vagina, and uterus, showing a lack of estrogenic and androgenic activity in vivo. It was also discovered that *T. terrestris* treatment increased rat sperm production while keeping circulating androgen levels constant [67].

8.7. Neuroprotective effects

Neuroprotection refers to the strategies and interventions aimed at preserving or preventing damage to the nervous system, including the brain and spinal cord. These approaches are designed to prevent or slow down the progression of neurological diseases, injuries, and conditions that may affect the nervous system's function. Some studies have suggested that *T. terrestris* may have neuroprotective effects due to its antioxidant and anti-inflammatory properties. In a previous study, male Wistar rats were given aluminum chloride to induce Alzheimer's disease, and the neuroprotective potential of *T. terrestris* was tested on these rats. According to the

findings, administering an oral supplement containing 100, 300, or 1000 mg/kg of *T. terrestris* L. methanol extract resulted in a significant improvement in memory function. This was accomplished by lowering the levels of oxidative stress markers and raising the levels of antioxidant enzymes [68]. Another study showed that an aqueous extract of *T. terrestris* with Tribulusterine as the predominant compound had a neuroprotective effect in an in vitro and an in vivo model. They observed that the extract reduced the expression of pro-inflammatory cytokines and markers of oxidative stress. In addition, it was found that the extract activated the Nrf 2 pathway, which controls antioxidant response elements, to provide protection from oxidative stress and to prevent the activation of stress kinases, which are implicated in neuroinflammation [69]. Researchers also found that gross saponins isolated from *T. terrestris* fruit significantly reduced the severity of ischemic stroke in rats [70]. Gross saponins were found to have a protective effect via activation of the PI3K-Akt and AMPK signaling pathways, which caused major changes in lipid and energy metabolism. Another study found that gross saponins of *T. terrestris* significantly reduced infarct volume, brain edema, neuro-behavioral abnormalities, pathologic brain changes, serum TNF-α and IL-1β, and brain NF-kB in rats suffering from cerebral ischemic injury [71]. Likewise, it has been reported that gross saponins from *T. terrestris* fruit have the potential to protect rats against ischemic stroke via controlling the variety of metabolic pathways, such as glycolysis, the tricarboxylic acid cycle, and the metabolism of amino acids, fatty acids, and neurotransmitters [72]. According to Alzahrani et al. [73], standardized *T. terrestris* extract (STTE) prevented the harmful effects of rotenone-induced oxidative damage and nigral dopamine neuronal loss in mice. This was accomplished by improving the histopathological changes and dopamine levels, which ultimately led to the downregulation of oxidative stress markers. In another study, using metabolomics and network pharmacology [72], looked into the potential protective effect of gross saponins of *T. terrestris* fruit (GSTTF) against ischemic stroke in rats. The findings suggested that by modifying the metabolic profile, including amino acid, lipid, and energy metabolism, GSTTF significantly reduced the size of the stroke in the rats, thereby reducing inflammation, oxidative stress, and cell death. In a nutshell, the findings of the published studies suggested that *T. terrestris* and its derivatives have the potential to protect the nervous system via restoration of damage caused by toxicity, oxidative stress stroke, and other neurological disorders. There is a need for additional research on the same subject to investigate the underlying mechanism that is responsible for the neuroprotective effects of the phytobiotic compounds found in *T. terrestris*.

8.8. Hepatoprotective activity

The liver plays a crucial role in the body's immune system, detoxification system, and metabolic processes. Increased free radical production occurs during metabolism, and oxidative stress can cause liver damage leading to liver diseases [74,75]. Additionally, several factors such as drinking alcohol, exposure to viral infections, and exposure to toxins can lead to liver harm. Regrettably, there are only a limited number of drugs available that have the potential to protect the liver therefore, medicinal plants and their bioactive substances can effectively protect the liver from damage and encourage liver regeneration by lowering oxidative stress and boosting the antioxidant defense [76,77].

