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GILOY: DERIVED EXTRACELLULAR VESICLES AN EMERGING APPROACH TO IMMUNOMODULATION

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ABSTRACT

Guduchi (*Tinospora cordifolia*) is a well-recognized and widely distributed traditional plant that is used successfully in Indian Ayurveda medicine. *T. cordifolia* has shown many promising biological activities, such as anti-oxidative, antimicrobial, anti hyperglycemic, anti-inflammatory, osteoprotective, hepatoprotective, antidiarrheal, and anti-stress effects. Guduchi is a rich source of protein and micronutrients, such as iron, zinc, copper, calcium, phosphorus, and manganese. It also holds many secondary plant metabolites, such as terpenes, alkaloids, flavonoids, steroids, and glycosides. Based on earlier studies in poultry, the supplementation levels of Guduchi range from 1 to 5 g/kg of diet (various sources, such as powder, extracts, roots, and leaves, have been used). It was suggested that this variation in supplementation levels depends on varied factors, including the extraction method, the supplementation proposed, the method of supplementation (either in feed or drinking water), and the species and physiological status of the birds. Dietary supplementation of poultry broilers with *T. cordifolia* yielded positive impacts on growth performance, body gains (increased by 4.8%), dressing percentage (increased by 7.1%), meat quality traits, and the shelf life of the meat. In addition, T. cordifolia exerted a palliative effect on the general health status of the birds through reducing live enzymes and plasma uric acids and enhancing the immune response, as shown by the leukocyte count, hemagglutinin titer, interleukin activity, and mortality levels. Further investigations concluded that *T. cordifolia* showed strong antimicrobial effects against Escherichia coli and Salmonella enteritidis, with later reductions in mortality. Moreover, *T. cordifolia* showed an ability to improve humoral and cell-mediated immunity against Newcastle disease, infectious anemia, gout, and aflatoxicosis. The current review discusses many beneficial properties of *T. cordifolia*, although the lack of pharmacological trials limits the use of this extract in poultry. Further research should be performed about the composition of the active compound, the possible mechanisms of action, and the effective doses to fully understand the activities and benefits of *T. cordifolia* as a growth performance improvement supplement.

KEYWORDS: Guduchi, *Tinospora cordifolia*, clinical pharmacology, feed supplement, poultry-vesicular body (MV), Keyboard Phytochemical diversity.

INTODUCTION

Medicinal plants have been an essential part of conventional health care around the world for ages since Ayurveda.[1] According to these natural resources offer a wide range of chemicals that are bioactive with a variety of therapeutic potential. *Tinospora cordifolia*, often called Amrita or Guduchi, holds a great significance in Ayurveda owing to the presence of various secondary metabolites.[2,3] Gilroy leaves have historically been used to cure a variety of ailments, such as diabetes, rheumatism, jaundice, and skin diseases.[4,5] Because of its historical use and the increasing popularity of natural therapies, scientists are looking into the possible therapeutic uses of Giloy leaves and the underlying mechanisms behind their medicinal action.[6] Extract of the giloy leaves helps to alleviate the digestive ailments

such as acidosis, gastroenteritis, parasitic infections, lack of appetite, stomach discomfort, extreme thirst, and nausea, as well as liver-related issues like hepatitis.[7] The latest study shows that giloy leaves immunomodulatory capabilities may be associated with its many potential uses. These characteristics may strengthen the immunological response within the body, providing a natural means of promoting general well-being.[8] Despite having a wide range of uses in traditional medicine, the immunomodulatory effects of giloy leaves are less known.[9]

Tinospora cordifolia is a member of the Menispermaceae family, which is part of the Ranunculales order in the Magnoliopsida class (commonly known as dicots) of the plant world. This classification includes it amid a wide range of blooming plants, while the o family is best recognized for its climbing vines and bushes. Tinospora cordifolia, often known as Guduchi or Gurjo, is an ancient medicinal plant from the Menispermaceae family of moonseeds.[10] The Menispermaceae family is abundant in tropical lowland environments, with 70 genera and 450 species. Tinospora is one of the most common genera in the Menispermaceae family, with around 15 diverse species.[11] Tinospora cordifolia is extensively widespread in Tropical India and may reach elevations of 1000 feet in South Asia, Indonesia, Philippines, Thailand, Myanmar, China, and Sri Lanka.[12] Ayurvedic and folk medicine systems often employ this compound, which may be found in a wide range of soil types (from acidic to alkaline) and only needs a small amount of soil moisture.[13] Tinospora cordifoli is a climbing shrub belonging to the Menispermaceae family that includes more than 400 plant species.[14] The present scientific name of this plant is Tinospora cordifolia (Willd.) Hook.f. & Thomson according to the 'USDA-ARS GRIN Taxonomy,' while its scientific name as per the 'International Plant Names Index' is Tinospora cordifolia. Thus, we have referred to it as Tinospora cordifolia in the later text. This plant has gained tremendous therapeutic interest and significance during the COVID-19 pandemic due to its enormous therapeutic potential.[15] It originated in Africa in the Oligocene epoch (28.57 million years ago) and was spread to Asia in the early Miocene epoch (21.54 million years ago).[16] Being a climber, it needs a supportive plant like *Jatropha curcas* (Jatropha), *Azadirachta indica* (Neem), *Moringa oleifera* (Moringa), etc., for its growth.[17] These supportive plants also play a significant role in enhancing the production of various secondary metabolites of *T. cordifolia*.[18] *T. cordifolia* produces an array of secondary metabolites in response to stress conditions, and their concentration also varies based on seasons and its dioecy nature.[19] The chemical constituents of this plant are broadly categorized as alkaloids, terpenoids, phenolics, polysaccharides, steroids, essential oils, aliphatic compounds, etc., which can be obtained from various parts of the plant.[20]

