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Review Article

Morphology, Biological Activity, Chemical Composition, and Medicinal Value of *Tinospora Cordifolia* (*willd*.) *Miers*

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ABSTRACT

This review aims to highlight the morphology, taxonomy, and biological activities of *Tinospora cordifolia* along with its ethnobotanical uses and its micropropagation techniques. Relating to the global pandemic, this review introduces a comprehensive update of COVID-19 scientific reports on *T. cordifolia* as an indispensable herb. This study also explores the nutritional values and elemental composition from proximate analysis along with its phytochemical and medicinal properties. *T. cordifolia* is a medicinal plant widely used for the treatment of various diseases such as diabetes and jaundice. This plant is mainly found in the southern part of Asia and is locally known as Gurjo or Guduchi. *T. cordifolia* exists in the form of a glabrous, ascending shrub belonging to the Menispermaceae family. Owing to its commercial importance, *it* has been of considerable interest in research in recent decades, incorporating a wide range of pharmacological properties, such as antidiabetic, immunomodulation, antioxidant, anticancer, hepatoprotective, and hypoglycemic values. These properties are enhanced by the presence of diverse compounds such as alkaloids, sesquiterpenoids, diterpenoids, phenolics, glycosides, steroids, and polysaccharides, aliphatic, and other miscellaneous compounds. This review provides new details that can facilitate the careful assessment of the plant as a therapeutic agent against emerging diseases. It also offers insights to the researchers involved in validating traditional claims to develop safe and efficient herbal medicines to several diseases including COVID-19.

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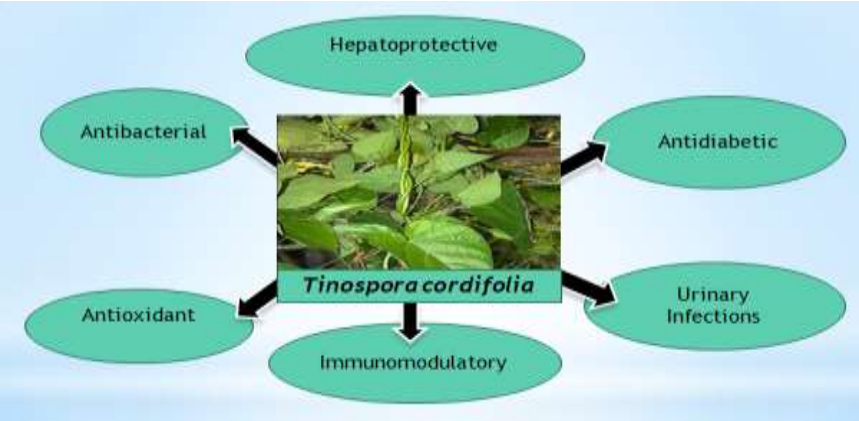
GRAPHICAL ABSTRACT



Introduction

Natural products chemistry is the research and medicinal applications of the secondary metabolites [1]. While there are about 250,000-400,000 plant species, just 15% of which were phytochemically assessed, and 6% have been examined for their biological activity [2-3]. Plant species have been utilized since ancient civilizations to combat human illness without acknowledging the chemical components and bioactivities [4-5]. Oils of both the *Cupressus sempervirens* (Cypress) and Commiphora (myrrh) species were the very first known natural products portrayed on Mesopotamian cuneiform clay tablets (2600 BC). It is still used to cure coughing fits, sinus infections, and inflammations [6]. Friedrich Bayer and Co. formulated a synthetic form of the acetylsalicylic acid (aspirin) in 1897. The other conventional drugs, including morphine (from the opium poppy), quinine (from cinchona bark), digoxin (from foxglove), are derived from plants. Plants encompass a variety array of bioactive molecules, making them a rich source of diverse pharmacological sources. Several naturally occurring plant isolates have been recorded to prevent free radical-induced harm attributed to the prevalence of phenolics, flavonoids, antioxidants, and secondary metabolites [7]. Modern drugs, often relying on their use in traditional remedies, have been extracted from natural origins "in press" [8]. *T. cordifolia* is widely recognized as Guduchi or Gurjo is a traditional medicinal plant belonging to the Menispermaceae family of moonseeds [9]. Family Menispermaceae is widespread in tropical lowland regions composed mainly of 70 genera and 450 species. *Tinospora* genus is among the prevailing genera in the family Menispermaceae, containing around 15 distinct species [10]. This family is a rich source of terpenes and alkaloids. They generally climb or twin, frequently with shrubs [11]. *T. cordifolia* owing to the Menispermaceae family, scattered in tropical India and reaching an altitude of 1000 feet in South Asia, Indonesia, the Philippians, Thailand, Myanmar, China, and Srilanka worldwide [12]. It is present in a wide variety of soil, acid to alkaline, and requires a modest amount of soil moisture is commonly used in therapeutic folk and ayurvedic systems [13].