T. terrestris has been reported to have the ability to protect liver damage and restore normal functions. The aqueous extract of *T. terrestris* and silymarin had a significant protective effect against liver damage induced by the hepatotoxin carbon tetrachloride in rats. The *T. terrestris* extract was found to have cytoprotective effects and to restore hepatic architecture by lowering the levels of liver enzymes such as ALT, AST, ALP, and lipid peroxidation while increasing the levels of antioxidants such as glutathione and superoxide dismutase (SOD) in the liver tissue [75]. Similarly, hepatoprotective effects of *T. terrestris*, Ashwagandha, and N-acetylcysteine were measured by Ref. [78], in the liver of Wistar rats that had undergone experimental fibrosis induced by carbon tetrachloride. Malondialdehyde, NF-kB, collagen 1, nuclear factor erythroid-2-related factor 2, and tumor necrosis factor all showed numerical declines in the treatment groups when compared to the control, but aspartate aminotransferase and alanine aminotransferase levels were unaffected.

In freshwater fish (*Oreochromis mossambicus*) liver toxicity could be induced by acetaminophen. *T. terrestris* extract supplementation significantly decreased the level of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP) and restore the oxidative damage caused by acetaminophen. Additionally, an in vivo study demonstrated that the oral supplementation of fruit extracts derived from *T. terrestris* had the potential to ameliorate mercury-induced liver damage. This was accomplished by monitoring the enzymological parameters of liver cells, which revealed that treatments were effective in reversing changes in liver enzymes [79]. It has been demonstrated that *T. terrestris* has a therapeutic role in terms of liver protection, and this ability is demonstrated by the fact that it can improve non-alcoholic fatty livers. Results suggested that the dietary supplementation of *T. terrestris* significantly normalized the serum biomarkers and other liver characteristics. Additionally, this pant has proven its potential to alleviate liver cirrhosis, fibrosis, hepatocarcinoma, and liver failure caused by non-alcoholic fatty liver [80].

Various studies have explored the effectiveness of *T. terrestris* in safeguarding and rejuvenating liver function when it comes to exposure to toxic substances such as heavy metals found in the environment. It has been discovered that *T. terrestris* is capable of successfully restoring liver markers that have been negatively impacted by toxic substances such as aluminum, cadmium, mercury, arsenic, CYP, and CCl4 [75,81]. Further analysis of the data revealed that *T. terrestris* has the potential to shield the liver from a wide range of threats. Since oxidative stress is linked to most of the aforementioned liver problems, it's reasonable to conclude that *T. terrestris* role as an antioxidant is a key factor in its ability to ameliorate liver-related toxicities.

8.9. Diuretic activity

Diuretics are substances that promote the elimination of excess water and electrolytes from the body by increasing urine production. *T. terrestris*' diuretic activity is thought to be due to its ability to increase urine production and excretion by the kidneys. This

plant's diuretic potential is attributed to its beneficial effect on renal function and aids in the prevention of kidney stone formation. Multiple toxicological studies have provided evidence supporting the safe use of *T. terrestris* in various treatments, as it has been shown to have no harmful effects in acute, subacute, and chronic toxicity assessments. Nutraceutical and renal protective properties of this plant have been widely explored in earlier studies [82].

According to the literature that has been published, *T. terrestris* contains several bioactive substances that are advantageous for protecting the renal system because they have anti-inflammation, antioxidant, and diuretic potential, all of which are crucial for maintaining the kidney's health. *T. terrestris* contains certain substances that promote kidney protection, including oleic acid, octadecanoic acid, rhodoxanthin, cholestane, pyrimidine, pregnene, gamabufotalin, and lanostane terpenoids [83]. Additionally, renal protection might be attributed to the presence of tigogenin, terrestrosid F, neotigogenin, gitonin, and tribulusamides A and B [82].