study reported that among the two species of *Tinospora* (i.e., *T. cordifolia* and *T. saneness*), *T. cordifolia*produces three times higher concentration of an alkaloid, berberine, than *T. saneness*, and thus the former is preferred in therapeutics.[21] Its bioactive compounds have known biological properties such as antioxidant, antipyretic, anti-diabetic, anti-inflammatory, anti-microbial, anti-viral, anti-arthritis, anti-osteoporotic, anti-HIV, anti-cancer, hepatoprotective, anti-malarial, immunomodulation, etc.[22] These properties make this species useful in the traditional treatment of several ailments, including fevers, cough, diabetes, general debility, ear pains, jaundice, asthma, heart diseases, burning sensation, bone fracture, urinary problems, chronic diarrhoea, dysentery, leucorrhoea, skin diseases, cancer, helminthiasis, leprosy, and rheumatoid arthritis.[23] Plants, as natural sources of medicine, have significant potential for disease treatment owing to their abundant resources and easy accessibility.[24] Various plants have anti-inflammatory, antimicrobial, and tumor-inhibiting effects, strongly supporting the research and development of plant-based medicines.[25] For example, the active ingredients in turmeric and dandelion can inhibit inflammatory responses and alleviate related disease symptoms.[26] Artemisinin is used to treat tuberculosis infection because its effective components can eradicate this deadly pathogen.[27] [7] Additionally, some plants have applications in cancer treatment, for example, certain compounds in *Tripterygium wilfordii* with tumor growth inhibition properties.[28] Despite this progress, traditional methods for preparing plant-based medicines keep the complexity of their natural components. This complexity can lead to toxicity and side effects, even when the therapeutic effects are produced.[29] Furthermore, the unclear treatment mechanisms of plant medicines make it challenging to understand their actions and associations with diseases. Therefore, novel strategies are needed to extract and purify effective components from plant-based medicines to elucidate their treatment mechanisms and expand the prospects of their application in disease treatment.[30] The emerging concept of exosomes has sparked interest in their application in plant-based medicine. Exosomes, widely distributed extracellular vesicles (EVs) in organisms, serve as natural conveyors for a variety of biomolecules. Their stable lipid membrane structure enables the secure delivery of bioactive molecules to damaged cells.[31] Furthermore, bioactive molecules encapsulated within EVs are typically more targeted and precise, thereby easing enhanced precision in disease treatment. Although significant research has focused on EVs derived from mammalian cells, plant-derived EVs have also garnered attention because of their distinct characteristics. Plant-derived EVs can evade the detection of immune function and therefore have a longer duration of action in the body.[32] Giloy is one such medicinal herb that is highly valued in Ayurveda. and is said to have several potential health benefits. It aids in treating distinct types of fevers and other health related problems. It is believed to be one of the

'immortality' plants and called as Amrit or amritavalli in Sanskrit.[33] Giloy scientifically is the Tinospora Cordifolia plant, belonging to the family Menispermaceae. Commonly known as Guduchi, Gurcha, and heart-leaved moonseed, this plant is cultivated in tropical and subtropical region and is known for its rich nutritional value. The stem, root and leaves of this plant are used in ayurvedic medicines to manage several health conditions. Fresh plant is more commonly used than dried plant, because of its high effectiveness.[34] The significant immunomodulatory qualities of *Tinospora cordifolia* leaves are attributed to a plethora of bioactive substances.[35] These active ingredients include alkaloids (found primarily in the stem) and steroids (beta-sitosterol, d-sitosterol, and g-sitosterol), as well as glycosides (18-norclerodane glycosides, furanoid determine glycosides, and tinocordiside) and palatine D, choline D, tinosporine, magnoflorine, tetrahydropalmatine, and isocolumbin).[36] Added components found in its aerial sections include diterpenoid lactones (furanolactone, tinosporon, and columbin) as well as many other substances such cordifolioside A, 11-hydroxymuskatone, N-methyl-2-pyrrolidone, octacosanol, heptacosanol, and nonacosan-15-one.[37] Further research into the exact mechanisms of these active ingredients will help to clarify the immunomodulatory potential of giloy leaves. The various mechanisms through which bioactive compounds of leaves help in boosting the immunomodulatory properties of the body have been illustrated in Fig .1

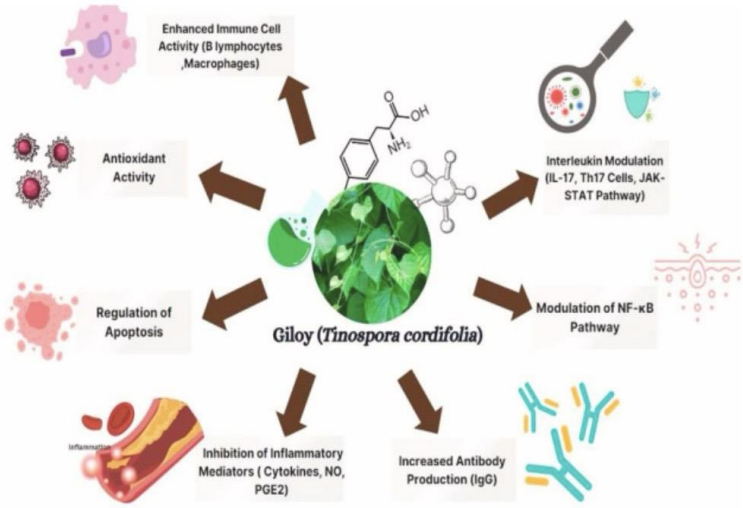
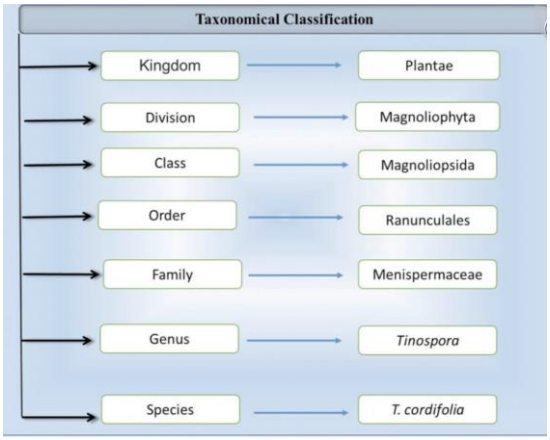


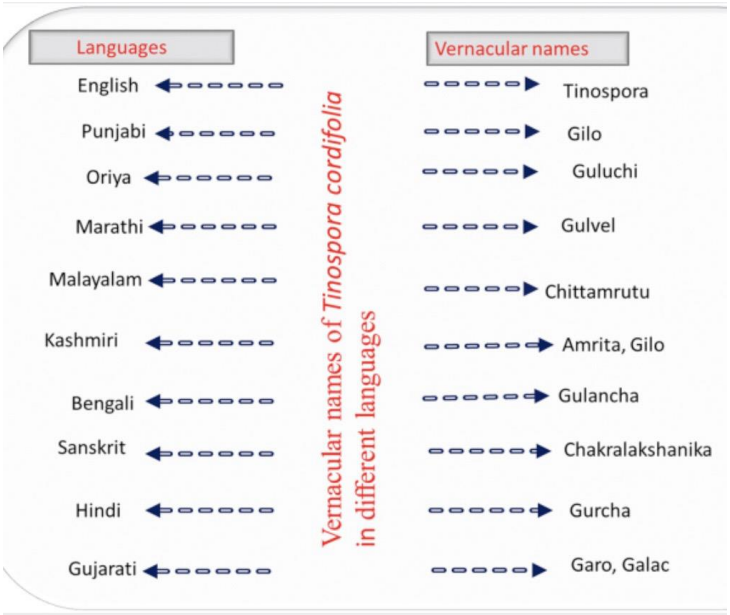
Fig. 1: Immunomodulatory effects of giloy leaves.

3.1 Botanical Description of Giloy: *T. cordifolia* is a large climbing shrub with many elongated branches. Its leaves are alternate, simple, pulvinate, and roundish, and they have long petioles up to 15-cm long. The lamina is broadly ovate, 7 nerved and deeply cord-ate at the base, 8- to 15-cm broad, 10- to 20-cm long, and membranous, and there is whitish tomentas with a less prominent reticulum and an upper pubescent region. The taxonomical classification of *T. cordifolia* is shown in Fig .2



Taxonomical classification of *Tinospora cordifolia*.