T. cordifolia is indeed one of the plants of tremendous promise regarding its ability to tackle the disease. This is an anti-allergic, anti-inflammatory, immunosuppressive, immunomodulatory, anticancer, hypoglycemia plant. Besides these, it is also known for its antibacterial and antioxidant properties [14].

Taxonomy of plant

T. cordifolia is an angiosperm belonging to the Menispermaceae family and is a division of Magnoliophyta, class Magnoliopsida, and order of Ranunculaceae. It is a thoroughly branched deciduous, twiner. It is known as "heart leave moonseed" [15]. The plant has many vernacular names. It is named in Latin as *Tinospora cordifolia* (Miers) Hook. F. & Thomson, known in Sanskrit as Guduchi, Madhuparni, Amrita, Chinnaruha, Vatsadaani, Tantrika, Kundalini, known in Nepal as Gurjo, widely recognized in Hindi as Giloya or Guduchi and regarded in Bengali as Gulancha [16].

Morphological description

T. cordifolia is a wide deciduous, glabrous, rapidly ascending shrub with several coiling branches extending approximately 3-4 feet in height and roughly 1 foot long [17]. *T. cordifolia*'s stem is quite scrumptious, with long filiform fleshy aerial branch roots [18]. The plant stem is greyish brown-black in color, bitter in texture, soft wooded, dry, cylindrical, and also in circumference from 5 mm to 25 mm [19]. The leaves are simple, 5-10 cm long, alternating, ex-stipulated, long petiolate (2.5-7 cm), rounded chordate with multi-coated reticulated midrib. From the branches appear long tentacle-like aerial roots [20]. The bark is slender, greyish, or texture creamy when exposed to meticulously peeled stem [21]. The flowers are yellow or yellow-greenish, and tiny. The male flowers are concentrated in adjunct and terminal racemes or racemose panicles, while the females are usually solitary [22]. The composite fruit is red, fleshy, with extensive drupelets on a thick stalk with border sub-terminal form, colored scarlet [23]. The curved seed has been documented for this plant. Hence, this family is also recognized as the moonseed family. Seeing as seeds are curved in shape, the embryo also turned in instinctively for curving form. Alternatively, the endocarp is decorated in varied contexts and gave valuable taxonomic characters [24].

Ethnomedicinal uses of T. cordifolia in Nepal

Nepal has more than 700 medicinal plant species in record. The species diversity in Nepalese plants provides excellent potential to discover medicinal products. *T. cordifolia* is indigenous to South Asia, is often used as a medicine in many places in Nepal [25].

More than 61 ethnic groups in Nepal are distributed throughout the countries. Tamang's major ethnic groups of Nepal have accounted for 5.5% of the country's total population. They employ *T. cordifolia* stem extract in health difficulties associated with menstrual cycle [26]. Raji ethnic tribe of Surkhet district chooses *T. cordifolia* for gastrointestinal disorder treatment. In fever and stomach disorders, they use climber tuber in gastric, diarrhea, and juice extracted from the tuber and root is drunk [27]. Residents have used *T. cordifolia* throughout the Chitwan district of Nepal in the treatment of fever, jaundice, cough, asthma, skin diseases, leprosy, splenopathy, uropathy, gonorrhea, gout, immunomodulator [28]. Tharu tribe of Parsa district has been using *T. cordifolia* to treat various human diseases [29]. Stem powder of *T. cordifolia* was found to be used in the cure of jaundice, diabetes, and rheumatoid arthritis in an exclusive survey conducted in the Parsa district. They squash *T. cordifolia* stem, keep overnight in water, and the next morning decant water to drink to cure stomach disorders. Similarly, stems and roots powder are used in urinary infections and chronic diarrhea. Leaves have been used for diabetes treatment [30].