Nephrotoxicity refers to damage to the kidneys caused by medications or other toxins. It can lead to a range of kidney problems, including acute kidney injury, chronic kidney disease, and kidney failure. The incidence of nephrotoxicity is a growing concern in both developed and developing countries, as more people are taking medications and being exposed to environmental toxins. Research has shown that treatments with *T. terrestris* may help to protect the kidneys against damage caused by certain medications [84,85]. Earlier studies have suggested that *T. terrestris* may have a protective effect against nephrotoxicity induced by certain medications, such as nonsteroidal anti-inflammatory drugs (NSAIDs) [84]. Gentamicin is an antibiotic that is used in clinical practice for the treatment of Gram-negative bacterial infections; however, due to its nephrotoxicity, its use is restricted to a relatively infrequent basis. The medicinal application of gentamicin significantly increased the levels of blood urea nitrogen (155 %), serum creatinine (187 %), and serum uric acid (123 %). However, the oral administration of *T. terrestris* (840 mg/kg) has been shown to mitigate gentamicin-induced experimental nephrotoxicity in a dose-dependent manner [86].

The diuretic activity of the water-based extract from the leaves and fruits of *T. terrestris* and the hair of Zea mays was investigated by using male Wistar rats. The findings revealed that the oral administration of the water-based extract of *T. terrestris* at a dosage of 5 g/kg induced a beneficial increase in urine production, slightly exceeding the diuretic effect of furosemide [37]. The mixture of Z. mays and *T. terrestris* extracts had an equivalent diuretic effect compared to using *T. terrestris* alone. Likewise in another study, it was reported that *T. terrestris* extracts given orally led to a notable rise in urine output and sodium excretion, along with the additional advantage of preserving potassium levels in dehydrated rats [87]. On the other hand, it has recently been suggested that the aqueous extract from the fruit of *T. terrestris* shows potent efficacy in the treatment of urinary stones. This could be achieved by breaking down the mineral components of the stone, preventing new stone formation, increasing urination, and protecting against kidney damage by preventing oxidative stress and lipid peroxidation [88]. Although these findings are encouraging, more clinical research is required to determine whether *T. terrestris* is truly effective in treating kidney disorders.

8.10. Antispasmodic activity

Antispasmodic activity refers to the ability of a substance to reduce or prevent muscle spasms or cramps. This can be particularly useful in the treatment of conditions such as irritable bowel syndrome (IBS), menstrual cramps, and other types of muscle spasms. The study investigated the influence of a freeze-dried combination of saponins from *T. terrestris* L. on various smooth muscle preparations in the laboratory. The results showed that the saponin mixture resulted in a significant reduction in the peristaltic movements of isolated sheep ureteral and rabbit jejunal preparations, with the degree of effect correlating with the dose administered. However, the saponin mixture did not affect the isolated rabbit aorta or its contractile response to norepinephrine. These results suggested that *T. terrestris* L. or its saponin mixture may have potential therapeutic value in the treatment of smooth muscle spasms or colic pain [89]. However, it is essential to emphasize the importance of conducting additional research to investigate the antispasmodic activity of this plant and saponin mixture in both humans and animals.

8.11. Antidiabetic activity

Diabetes is a long-lasting condition characterized by the body's inability to effectively control the levels of glucose (blood sugar). This can occur when the pancreas does not produce enough insulin (Type 1 diabetes) or when the body develops insulin resistance and cannot effectively utilize insulin (Type 2 diabetes) [77]. With the advancement of science and technology, numerous studies have suggested that natural bioactive compounds originated from medicinal plants widely used to control blood glucose levels in diabetic patients [90]. It is well known that the secondary compounds present in plants can hinder the functioning of crucial enzymes that play a role in breaking down carbohydrates [91]. Another study indicated that administering a single dose of the methanol extract derived from *T. terrestris* significantly reduced fasting blood glucose levels, similar to the effects observed with glibenclamide treatment [92]. It is interesting to note that *T. terrestris* was used as a treatment for diabetes in traditional folk medicine. According to the findings, *T. terrestris* could be an effective complementary treatment for diabetic women, helping them better control their blood glucose levels while also improving their lipid profiles [44]. Recently, it was hypothesized that *T. terrestris* saponins prevent nonalcoholic fatty liver disease in male rats and function as antidiabetic agents. In rats with induced type 2 diabetes, dietary supplementation with *T. terrestris* saponins or saponins combined with inulin substantially decreased steatosis while simultaneously restoring the plasma lipid profile [93]. Similar findings were made in another study, which discovered that three kinds of medicinal plants, including *Dioscorea deltoidea*, *T. terrestris*, and *Panax japonicus*, could treat laboratory rats against glucose metabolism problems in laboratory rats [94]. Additionally, as compared to untreated mice, medication successfully corrected lipid and carbohydrate metabolism while reducing daily urine output, blood glucose levels, blood in urine, and total cholesterol. *T. terrestris* may have antidiabetic properties, but more studies are needed to fully understand the underlying mechanism of action behind the antidiabetic effects of *T. terrestris*. Based on the current