The flowers are small, unisexual, and greenish yellow on axillary and terminal racemes. Female flowers are usually solitary, but male flowers are clustered. Sepals are in 2 series of 3 each, and the inner sepals are more significant than the outer sepals. The 6 petals are obovate, membranous, and smaller than the sepals. The fruits are in aggregates of 1 to 3 and present as orange and ovoid smooth drupelets on thick stalks with subterminal style scars.[38] This plant is widely grown in various parts of the world and is known with different local Names.fig3



Vernacular names of Guduchi (*Tinospora cordifolia*) in different languages.

Tinospora, a large deciduous, glabrous perennial plant, is extensively spread throughout India, especially in the tropical parts up to 1.2 km above sea level. It is found in neighboring countries such as China, Sri Lanka, Bangladesh, Pakistan, and Burma.[39] *Tinospora* plants are mostly grown in warm climates. *Tinospora* prefers medium-black or red soil for its cultivation. It can also be successfully grown in a large variety of soils, ranging from sandy to clay loam. However, the soil should be well drained with sufficient moisture and rich with organic matter for its growth.[40] It is supposed to be the ambrosia of God Indra, considered a holy liquid. Another species of *Tinospora*, T. *crispa*, a small herb, locally known as Faridbel, is a woody, lofty and entirely glabrous climber. This widely grows herb is found in temperate as well as tropical region of India. Third species, *T. sinensis*/*malabarica* also known as Malabar gulbel, have giant deciduous climber, shining light colored stem, long orbicular-cordite leaves larger than *T. cordifolia*, dioecious flowers, and aerial roots from branches.[41] Flowers are unisexual, small on separate plants and appearing when the plant is leafless, greenish yellow on axillary and terminal racemes. Male flowers are clustered, but female flowers are usually solitary. It has six sepals in two series of three each. The outer ones are smaller than the inner. It has six petals which are smaller than sepals, obovate, and membranous. Fruits aggregate in clusters of one to three. They are ovoid smooth drupelets on thick stalks with sub terminal style scars, scarlet or orange colored.[42] Endophytic fungi colonize the living, internal tissues of their host without causing any harmful effects. A recent study has shown that 29 endophytes belonging to different taxa were present in the samples collected from *Tinospora cordifolia*.[43] Giloy is a large, deciduous, woody climber with heart-shaped leaves and long, fleshy stems. The stems are rich in starch and have a mucilaginous texture. Aerial roots often develop from mature branches, contributing to the plant's regenerative nature.

3.2 Traditional & Medicinal Uses

T. cordifolia is called Guduchi in Sanskrit and is used to treat several diseases.[44] The plant has received special attention in Ayurveda, Chinese, and other ancient medicinal systems. It is also known as 'Heavenly elixir' or 'Amrita' due to its medicinal and rejuvenating potential.[46] In Ayurvedic texts, Charka, Sushruta Samhita, Astanga Samgraha and other treatises, such as Bhava Prakash and Dhanvantari Nighantu, *T. cordifolia* has been used to treat asthma, jaundice, diabetes, leprosy, pyrexia, anorexia, gout, skin infections, chronic diarrhoea, dysentery, etc. *T.*

cordifolia is appointed as a Rasayana drug in Ayurveda and recommended to enhance general body resistance, promote longevity, and help relieve stress, anxiety, and fatigue.[47] In folk medicine, the whole plant, roots, stem, bark, and leaves of *T. cordifolia* in decoction, juice, powder, and paste form are used to treat pyrexia, jaundice, leukorrhea, gastrointestinal disorders, cough, skin diseases, asthma, eye disorders, poisonous bites, and stings.[48]

Medicinal uses

Giloy is used in Ayurveda for managing several health conditions. These include:

1. Managing Fevers

A. Chronic Fever

Giloy is used to manage chronic and recurrent fevers. It is an anti-inflammatory, antipyretic herb that aids in improving your immunity to fight against infection and helps in speedy recovery.[49]

B. Dengue Fever

Giloy is well known for its antipyretic property. Intake of giloy during dengue fever may help in improving the immunity and increasing the platelet count. This may avoid the risk of dengue fever complications and aid in speedy recovery. You can also take it along with tulsi leaves to help improve the platelet count.[49]

C. Hay Fever

Giloy is said to be useful in managing hay fever/allergic rhinitis. It reduces symptoms like runny nose, sneezing, nasal obstruction, and watering of eyes. To reduce temperature, you may mix Giloy powder with honey and eat have before sleep.[49]

D. Controlling Blood Sugar Levels

In Ayurveda, Giloy is known as a 'Madhunashini' which means 'destroyer of sugar. It may aid in the insulin secretion and utilisation, which leads to improved blood sugar levels. Initial research has shown that regular consumption of Giloy juice can help lower blood glucose levels in individuals with type -2 diabetes.[50]

E. Improving Digestion

Giloy may aid in improving digestion and it may also reduce digestion-related problems like diarrhea, colitis, vomiting, **hyperacidity**, abdominal pain, loss of appetite, and excessive thirst. It also helps in detoxifying body and enhancing liver function.[51]

F. Good for Eyesight

Giloy is potentially effective in improving eyesight when applied topically. All you need to do is boil Giloy powder or Giloy leaves in water once it cools down apply it over the eyes.[51]

G. Improve Respiratory Health

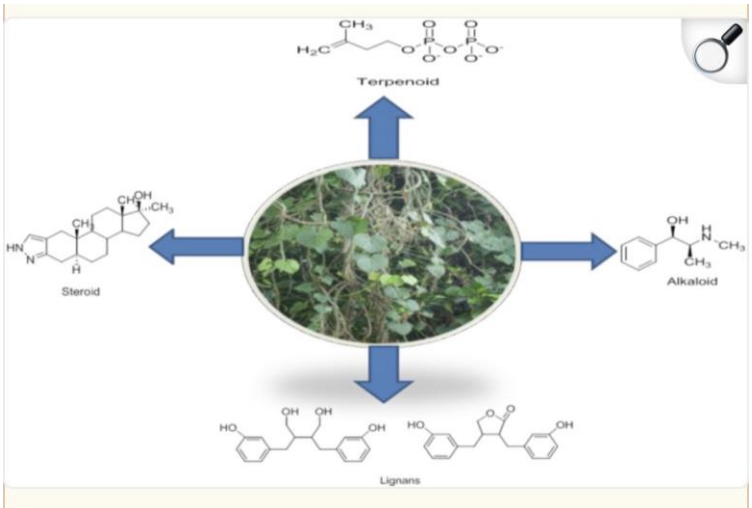
Giloy has been used as a medicine to treat bronchitis and chronic cough. Giloy can help ease the inflammation and irritation in the respiratory tract to help you breathe more freely and therefore it is used for managing asthma by ayurveda.[51]