Residents from the district of Rupandehi, use the juice of fresh leaves and stems from treating rheumatic hyperacidity, as stem decoction in gonorrhea and Jaundice, as well as root extract, is used in fever, cold cough [31]. Local people of Siraha district Nepal are using stem and leaves in the treatment of diabetes [32]. In Tanahun district of Western Nepal, *T. cordifolia* stem Juice

applied on sprain and drink for body cooling [33].

Even though the *T. cordifolia* plant has promising action against many diseases, it trades commercially in Dhading and Dharan district with low prices [34-35]. *T. cordifolia* enlisted as a rare species because it is decreasing from the natural habitat. This indicates that climate change might have influences affect and significantly changed the composition of the vegetation [36]. Traditional vegetative propagation has limited applicability for large-scale cultivation of this plant. Micropropagation technique can be most useful for its mass propagation as well as for its conservation [37].

Biotechnological advancement and micropropagation in *T. cordifolia*

Plant species have various medicinal values [38]. Regardless of its wide medicinal uses in conventional and contemporary medicines systems the plant *T. cordifolia* rapidly declines from its natural habitat. Although the conventional approach is not enough to mitigate depletion, biotechnological approaches for accelerated dissemination, scaling up secondary metabolites, and conserving valuable, scarce, and vulnerable medicinal plants should also be used [39]. The culture of plant tissue in the current sample was exceptionally successful as a consequence of the regeneration, induction, and micropropagation of calluses. In vitro, micropropagations are one of the best alternative methods for the rapid clonal mass propagation for a good and healthy high yielding plant with the minimum disease [40]. Cell culture is a requirement for certain other biotechnology methods for developing organisms, such as genetically engineered organisms and effective metabolite in vitro development [41]. The plant is cultivated as an aesthetic alternative and propagated successfully by tissue culture. It is best suited for growing in virtually any kind of soil and under various atmospheric conditions. Growing on the neem tree is adequately trained; this will then display a greater medicinal aristocracy. This can also be improved by sowing the seeds in monsoon, but the growth of seedlings is very slow compared to cuttings [42]. Seed viability, however, is very small, and seedlings are key issues of big clonal propagation. The plant is very resilient and can also be harvested in areas of tropics and subtropics but chiefly in dry and rainy habitats. It does not withstand heavy precipitation and waterlogging situations [43]. Biotechnological tools may play a significant part in the discovery, replication and survival of this species' sensitive genotypes. Also, biotechnological methods and techniques have opportunities for the replication and genetic improvement of suitable genotypes, and the better micropropagation has potential for industrial processing of secondary plant metabolites.

Natural binder

Mucilage was derived from the fresh stem of *T. cordifolia* which was further defined for physicochemical parameters. Diclofenac sodium tablets were prepared from the mucilage of *T. cordifolia* which acts as a natural binder when it is a concentrated method of dry granulation. Experimental results have revealed *T. cordifolia* mucilage use in the formulation of continuous release dosage formulations as a drug retardant [44].

Tinospora cordifolia and its probable role in the treatment of COVID- 19

COVID-19 (Coronavirus disease 19) has emerged as the world's most dangerous pandemic threat since its December 2019. Resolving the issue for this deadly virus has become a big challenge for the researchers and medical professionals. The finest ways to prevent COVID19 infection are breaking the chain of infection, boosting the body’s immune system, detecting early and

appropriate preventive medical care for the infection [45]. In viral respiratory infections, several phytomedicinal plants help to build the immune system. *T. cordifolia* is one of the traditional medicinal plants used as tonic and vitaliser to enhance the body's natural resistance diuretic [46]. *T. cordifolia* stem and whole herbs have demonstrated immunomodulatory activity and hence suggested for the broad-spectrum antivirals and protease inhibitors [47]. It has been shown that the *T. cordifolia* aqueous extract activates macrophages which form the first line of defense against pathogens that invade the living system [48].