literature on the promising evidence of *T. terrestris*' anti-diabetic properties, further study is needed to completely understand the hypoglycemic potential and underlying mechanism involved in diabetes treatment.

8.12. Immune boosting activity

The immune system is the part of the body that protects against infectious pathogens and other pathophysiological conditions. On the other hand, the immune system can overreact or underreact, leading to various pathological disorders. Immunomodulation is the process of modifying or regulating the response of the immune system to a pathogen, foreign substance, or abnormal cell growth. Evidence has accumulated over the past few decades to support the use of medicinal plants for their immune-enhancing properties, which can strengthen the body's innate resistance to a wide variety of diseases [95–97].

Previous research has suggested that *T. terrestris* may have the ability to boost one's immune system by either increasing the production of particular immune cells or by stimulating the activity of the immune system as a whole. However, limited studies have been found in the literature regarding the immune-boosting effects of *T. terrestris* plant. *T. terrestris* fruit extracts and *Xanthium strumarium* have been shown to significantly inhibit the elevated effects of autophagy by decreasing autophagic flux, cell growth, and metastatic characteristics of oral cancer cells, implying that it may contain a functional ingredient to suppress oral cancer cells [98]. Furthermore, Tian et al. [99] investigated the antioxidant and bactericidal properties of *T. terrestris* total flavonoids and fatty acid extracts. They observed that both extracts demonstrated antibacterial and antioxidant activity, suggesting that total flavonoids extracted are more attractive candidates for the study and development of natural antioxidants and therapeutic agents than fatty acids. Additionally, dietary inclusion of *T. terrestris*-derived extract at the level of 200–400 mg/kg repaired the liver and intestinal injuries and enhanced the immunological response *of S. iniae*-infected tilapia fry fish [100]. Ghosal et al. [101] examined the performance and immune-boosting potential of different dietary treatments containing *T. terrestris* fruit extract. Final weight, length, and specific growth rate were all considerably enhanced across all treatments. Immunostimulatory effects enhanced respiratory burst, hematological, antioxidant, and hepatoprotective activity, as well as phagocytic and lysozyme activities, in comparison to the control.

Dietary supplementation of *T. terrestris* effectively attenuates the oxidative stress and inflammatory responses induced by acute aerobic exercise and improves delayed onset of muscle soreness in healthy men. The findings revealed that consuming *T. terrestris* for four weeks stabilized reduced glutathione and oxidized glutathione levels while dramatically lowering thiobarbituric acid reactive compounds, protein carbonyls, creatine kinase activity, and white blood cell count rise in the treatment group [102]. [103] tested the effect of *T. terrestris* extract on IL-6, TNF, and Comet assays for immunomodulatory properties. The results showed that *T. terrestris*-treated rams had a significantly greater increase in both body weight and lymphocyte transformation compared to the control group. Results from in vitro studies showed that a 0.5 L/mL dose of *T. terrestris* dramatically increased IL-6 and lymphocyte transformation while reducing serum MDA levels compared to control. The study of Tilwari et al. [104], suggested that the aqueous and alcoholic extracts of *T. terrestris* fruits show potent immunomodulatory activity by improving the humoral antibody titer and delayed hypersensitivity reaction in Wistar rats. Broiler chickens were treated with *T. terrestris* vine powder equivalent to an antibiotic growth promoter. The results showed that the supplement did not affect productivity indicators apart from carcass yield. However, birds given 1 or 5 g/kg T. *terrestris* powder had higher antibody titers against Newcastle disease virus and avian influenza virus compared to other groups [105]. In conclusion, the research presented above indicated that *T. terrestris* may have the capability to positively influence the immune system. However, additional research is required to verify these findings and establish the optimum dosage suitable for immunostimulation.