H. Skin Benefits

Since giloy is high in antioxidants, it can avoid oxidative damage to the skin and that may slow down aging in skin. It may also improve blood circulation, which in turn bestows a natural glow to your skin[9]. It also known for its antimicrobial and anti-inflammatory property and used as a medicine to deal with skin infections, eczema, and psoriasis.[52]

3.3 Phytochemical Constituents

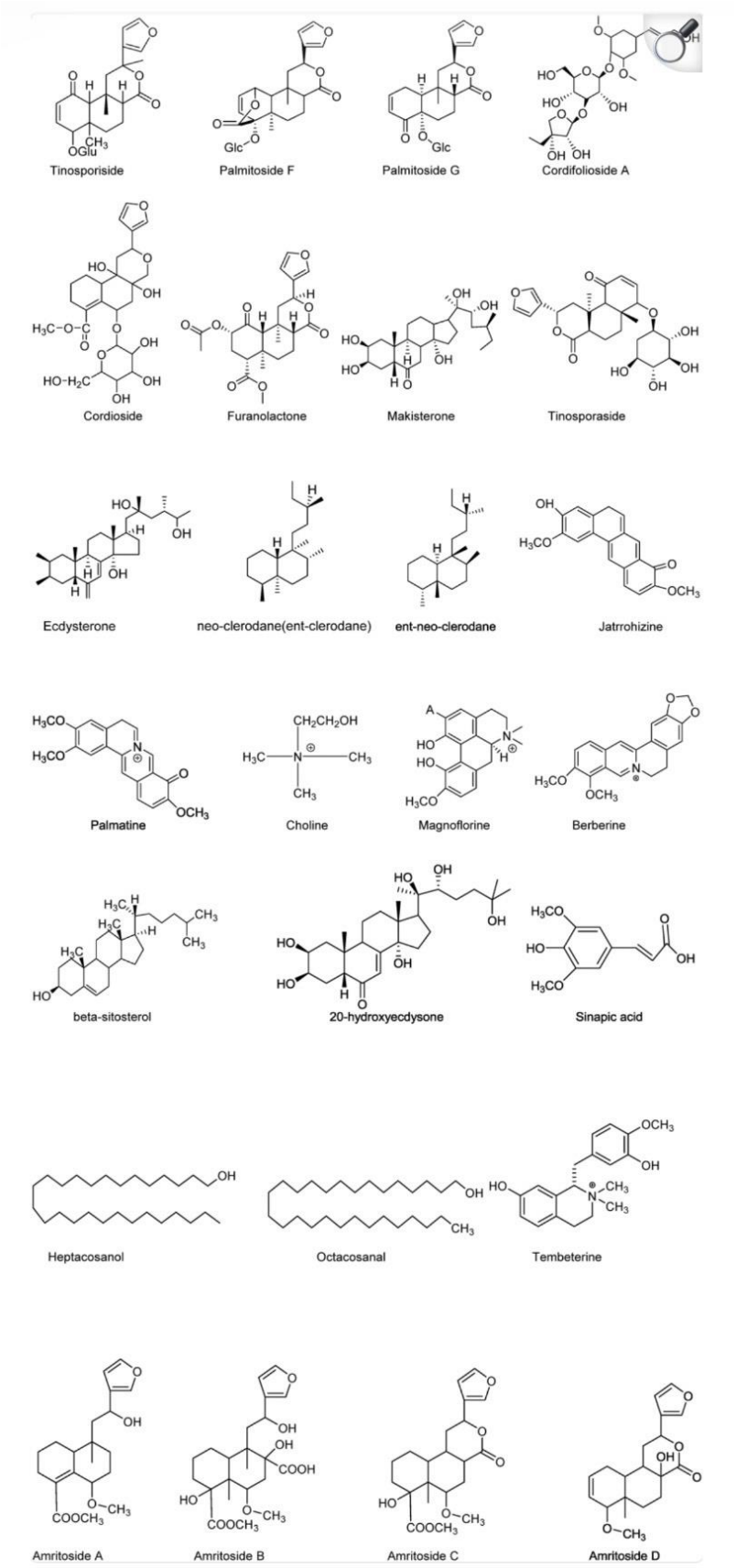
The chemical constituents of *T. cordifolia*belong to different classes such as alkaloids, glycosides, steroids, phenolics, aliphatic compounds, polysaccharides, leaves are rich in protein (11.2%), calcium, and phosphorus.[53] The stem holds clerodane furono diterpene glucoside (amritoside A, B, C, and D) and the structure has been proved by different spectroscopic studies.[54] Some of the major constitutes in fig. 4.



Major constituent of Tinospora cordifolia: terpenoid, alkaloid, lignans, steroids.

Whereas the structure of the active chemical constituent for *Tinospora cordifolia* has been depicted in fig 5.

Structure of the chemical constituent



3.4 Concept of Immunomodulation

Advances in stem cell (SC) technology have opened interesting perspectives in the field of translational medicine in terms of regenerative and therapeutic strategies. Classically, stem cells can be classified into two main categories: embryonic stem cells (ESCs) and adult (or tissue).[55] ESCs are pluripotent cells that have the ability to differentiate into cells from any of the three embryonic germ layers: mesoderm, ectoderm, and endoderm. Furthermore, they can self-renew and proliferate indefinitely. As they are derived from embryos at 5–6 days post conception; their use is fairly limited due to ethical concerns on availability as well as for the risk of forming teratomas.[56] Another sub type of SCs is the recently described induced pluripotent stem cells (iPS) which are adult cells that are engineered by manipulating the expression of certain genes to induce re-programming of the cell back to a pluripotent state.[57] The biological effect of SCs partly depends on a paracrine mechanism whereby, secreted factors including growth factors, miRNAs, and EVs, influence stem cell regeneration and differentiation as well as mediate crosstalk to and from local and distant tissues.[58] SC-secreted factors have been reported to show several properties such as anti-apoptotic and angiogenic effects, cell-mobilization, maintenance of homeostasis as well as immune-modulation amongst others.[59]