COVID-19 enters into a host cell by binding to ACE2 (Angiotensin Converting Enzyme-2) via its spike protein receptor-binding domain (RBD). If this interaction could be disrupted, virus accession could be avoided, thereby significantly reducing the infection rate. The phytochemical compound, "tinocodiside" has the activity of which is known to bind to the complex ACE2-RBD and therefore, can discourage the entry of the virus [49-50]. They may revive lung health by reducing oxidative stress and enhancing endothelial dysfunction [51]. The stronger docking between ligands and viral targets was revealed in the study of molecular docking with the least binding energy.

Therefore, it was reported that phytoconstituent, cordifolin extracted from *Tinospora cordifolia* evoked the least binding energy to exhibit antiviral activity [52]. Similarly, the results of the simulation also demonstrated that berberine can form 3-chemotrypsin-like protease ($3CL^{pro}$) docked complex with better stability and could act as a better CoV-2 protein inhibitor compared to other inhibitors. Since berberine is in good binding interaction mode with less binding energy and greater non-bonded interaction capacity, therefore it established a strong candidacy to represent potential inhibitors in monitoring the role of the $3CL^{pro}$ protein as well as further better control against viral replication [53].

Molecular docking findings showed that tinocordiside exhibited binding affinity as predicted to act as probable SARS-CoV-2 (Severe Acute Respiratory Syndrome) Coronavirus-2) main Proteases (M^{pro}) inhibitor. Such phytoconstituents not just to inhibit the transmission and propagation of viral protein into the host cell within the human body. Additionally, they are also safer to repurpose against COVID-19 without any toxicity [54].

Nutritional and elemental analysis

T. cordifolia typically contains fiber (15.9%), ample protein (4.5%-11.2%), adequate carbohydrates (61.66%) and low fat (3.1%), high potassium (0.845%), chromium (0.006%), iron (0.28%), calcium (0.131%). Its nutritional value stands at 292.54 calories per 100 g [55]. Reported that the elemental composition of *T. cordifolia* deseeded fruit were iron, copper, zinc, magnesium potassium, and sodium. The lack or abundance of these trace elements related to the biological functions of the different disorders. Here we mentioned the function of the elements and problems linked to these deficiencies [56].

Table 1, Role of elements and problems associated with their deficiency [57-67]

S.N.	Element	Role of element	Deficiency
1.	Ca	Helps develop healthy bones, teeth, and protect them. It is also vital for adequate cardiac muscle functioning, regulation of blood coagulation with cell permeability, and milk clotting.	Cramping of the uterus, rickets, irritability, back pain, premenstrual, osteoporosis, indigestion.
2.	Cu	Helps in the growth, development, and maintenance of bone, connective tissue, brain, heart, and many other body organs	Cardiac abnormalities in human and animal, anemia, and neutropenia.
3.	Zn	Helps to construct and maintain DNA, required for growth and repair of body tissues, which is necessary for growth and repair of body tissues, essential elements of ligaments and tendons, and zinc supplements.	Growth delay, diarrhea, pneumonia, distributed neuropsychological performance and abnormalities of fetal development
4.	P	Helps to maintain blood sugar level and heart contraction, for normal cell growth and repair, needed for bone growth, regulate kidney function.	Bone disease, fragile bone, hypophosphatemia, anxiety
5.	N	Helps to maintain tissue excitability, carry normal muscle contraction, help in formation of gastric juice in stomach.	Kidney problems, muscles pain.
6.	Na and K	Helps to maintain the blood pressure by working Potassium with sodium to maintain the body's water balance, acts as nerve impulses, regulate heart rhythms.	Nervous irritability mental disorientation, low blood sugar, insomnia, and coma hypertension.
7.	Fe	Helps to make body tendons and ligaments, controls brain function, helps in formation of hemoglobin, carries oxygen around the body.	Anemia, weakness, depression.
8	Mg	Helps in functions and formations of bones and muscles, prevents high disorder, high blood pressure and depression.	Transmission of nerve and muscle, irritability, and nervousness.
9	Cr	Helps in works with insulin to stabilize blood sugar level, absorbs energy from blood, increase muscle mass by reducing fat mass in human body.	Growth failure, cataract, hyperglycemia, neuropathy, atherosclerosis, and diabetes.