9. Limitation and recommended dose of *T. terrestris*

Regarding the recommended dose of *T. terrestris*, there is no universally agreed-upon dosage due to the lack of standardized research and varying formulations of the supplement. The appropriate dose may also depend on factors such as age, overall health, and the specific product being used (e.g., extract, powder, capsules). Despite the lack of well-defined dosage guidelines, some studies have used the following dosages for *T. terrestris* supplementation. For athletic performance, a dosage of 3.21 mg/kg of body weight per day (equivalent to approximately 200–450 mg for an average-weight individual) was used for 20 days [106]. However, more research is needed to determine the optimal dosage for athletic performance. Another study examined the effects of *T. terrestris* on infertility in women and applied a dose ranging from 500 mg to 6000 mg per day to obtain the desired effects [107]. Based on the findings of previous studies, the recommended doses have ranged from 3.21 mg/kg to 500–600 mg/day. However, it is essential to consult with a healthcare professional or a qualified practitioner before starting any new supplement regimen.

Generally, the dietary supplementation of *T. terrestris* is safe if used within permissible levels, however, the higher dose and prolonged intake of *T. terrestris* products caused significant toxic effects, including behavioral changes, organ damage, and even death in some cases [108]. Another study revealed that sheep who consumed a combination of *T. terrestris* and alfalfa (Medicago sativa) experienced hepatogenous photosensitivity approximately 11 days later. The observed signs included feelings of sadness, yellowing of the skin and eyes, loss of weight, inflammation of the outer membrane of the eye, and a reddening of the snout, nose, ears, and eyelids [109]. It has been reported that the chronic toxicity might be attributed to *T. terrestris* extract supplementation in rats [110]. The researchers found that long-term administration of high doses of the extract resulted in adverse effects on liver and kidney function. They concluded that prolonged use of *T. terrestris* should be done with caution, considering the potential toxicity to these organs [110]. Despite the potential nutraceutical effects majority of individuals may not experience the adverse effects when using *T. terrestris*, it is essential to be aware of the potential risks associated with its use, especially when consumed in high doses or for an extended period.

Table 6
T. terrestris uses in Poultry Industry.

Sr. No.	*T. terrestris* used in Poultry	References
1	*T. terrestris* extract has a positive effect on sexual desire and spermatogenesis in Japanese quail, T. terrestris also improve the reproductive and help potential of the rooster.	[135,141, 142]
2	Help in ovulation (Guinea fowls).	[125]
3	*T. terrestris* has a positive effect on Cardio-vascular diseases.	[63,143]
4	Tribulus plant parts contain compounds with proven antimicrobial, antihypertension, diuretic and libido enhancer, and antitumor activity.	[144]
5	Natural antibiotic growth promotor	[145]
6	*T. terrestris* possesses saponins, flavonoids, alkaloids, and glycosides which are a good alternative to allopathic medicines.	[146,147]
7	Increase egg-laying capacity and egg quality	[125]
8	Improve the health performance of broiler chicken.	[105,148]
9	Nutrient digestibility increases by adding *T. terrestris* extract.	[149]
10	*T. terrestris* used to control the intestinal parasitosis.	[150,151]

10. Usage in poultry

Recent research has demonstrated that adding medicinal herbs and natural products to feed can enhance the health, performance, and nutritional digestibility of broilers and layers. Moreover, these additives boost immunity against diseases and aflatoxins [111–114]. The Zygophyllaceae family includes *T. terrestris* [105]. It is reported that the leaf, root, seeds, and fruits of *T. terrestris* all had some degree of phytotherapeutic activity. Protodioscin, glycosides, alkaloids, and flavonoids are the only compounds with potential biological action that are abundant in *T. terrestris* as compared to steroid glycosides (saponins) [17].