Furthermore, apart from secreted factors, stem cell-derived EVs have also been reported to mimic the effect of SCs after internalization by target cells (injured cells in the context of regeneration), mainly through receptor–ligand mediated interactions and/or direct fusion, leading to horizontal transfer of proteins and nucleic acids.[60] Ratajczak et al. first reported that EVs released by ESCs might modulate the phenotype of target cells, supporting self-renewal of hematopoietic progenitors and multi-potency by transfer of growth factors and messenger-RNA (mRN).[61] Later studies confirmed this horizontal transfer of genetic material in other contexts, such as endothelial progenitor induced angiogenesis and modulation of bone-marrow cell phenotype by EVs released by injured tissues.[62] It is still widely debated as to whether the immuno-modulatory action of MSCs relies on direct cell-to-cell interaction or on the paracrine action of soluble mediators released by these cells. Either one or both mechanisms are a possibility. Both, *in vivo* and *in vitro* studies have proven that MSCs exhibit an immunosuppressive role by suppressing T lymphocyte proliferation.[63] A possible explanation for this role could be the presence of proteins and factors such as: TGF-β, hepatocyte growth factor (HGF), nitric oxide (NO), indoleamine 2,3-dioxygenase (IDO), human leukocyte antigen G (HLA-G), prostaglandin E2 (PGE-2), Inter Leukine (IL)-6, and IL-10.[64] The immuno-modulatory effects of MSCs can therefore be speculated to be achieved either through the release of the above-mentioned factors and proteins directly into the extracellular milieu as soluble molecules, or they may be packaged into EVs together with nucleic acids and other post-transcriptional modulators which could influence the inflammatory response when released.[65] The ability of MSC-derived EVs to mimic the effect of the cell of origin has been studied on various effector cells of the immune system.[66] The inhibitory effect of MSC-derived EVs on the activation of cells of the immune system has been showed by diverse studies. For example, Conform et al. reported an inhibitory activity of MSCs and MSC-derived EVs on B-cell proliferation, which was further confirmed by a study conducted by Di Trapani et al.[67] A conceivable way by which MSC-EVs exhibit these immunomodulatory properties could be through an adenosine A2A receptor mediated mechanism.[68] In addition, the extracellular environment could also play a role, for instance it has been reported that an inflammatory environment (mimicked in culture by the presence of IFN-γ and TNF-α) may not only alter the release but also influence the biological activity of MSC-derived EVs toward a more immunosuppressive role. In fact, MSC-derived EVs may polarize monocytes toward M2-like phenotype, which in turn induces $CD4^+$ T cell to differentiate into regulatory T cells.[69] Giloy leaf extract has a high concentration of bioactive components such as alkaloids, glycosides, and terpenoids, contributing to its well-known immunomodulatory activities. The leaf extract forms bioactive components that stimulate a variety of immune cells, including natural killer (NK) cells, B cells, and T cells, resulting in the generation of favourable immune-stimulating cytokines.[70] In addition, among HIV-positive patients, giloy leaves lower total leucocyte, neutrophil, and eosinophil counts.[70] These immune-stimulating effects are linked to several bioactive chemical compounds found in the leaf, including 11-hydroxymuskatone, N-methyl-2-pyrrolidone, cordifolioside A, magnoflorine, tinocordioside, and Synringin.[71] These compounds specifically target immune cells present inside the human body such as B lymphocytes and macrophages, implying a regulated activation of the immune response.[72] This increases hemoglobin levels and polymorphonuclear leukocytes, saying an overall increase in immune response.[73] These compounds are well known for their ability to promote a greater immune response by enhancing the proliferation and differentiation of lymphocytes. Thus, it increases total WBC, bone marrow cellularity, and alpha esterase-positive cells in the marrow of bone which leads to an increase in humoral immune response. Some of the bioactive components raise IgG antibody levels, which are important components of the immunological response for complimentary inhibition of the pathway.[74] Giloy leaves anti-inflammatory mechanisms that have been studied. According to studies giloy leaf extract prevented lipopolysaccharide (LPS)-stimulated macrophages from releasing prostaglandin E2 (PGE2) and nitric oxide (NO).[75] Studies proved by that giloy leaf extract suppressed the activation of the transcription factor-kappa B (NF-κB) signalling pathway, which is crucial for the inflammatory response.[76] Wilkinson showed that giloy leaf extract inhibited the activity of an enzyme

produced by the human body cyclooxyrgenase-2 (COX-2), which plays a role in PGE2 synthesis.[77] These studies suggest that giloy leaves have multiple anti-inflammatory mechanisms, including the inhibition of NO and PGE2 production, the reduction of pro-inflammatory cytokine expression, and the suppression of NF-κB and COX-2 activity. Another study reported that tgiloy leaf extract reduced the expression of tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β), two pro inflammatory cytokines in LPS-stimulated macrophages.[78]

4. METHODOLOGY

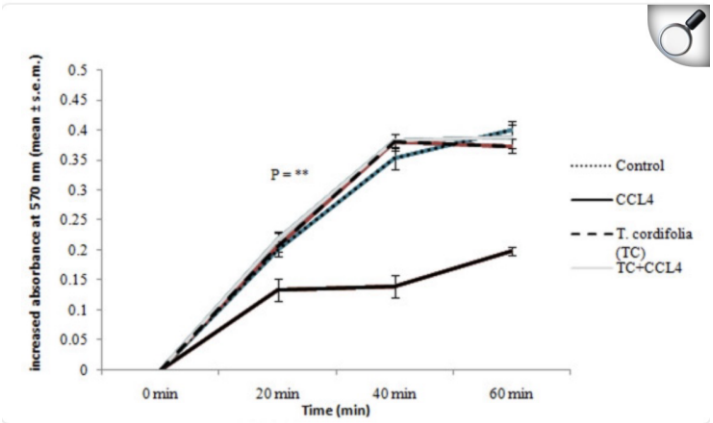
4.1. Immunomodulatory Activity of Tinospora Cardifolia

The significant immunomodulatory qualities of Tinospora *cordifolia* leaves are attributed to a plethora of bioactive substances.[79] These active ingredients include alkaloids (found primarily in the stem) and steroids (beta-sitosterol, d-sitosterol, and g-sitosterol),as well as (18-norclerodane, glycosides, furanoid diterpene glycosides, and tinocordiside) and palmatine D, choline D, tinosporine, magnoflorine, tetrahydropalmatine, and isocolumbin).[80] Added components found in its aerial sections include diterpenoidlactones (furanolactone, tinosporon, and columbin) as well as many other substances such cordifolioside A, 11-hydroxymuskatone, N-methyl-2-pyrolodine heptacosanol, and nonacosan-15-one.[81] Interestingly, the alkaloid palmatine is also present in the root. RR1, a polysaccharide-extracted from the leaves, has been found to possess immune stimulatory properties and has the potential to be used as an adjuvant to boost immunity.[82] Additionally, the various nbioactive ingredients present in giloy leaves affect the immune system by increasing cytokine synthesis, enhancing immune cell mitogenicity, and activating specialized immune cells like B cells and macrophages, which can trigger targeted immune responses.[83] Further research into the exact mechanisms of these active ingredients will help to clarify the immunomodulatory potential of giloy leaves.