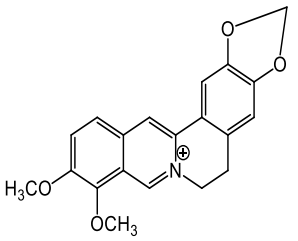
Chemical constituents of *T. cordifolia*

Literature analysis of plant phytochemical assessments indicates the existence of a wide variety of phytoconstituents. This plant has isolated a wide range of chemical constituents and their structures have been developed. Alkaloids, diterpenoid lactones, glycosides, hormones, sesquiterpenoids, phenolics, aliphatic compounds and polysaccharides are active ingredients [68-69].

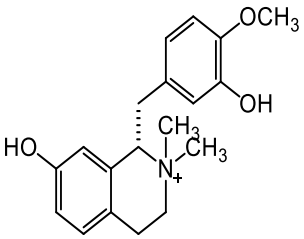
Table 2, Phytochemistry of *T. cordifolia* plant

S.N.	Phytochemical Class	Phytoconstituents	References
1.	Alkaloids	Berberine, Tembeterine, Choline, Aporphine alkaloids, Jatrorrhizine, Magnoflorine, Tetrahydropalmatine, Tinosporin, Palmetine, Isocolumbin.	[70-75]
2.	Terpenoids	Tinosporide Furanolactone diterpene, Furanolactone clerodane diterpene, phenylpropene disaccharides cordifolioside A, B and C, cordifoliside D and E, Tinocordioside, cordioside, palmatosides C and F, furanoid diterpene, Tinosporaside, ecdysterone makisterone and several glucosides isolated as poly acetate	[76-80]
3.	Glycosides	norclerodane glucoside,furanoid diterpene glucoside, cordiofolioside A, cordiofolioside B, palmatosides C, palmatosides P1, cordiofolioside C,cordiofolioside D, cordiofolioside E	[81-84]
4.	Sesquiterpene	Tinocordifolin	[85-86]
5.	Steroids	β–sitosterol, δ-sitosterol, 20 β-hydroxyecdysone, Ecdysterone, Makisterone A, Giloinsterol	[87-89]

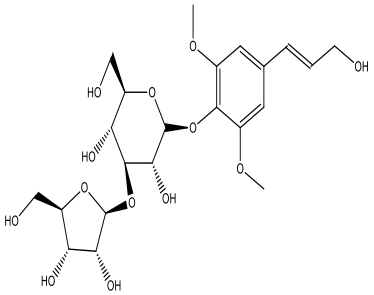
Structure of some major chemical constituents;