> The chicken sector has seen fast expansion, which has made the business more difficult. There is also a need for more high-quality feed. Organic acids, lavender oil, saponins, flavonoids, and other compounds, as well as inorganic ones like antibiotics and growth stimulants, make up most of the phytogenic feed additives [115].

As a result, it is becoming increasingly common practice to utilize phytogenic feed additives as performance enhancers instead of antibiotics [116,117]. *T. terrestris* L., is like a shrub found widely throughout China, Turkey, Korea, Japan, the western portion of Asia, the southern part of Europe, and Africa [118]. A study was carried out to determine the impact of *T. terrestris* L. as an alternative to antibiotic growth promoters, on broiler chicken carcass characteristics, growth performance, and immunological response [105].

The management of poultry illnesses was helped by the saponins derived from *T. terrestris*. Feeding broiler chickens 1g *T. terrestris* powder/kg of feed [119] or 0.06 & 0.12 g of *T. terrestris* crude extract [120] had no appreciable impact on the performance of their growth. On the other hand, broilers' growth performance was enhanced by a diet containing 0.8 g of *T. terrestris* powder/kg feed [121]. In Table 6, the use of *T. terrestris* has been summarized in the poultry industry.

The increased viscosity of the cell membrane inside the liver of broiler birds that obtained an overdose of *T. terrestris* caused cell injury and degenerative alterations, which raised liver function tests [122]. The phytobiotics or naturally derived feed additives (PFAs) have demonstrated several positive impacts on both overall productivity and the well-being of the birds [85].

The bird is a homeotherm species that can only thrive in a limited range of thermoneutral conditions. Cold stress circumstances have negative impacts on the productivity of laying hens, such as reduced egg output or egg weight and lower feed effectiveness [123]. The effects of *T. terrestris* aqueous extract supplementation on laying hen performance, egg quality traits, and blood biochemical markers in poultry housed at low ambient temperature (6.83 °C) were investigated. The results exhibited that egg weight, egg mass, and shell thickness increased while serum cholesterol and FCR reduced significantly in *T. terrestris*-treated groups as compared to the control group [124]. *T. terrestris* extract is also known to increase egg weight, yolk weight, egg production, and egg fertility in guinea fowls [125].

11. Immuno-modulatory effects of *T. terrestris*

T. terrestris, a traditional Asian medicinal plant, and used for therapeutic purposes in the form of whole dried herbs and ripe fruits. It is made up of a variety of chemical components, the most common of which are steroids and saponins [126]. The phagocytosis response to saponins extracted from T. terrestris fruits increased in a dose-dependent manner, indicating the promotion of a non-specific immune response. A considerable dose-dependent rise in the humoral antibody titer and delayed-type hypersensitivity reaction was seen in an alcoholic extract of the entire T. terrestris plant, indicating increased specific immunological response [40].

As an inflammatory mediator, nitric oxide (NO) regulates both the occurrence and advancement of inflammation [127]. The production of nitric oxide is linked to the presence of proinflammatory cytokines TNF- and IL-6, which play a role in triggering and advancing inflammatory conditions. TNF- is a well-known cytokine involved in regulating the immune system and is essential in most inflammatory diseases [128]. Multifunctional cytokine IL-6 is important in immune responses and chronic inflammatory disorders. High levels of IL-6 can cause several pathological conditions that can result in inflammatory illnesses [129]. In lipopolysaccharide-stimulated RAW264.7 cells (Monocyte/Macrophage), the alcoholic solution derived from *T. terrestris* showed the ability to hinder the production of cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS). In macrophage cell lines, it also reduced the levels of proinflammatory cytokines such as tumor necrosis factor-alpha (TNF-alpha) and interleukin (IL-4).