4.2 Effect on Macrophages

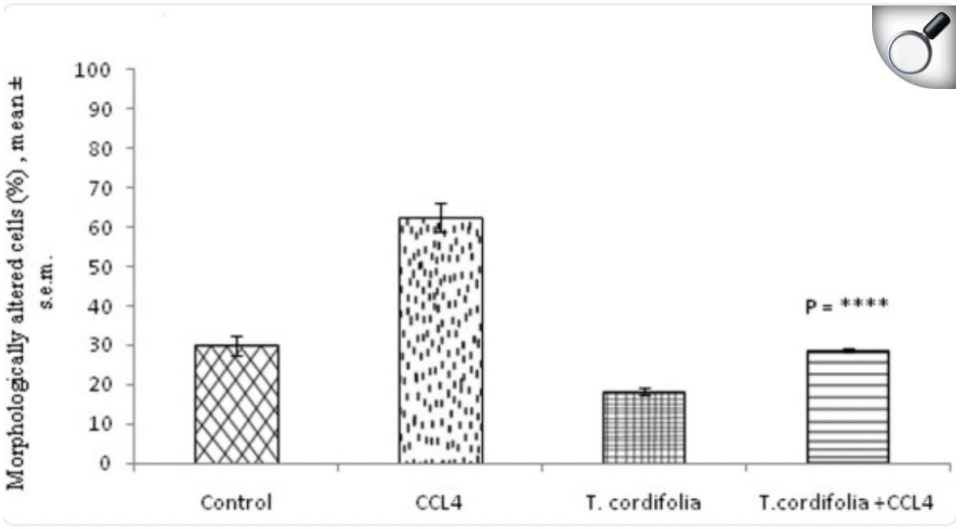
Effect of *Tinospora cordifolia* on morphology of peritoneal macrophages isolated from CCl4 intoxicated male albino mice Morphology of macrophage plays a prominent part of their function. To show the effect of both CCl_4 and *T. cordifolia* on the number of differentiated macrophages, the macrophage cells of extensive rough surface or perfect spherical surface was measured and counted as morphologically altered macrophage. From this experiment, it was found that CCl_4 treatment increases the number of altered macrophages from 30 ± 2.63% to 62.4 ± 3.54%. However, the administration of *T. cordifolia* in CCl_4 intoxicated mice, the number of altered macrophages became almost normal level of 28.68 ± 0.52%. Administration of *T. cordifolia* in control mice also showed some significant reduction of altered macrophages up to a level of 18.32 ± 1.02%.

Figure 2.



Effect of *T. cordifolia* on cell adhesion properties of peritoneal macrophages isolated from CCl_4 intoxicated male albino mice. The results were expressed as mean ± standard error mean.

Figure 1.



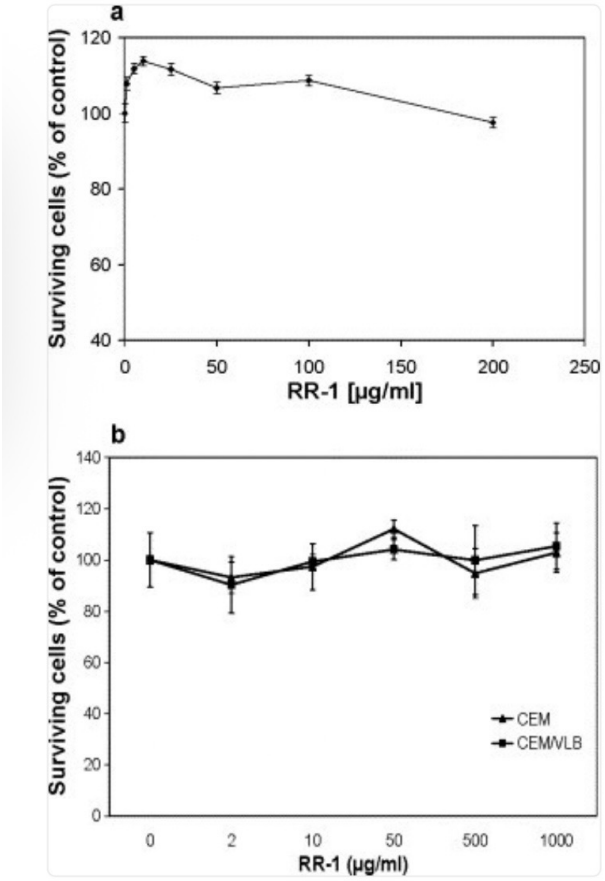
Effect of *T. cordifolia* on morphology of peritoneal macrophages isolated from CCl_4 intoxicated male albino mice. The results were expressed as mean ± standard error mean.

Fig. 1: Effect of *Tinospora cordifolia* extract on the adhesion property of CCl_4 intoxicated mice peritoneal macrophages.

In vitro cell adherence assay reflects the *in vivo* capacity for cellular adherence with treatment by *T. cordifolia* extract in immunocompromised mice. To address this fundamental characteristic of macrophages, the cell adhesion property was assayed *in vitro*. Adhesion of cells increased gradually after *T. cordifolia* administration in CCl_4 intoxicated mice. Fig 2

4.3. Effects on Lymphocytes

Normal lymphocytes (10^6/ml) were treated with 0–100 µg of RR1 for 24 h in a CO_2incubator maintained at 37 °C in RPMI medium. The cells were then stained with specific fluorochrome-conjugated monoclonal antibodies for 30 min at room temperature and analyzed in a Coulter Elite Flow Cytometer by four- and five-color immunotyping assay protocol of Alamo and Melnick.[84] The percentage of activation of lymphocyte subsets such as NK, T and B cells was calculated. To evaluate the enhanced cytotoxicity of activated lymphocytes, a functional assay was adopted using RR1 activated lymphocytes as effecter cells and human leukemic cells (CEM) as targets.[85] Briefly, normal lymphocytes (10^6/ml) were treated with different concentrations of RR1 in RPMI medium for 24 h in a CO_2 incubator at 37 °C. On the next day, target cells (CEM 1×10^6/ml) were labeled with 4.6 µM membrane labeling dye PKH26 (Sigma) in 1 ml phosphate-buffered saline (PBS) at room temperature for 3 min. The labeling was stopped by adding an equal volume of fetal bovine serum (GIBCO, Life Sciences, MD) for 1 min. The labeled tumor cells were then incubated with RR1 treated lymphocytes in an effecter to target ratio 1:1 for 4 h and untreated lymphocytes were used as control. The percentage of cells killed by the activated NK cells was decided by fixing the mixture with 1 ml of 2% Para formaldehyde solution for 30 min on ice followed by suspending in 0.5% Tween 20 in PBS. The cell mixture was stained with 7.5 µl of anti-active caspase-3-fluorescein isothiocyanate (FITC) antibody (BD Biosciences, CA) for 30 min at room temperature, washed with PBS and analyzed in a Coulter Elite Flow Cytometer. The results of MTT assay given and b show that RR1 has no direct cytotoxic or cell-proliferating effect either on norma lymphocytes or on tumor cell lines (CEM and CEM/VLB) even at a concentration as high as 100 µg/ml.fig 6.



Cytotoxic analysis of RR1 in normal lymphocytes (a) and tumor cell lines (b). Cells (10^6) were treated with RR1 for 24 h and cytotoxicity assay performed using MTT cell proliferation kit (Roche Biochemicals). The percentage of surviving cells over control was plotted against RR1 concentrations.