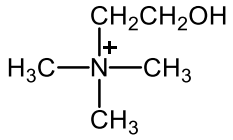
Berberine



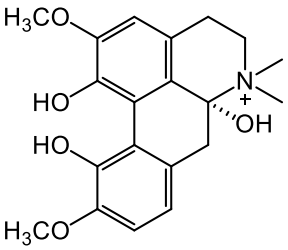
Tembeterine



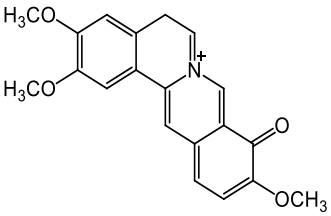
cordifoliside



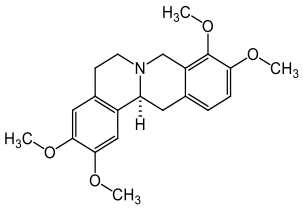
Choline



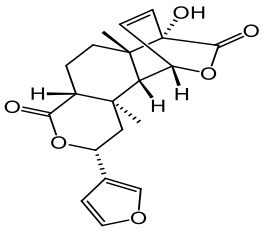
Magnoflorine



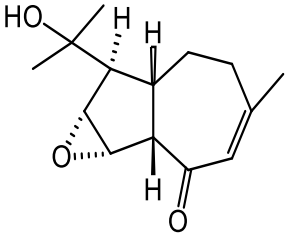
Palmetine



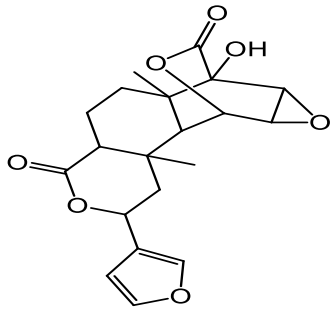
Tetrahydropalmatine



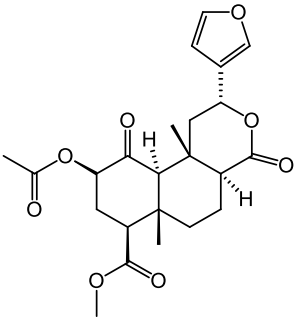
Isocolumbin



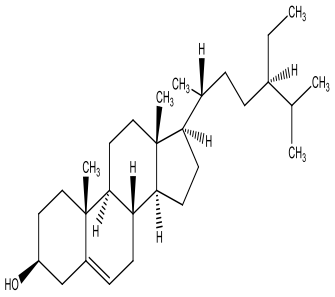
Tinocordifolin



Tinosporide



Furanolactone



β–sitosterol

Fig. 1, Chemical constituents present in *T. cordifolia* [70-89].

Medicinal Properties

Antidiabetic property: *T. cordifolia*'s stem is widely used for diabetes control by monitoring blood glucose rates [90]. The Aquatic extract is efficient in lowering blood sugar rates than glibenclamide [91]. Plant extracts are potent towards fructose-induced hyperglycemia, oxidative stress, hypertriglyceridemia, hyperinsulinemia. *T. cordifolia* aqueous extract treatment avoided a 21.3% rise in glucose levels of 51.5% of insulin, 54.12% of triglycerides, and 59.8% of the fructose-fed rats of the glucose-insulin index [92]. The various solvent extract of *T. cordifolia* stem has been observed having positive antidiabetic activity in orally to suppress blood sugar level in streptozotocin (STZ) mediated diabetic rats [93].

Antioxidant activity: *T. cordifolia* has shown promising antibacterial and antioxidant behaviors. The plant's leaf extracts encompass several phytochemically active compounds, including alkaloids, glycosides, flavonoids, hormones, tannins, terpenoids, saponins, and sugar. The methanol, chloroform, and ethyl acetate extract were extremely antibacterial in the bacteria being tested. They also recorded admirable antioxidant activity in methanol and water extracts [94-95]. The juxtaposition between antioxidant behavior and the overall phenol content was established. The ethanolic bark extracts possess a higher phenolic content such that it exhibits the maximum free radical scavenging level (71.49%). The finding indicates that *T. cordifolia* should be used as a potential drug vector for degenerative diseases caused by free radicals [96].

Antibacterial activity: Methanolic extract of *T. cordifolia* was documented against microbial infection. Using a particular solvent extract from various parts of the herb, *T. cordifolia*'s antibacterial behavior was observed. Antibacterial activity of guduchi is against the urinary tract pathogens in which a different degree of inhibition against various microorganisms was demonstrated [97]. The experiment was conducted for the plant-mediated synthesis of silver nanoparticles using *T. cordifolia* dried stem powder. Additionally, antibacterial activity was tested and compared with antibiotics. Further synthesized silver nanoparticles were characterized by EDAX analysis, XRD, UV-Visible spectrophotometer, FTIR, and TEM. Those nanoparticles were found to kill the resistance bacteria by exhibiting antibacterial activity [98].