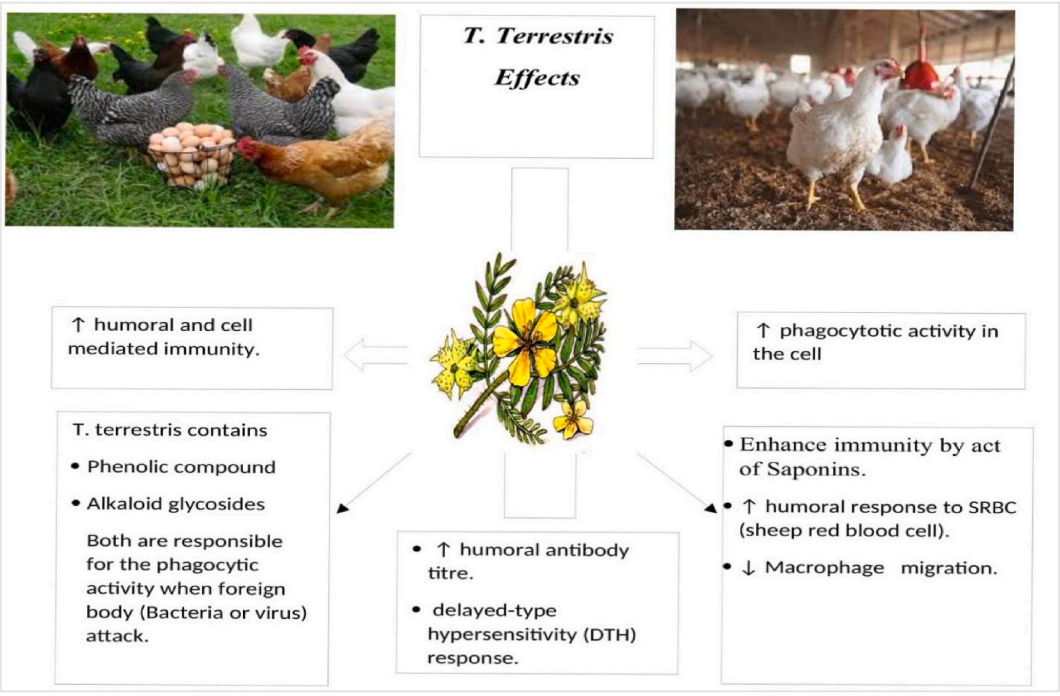

Fig. 6. Tribulus terrestris effects on the Immune system.

Consequently, *T. terrestris*'s ethanolic extract hinders the discharge of inflammatory cytokines and agents, rendering it beneficial in addressing various inflammatory conditions [130]. Kashamov (2007) [131] looked into how adding *T. terrestris* dry extract to the diet of broiler parents affected their reproductive characteristics. At the age of 40 weeks, an experiment was conducted with 154 hens and 20 cocks from the White Plymouth Rock mini population, separated into two groups of 77 hens and ten cocks each. The diets of the two groups of birds were identical. For twelve weeks, experimental birds were fed a dry diet extract of *T. terrestris* at the dose rate of 10 mg per kg body weight once daily. The cocks blood testosterone level, egg incubation, and fertilization were measured. At the end of the trial, the level of serum testosterone in experimental cocks was 29 % greater than that of the control group. The experimental group had a higher percentage of fertilized and incubated eggs than the control group. The impact of *T. terrestris* on the immune system of chicken is depicted in Fig. 6.

In another study, 255 Ross 308 one-day-old, mixed-sex broiler chicks were used to see the impact of *T. terrestris* on the health and well-being of broilers. Broiler chicks' growth performance, body composition, and digestive organs were not affected by *T. terrestris* extracts ($P > 0.05$) [120]. The effect of a dry extract of the annual plant *T. terrestris* on major biochemical and hematological parameters in guinea fowl blood was examined. Thirty gray-pearl Guinea fowl 32 weeks old were divided into two groups, i.e., experimental and control, with 12 females and three males in each group. All of the birds were fed with the same guinea fowl diet. The experimental group's compound feed was supplemented with Vemoherb-T (*T. terrestris*) at a daily dose of 10 mg/kg body weight for 12 weeks. In both sexes of guinea fowl, adding Vemoherb-T boosted hemoglobin levels, and erythrocyte and leukocyte counts, while eosinophils number decreased. The total calcium and protein levels increased significantly in the blood serum of treated birds [132].