4.4. Cytokine Modulation

Cytokines play crucial roles in regulating various aspects of immune responses. Among cytokines, interleukin (IL)-12 plays a vital role in coordinating innate and cell-mediated adaptive immunity.[86] protective measures are correlated with synthesis of IL-12 and interferon (IFN)-γ, the cytokines of Th1 pathway of T cell differentiation associated with the adaptive immune system.[87] Stimulation of multiple receptors is reported to exhibit synergistic effect in cytokine production.[88] Polysaccharides are known immune stimulants of which β-glucans have recently received considerable attention. β-Glucans or other biological response modifiers (BRMs), because of their structural identity with the conserved "pathogen-associated molecular pattern" activate the immune system by binding to specific receptors (pattern recognition receptors) of the innate immune system and stimulate the phagocytic, cytotoxic, and antimicrobial activities by the synthesis and release of cytokines, chemokine and reactive oxygen and nitrogen intermediates.[89] The modulation of immune responses to alleviate the diseases has been of interest for many years and the concept of 'Rasayana' in Ayurveda is based on the related principles.[90] Further immunomodulation using medicinal plants can offer an alternative to conventional chemotherapy for a variety of diseases especially when the host defense mechanism must be got under the conditions of impaired immune responsiveness.[91] Indian medicinal plants are rich sources of substances which are claimed to induce para-

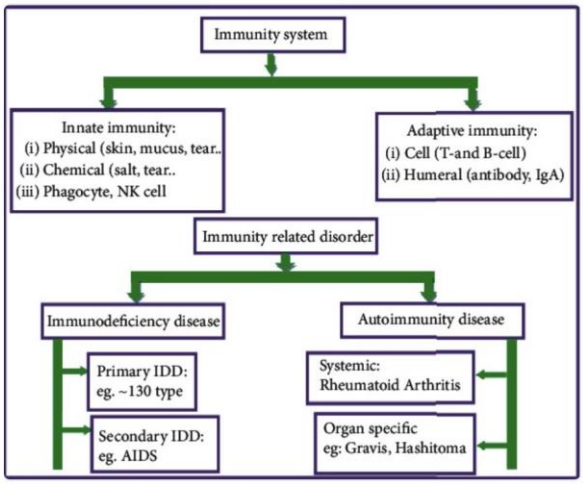
immunity, the non-specific immunomodulation of especially granulocytes, macro-phages, natural killer cells and competent functions.[92] Among the suppressive synthetic substances, cyclophosphamide has been extensively studied.[93] However, the major drawback of this drug is myelosuppression, which is undesirable.[94] Immunostimulation and immunosuppression both need to be tackled in order to regulate the normal immunological functioning. Therefore, the stimulatory or suppressive agents have been shown to own activity to normalize or modulate the pathophysiological processes and are hence called immunomodulatory agents.[95] In earlier studies, the immunomodulatory activity of *Tc* was studied through different parameters viz. differential leukocyte count.[96] the aim of the present study was to study the immunomodulator potential of ethanolic extract of *Tc* at cellular and molecular level using male rats.

4.5. Effect on Innate Immunity

The possibility of bioterrorism, outbreak of severe acute respiratory syndrome (SARS) and Bird Flu virus, continuing spread of HIV/AIDS and emergence of resistant pathogenic strains against current medications compel investigators to look for new protective measures against these threats. Immune activation is an effective as well as protective approach against emerging infectious diseases.[97] Although immune system has a wide array of microbial detection and host defense mechanisms, pathogen evasion of the immune surveillance and destruction is a frequent occurrence. This escape of immune surveillance is also an important characteristic of several malignancies.[98] The fundamental role of innate immunity in host defense is becoming clearer as analysis of the human genome continues to find new genes serving innate immune function. The innate immune system detects the pathogens or the non self intruders using specific receptors and responds at once by activation of the immune competent cells, synthesis of cytokines and chemokine, and release of inflammatory mediators to eliminate or hold the intruders. Innate immune activation also triggers and paves the way for adaptive immune response by antigen-specific T and B lymphocytes. The natural killer (NK) cells play a decisive role in the innate immune defense against virus-infected and malignant cells by virtue of their ability to recognize and destroy abnormal cells.[99] Cytokines play crucial roles in regulating various aspects of immune responses. Among cytokines, interleukin (IL)-12 plays a vital role in coordinating innate and cell-mediated adaptive immunity.[100] Polysaccharides are known immune stimulants of which β-glucans have recently received considerable attention. β-Glucans or other biological response modifiers (BRMs), because of their structural identity with the conserved "pathogen-associated molecular pattern" activate the immune system by binding to specific receptors (pattern recognition receptors) of the innate immune system and stimulate the phagocytic, cytotoxic, and antimicrobial activities by the synthesis and release of cytokines, chemokine and reactive oxygen and nitrogen intermediates.[101]

4.6 Effect on Adaptive Immunity

Adaptive immunity is mediated by cell (T and B cells) and humeral (macromolecule-like antibodies in plasm cells of blood and immunoglobulin). It employs diverse antigen receptors that are not encoded in germ-line cells but rather de novo generated through DNA rearrangement mechanisms in the somatic immune tissues of mammalian organisms.[102] Immunity-related disorders are of two types: immunodeficiency and autoimmune disease.Fig.7.



Graphical classification of the immune system and immunity-related disorder.

An immune response opposed to its healthy cells and tissues is called autoimmunity, leading to autoimmune diseases.[103]

5. Mechanism of action

Ayurvedic pharmacology is based on biophysical, experiential, inferential and intuitional mechanisms. The action of a substance is based on five mechanisms of action or attributes of a substance, namely, *rasa* (taste appreciation of the substance by the chemical receptors on the tongue — Six tastes are described namely sweet (*madhura*), sour (*amla*), salty (*lavana*), bitter (*tikta*), pungent (*katu*)and astringent (*kasāya*), *guna* (10 pairs of opposite or mirror image attributes; attribute or property of any substance), *vipaka* (intestinal digestion and tissue metabolism; *madhura*- neutral, *amla*- acidic, *katu*- alkaline), virya (potency; *ushna*- hot, *sheeta*- cold) and *prabhav* (specific action through specialized receptors). All these mechanisms related to drug action are biophysical in nature. *Karma* is the action that involves the activity or performance. It is the final effect- of the drug. The properties, action (pharmacodynamics) and uses (sign) of *T.*[104] *cordifolia* are given in. Table 1: [104]

Rasa	*Guna*	*Virya*	*Vipaka*	*Prabhava*
Tikta, Kasaya	*Laghu, Guru, Snigdha*	*Ushna*	*Madhura*	*Vishaghna*
Bitter, Astringent	Light, Heavy, Unctuous	Hot potency	Neutral	Anti-toxic

Rasa: Taste appreciation of the substances by chemical receptors on tongue; sweet, sour, salt, bitter, pungent and astringent, Guna: Ten pairs of opposite or mirror image attributes; attribute or property of any substance, Virya: potency; ushna- hot, sheeta- cold, Vipaka: Intestinal digestion and tissue metabolism; madhura- neutral, amlaacidic, katu- alkaline, Prabhava: Specific action through specialized receptors