Hepatoprotective activity: Hepatoprotective behavior is well known in various sections of *T. cordifolia*. The hepatoprotective role of *T. cordifolia* is may be due to multiple factors, such as the ability to promote hepatic regeneration, and the properties of antioxidant or free scavenging [99]. However, in comparison with *Tinospora sinesis, T. cordifolia* has the lower hepatoprotective capacity [100]. It aids prevent fibrosis and promotes hepatic tissue regeneration. It benefits tremendously in fatty liver [101].

Immunomodulatory activity: *T. cordifolia* is renowned as a Rasayana plant and has been used for far too many decades in Ayurveda as a revitalizing herb and other medicinal regimens [102]. The various extracts of *T. cordifolia* have immunomodulatory properties, and anti-tumor effects. Synergic findings have been shown in the removal of cyclophosphamide tumors in animals [103-104]. *T. cordifolia* is predominantly antimicrobial to urinary tract infection bacteria, acting as an immunomodulator, helping to remove pathogenic organisms, and boosting the immune system of the patient to mitigate inflammation. *T. cordifolia* activates macrophages and other immune cells such as interleukins and TNF promote the immune potential of the animal [105].

Aphrodisiac activity: Hydroalcoholic and aqueous extracts of *T. cordifolia* stems were phytochemically tested for the identification of steroids, gums, sugars, fats, saponins, alkaloids, glycosides, and mucilage. *Hydroalcoholic cordifolia* stem extracts at lower concentrations

(200 mg/kg body weight) and aqueous extracts (400 mg/kg body weight) exhibited significant aphrodisiac properties relative to higher aphrodisiac activity concentrations (400 mg/kg body weight) in male Wistar albino rats [106].

Nephroprotective activity: The vital function of *T. cordifolia* in the nephrotic syndrome, which is an illness that causes kidney damage, has shown that the plant has sufficient immunomodulating, antioxidant, anti-inflammatory, and nephroprotective properties and can thus, be used to treat nephritis. The implications of therapy with steroids and the frequency of NS rebound are both minimized. *T. cordifolia* also allows new pharmaceutical drugs to improve their potency and health. It can also be combined with modern therapeutic medications in treating Nephritic Syndrome with steroid-resistant and steroid-dependent and frequency relapse [107].

Toxicology: *T. cordifolia* roots, stems, and leaves have no detrimental impact on the human body when administered orally [108]. The toxicity of *T. cordifolia* in humans is still little understood. No adverse effects were observed when the extract of *T. cordifolia* stem was administered to rabbits at the maximum oral doses of 1.6 g/kg, and in rats at 1000 mg/kg of the whole plant extract. But, when mice were given 500 mg/kg of stem extract body weight, there was 40% mortality [109].

Others use: *T. cordifolia* stem aqueous extract manifests radioactivity defense [110]. In jaundice treatment, *Tinospora cordifolia* stem is used, as it removes body heat [111]. Polyherbal *T. cordifolia* formulation was shown to have a positive effect on HIV patients [112]. It is sometimes used in combination with other drugs as an alternative to the snakebite and scorpion string [113]. Plant stem juice is useful for discharge in asthma, dyspepsia, vaginal, and urethra. The root and stem powder are used along with milk for cancer treatment. The whole *T. cordifolia* plant is used in swine scabies, diarrhea, urinary diseases, syphilis, skin diseases. *T. cordifolia* is also effective in Parkinson's disease as well as bronchitis, to promote survival, boost body resilience, and boost the immune system [114-115]. Methanolic extract of *T. cordifolia* showed excellent wound healing activity by increasing granulation tissue tensile strength [116].

Conclusion

T. cordifolia is a traditional medicinal herb, with myriad biological activities used predominantly as therapeutic drugs in South Asia. Despite having tremendous medicinal properties, *T. cordifolia* has been decreasing from the natural habitat rapidly. Consequently, it is crucial to pick, classify, and preserve the planting material through biotechnological advancement is much needed.

Conflict Of Interest

The authors declared that they have no conflicts of interest.

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