By using the NDV Haemagglutination (HA) titer in vivo vero cell line culture, researchers evaluated the anti-viral potential of crude extracts of medicinal plants. It was concluded that saponin, a well-known antiviral compound derived from crude extract of *T. terrestris* exhibited *anti*-NDV activity on the vero cell line without causing a harmful effect. Furthermore, *T. terrestris* alcoholic extracts could be beneficial as preventative measures against NDV epidemics [133]. *T. terrestris* powder, used as an antibiotic growth promoter, acts as a substitute for improved broiler chicken growth performance, carcass traits, and immune responses. Puncture vine (*T. terrestris*) powder could influence the broiler chicken's immune responses and growth performance [105]. As an alternative to antibiotics, *T. terrestris* powder can be employed in broiler diets [121]. The effects of dietary aqueous extract of *T. terrestris* on egg quality, production performance, and blood parameters in laying hens exposed to cold stress were studied in a total of 144 laying hens [124]. Results indicated that significant improvements were observed concerning the productive performance of the layer treated with dry extract of *T. terrestris* at a dose of 10 mg/kg body weight. Guinea fowls and quails exhibit moderate to severe fatty infiltration and liver degeneration, mainly in the males of both species [134]. Nikolova et al. [135] explored how different doses of *T. terrestris* dry extract affected egg production, testosterone levels in the blood, and the histological structure of the gonads and kidneys in Japanese quail. A dose rate of 10 mg/kg of *T. terrestris* extract increases the synthesis of male reproductive cells, whereas a dose of 4 mg/kg causes spermatozoa generation to be delayed. The kidney structure was preserved, and the larger doses resulted in a certain reduction of the kidney parenchyma.

12. Conclusion and future perspective

This extensive review provides a detailed understanding of *T. terrestris*, encompassing its phytochemistry, phytopharmacology, positive impacts, and therapeutic applications. The entire *T. terrestris* plant's phytochemical and pharmacological activities have been intensively explored, including diuretic, anti-urolithiasis, anti-hypertensive, analgesic, *anti*-hyperlipidemic, immunomodulatory, antidiabetic, anticancer, anti-helminthic, aphrodisiac, antibacterial, hepatoprotective, and anti-inflammatory properties. Because of its potassium-sparing, cardioprotective, and *anti*-hyperlipidemic properties, *T. terrestris* may have the potential of herbal therapy for successful blood pressure control. Other pharmacological characteristics of the plant have also been reported. Dietary supplements containing *T. terrestris* extracts are claimed to improve rat sperm production while keeping circulating androgen levels constant. As an aphrodisiac, *T. terrestris* has found widespread use. *T. terrestris* protects against neuronal damage primarily through its anti-inflammatory and antioxidant properties. The underlying mechanisms of action behind the phytochemical's function may vary across different species and remain incompletely understood, therefore further research is needed to explore completely. Moreover, future research is necessary to identify relevant markers at the biological and molecular levels, which contribute to the diverse range of health benefits associated with *T. terrestris* in both humans and animals. To facilitate the development of novel medications, pharmacological studies involving this plant should be continued and extended to clinical trials, to fully comprehend how *T. terrestris* affects the progression of diseases.

CRediT authorship contribution statement

Muhammad Saeed: Conceptualization, Writing – original draft. **Mahzaib Munawar:** Formal analysis, Writing – review & editing. **Jannat Bi Bi:** Formal analysis, Writing – review & editing. **Shabbir Ahmed:** Investigation, Methodology, Writing – review & editing. **Muhammad Zia Ahmad:** Software, Writing – review & editing. **Asghar Ali Kamboh:** Methodology, Writing – review & editing. **Muhammad Asif Arain:** Visualization, Writing – review & editing. **Muhammad Naveed:** Validation, Writing – review & editing. **Huayou Chen:** Supervision, Writing – review & editing.

Declaration of competing interest

The author declared that they have no conflict of interest.

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