6. Preclinical Evidence

T. cordifolia is a popular medicinal herb used in different Ayurvedic formulations. An earlier computational study from our group showed that tinocordiside, one of the major phytocompounds present in *T. cordifolia* could potentially inhibit host-pathogen interaction during COVID-19 infection by disrupting electrostatic interactions between human host ACE2 receptor and SARS-CoV-2 viral spike (S) protein.[105] Giloy Ghanvati, the aqueous extract of *T. cordifolia* in the form of tablets, effectively attenuated SARS-CoV-2 viral recombinant spike (S) protein-induced pathological symptoms in humanized zebrafish, which had their swim bladders xenotransplanted with human A549 lung cells.[106]

T. cordifolia, in different forms such as extract, decoction and pills, almost became a household medicine in India to fight against COVID-19. Pilot-scale clinical trial (CTRI/2020/05/025273) conducted by by Devpura has also included *T. cordifolia* as one of the components administered orally to the COVID-19 patients. Otherwise also, different parts of *T. cordifolia*, namely, roots, stems and leaves, have an array of reported medicinal uses, such as, metabolism enhancement, endocrine modulation, anti-oxidative, anti-toxic, anti-biotic, anti-parasitic, anti-cancer, anti-hyperlipidemic, anti-anxiety, anti-arthritic, cardio-protective, hepato-protective, nephron-protective, neuron-protective, osteo-protective and adaptogenichas also included *T. cordifolia* as one of

the components administered orally to the COVID-19 patients. Otherwise also, different parts of *T. cordifolia*, namely, roots, stems and leaves, have an array of reported medicinal uses, such as, metabolism enhancement, endocrine modulation, anti-oxidative, anti-toxic, anti-biotic, anti-parasitic, anti-cancer, anti-hyperlipidemic, anti-anxiety, anti-arthritic, cardio-protective, hepato-protective, nephron-protective, neuron-protective, osteo-protective and adaptogenic[107] G1-4A, a known polyclonal B cell mitogen from the crude extract of dried *T. cordifolia* stems, has been reported to enhance immune response in mice, through macrophage activation and IL-1 secretion The stem extracts of *T. cordifolia* are known for their ability to regulate blood glucose.[108] Irrespective of its prominence in Ayurveda, a few recent case reports have linked clear hepatotoxicity in clinical subjects with consumption of *T. cordifolia*.[109] From safety point of views, a single study has reported non-toxicity of *T. cordifolia* at a single dose of 2000 mg/kg/day.[110] However, to the best of our knowledge there is no report on repeated dose toxicity assessments of *T. cordifolia*. Therefore, a 28-day repeated dose with 14-day recovery study as per OECD 407 guidelines was conducted, which is now reported in this manuscript. Classically water has been the choice of solvent for the extraction of medicinal herbs, although water and alcohols (ethanol, and methanol at times) have been extensively used nowadays with regulatory compliance.

6. Safety and toxicity Considerations

Acute poisoning tests on *T. cordifolia* did not show any harmful effects or deaths, even when the plant was given at a high dose of 9 g/kg body weight.[111] According to the acute toxicity tests, giving mice a 3 g/kg dose of *T. cordifolia* aqueous extract had no negative effects.[112] Studies on humans have shown that *T. cordifolia* does not have any harmful effects, even when given at excessive amounts (900 mg/day) to HIV patients and people with allergic rhinitis. Clinical studies on *T. cordifolia* showed that a dose of 500 mg/day for 21 days was safe for people and did not seem to have any negative effects on their kidneys, heart, intestines, or nervous system.[113] In a study, scientists administered a dosage of 3 g/kg of *T. cordifolia* to rats and saw no adverse effects and did not result in any fatalities among the subjects.[114] Administering a dosage of 0.1 g/kg of *T. cordifolia* to rats for 12 weeks does not adversely affect their liver or renal function. Researchers gave the drug to rats, and it increased the number of white blood cells and neutrophils. However, this did not happen in healthy people[115] During long-term monitoring studies, finding and displaying signs and symptoms can give researchers vital information about the right way for drugs to work and how much to give during the experiment.[116] Adding *Curcuma longa* and *T. cordifolia* to normal anti-tuberculosis treatment for all TB patients was said to reduce the number and severity of liver damage events.[117] In the first part of the study, giving *T. cordifolia* to healthy volunteers was found to be safe and well-accepted.[118] Several studies have been done on the phytochemical makeup and biological qualities of different medicinal plants. According to what they found, *T. cordifolia* does not have any significant side effects, acute or chronic toxins, or LD50 values. For therapeutic reasons, it is suggested that a half-dose of this drug, or 500 mg per kg, be given. Even so, the *Tinospora* species has not been the subject of many thorough toxicological tests and safety studies. Most of the time, low to moderate doses are proper to use.

8. Future prospectives

there lies an enormous scope for utilising the properties of *T. cordifolia* extracts in various kinds of formulations and food products. However, the sensory aspects of food items, particularly in terms of flavor and appearance, should not be negatively affected by the addition of it. Since the active ingredients of *T. cordifolia*, like that of any other herbal medicine, may leave behind a potent bitter taste, a critical need for a thorough investigation of alternative procedures for the elimination of the bitterness is essential in the case of juice, powder, or extracts from this plant. Thus, it is important to address some difficulties before incorporating it in different formulations. It is highly recommended to carefully analyze the stability, efficacy, daily intake, and potential risk of the various formulations and value-added food products developed from *Tinospora.*The possible use of bioactive components of *Tinospora* incorporated in food product packaging materials also needs to be explored.

The retention of active components and bioactive properties of *Tinospora* is crucial, requiring detailed examination and further studies. Stability of *Tinospora* bioactive compounds during processing and storage of various pharmaceutical and food formulations can be improved by using various techniques such as nano-emulsion and double emulsion. Examining how bioactive components behave and interact within a variety of dietary matrices provides researchers with vital information for future improvements in this field. However, as with other natural products, it is essential that the health claims of *Tinospora*-based medicinal and food products be confirmed through non-clinical and clinical trials, along with proper documentation of high-quality data before they are commercialised.

9. CONCLUSION

Despite the untreated and less effective treatment of various diseases, there has been an increase in demand for herbal medicines such as *T. cordifolia* in India, other Asian countries, and worldwide. The magical fact behind this is that herbal medicine shows effective treatment in terms of short- or long-term medication and has fewer side effects than other normal treatment therapies. Herbal medicine plays a beneficial and protective role against various diseases. This well-fitted approach to herbal medicine not only targets the ailment site but is also

beneficial in boosting the immune system and improving compatibility with the human body.

The multidirectional pharmacological approaches of the *T. cordifolia* plant have been explored in the present review. Due to its therapeutic efficacy in boosting immunity, we believed that T. cordifolia could also be effective against various diseases, although researchers scientifically and doctors medically worldwide are trying to develop an effective vaccine using herbal medicine. Also, it could be one of the herbal candidates for bioprospecting and drug development for disease treatment. The presence of chemical constituents shows that *T. cordifolia* plant could serve as a "leader in the traditional system of medicine" for the development of novel agents against diseases in the coming years. The present review provides a diversified therapeutic approach for present or future studies to carry out research on the miracle plant so that they could get medicinally important herbal drugs and use them in the treatment of various diseases. These research advances highlight the diverse pharmacological activities of *T. cordifolia*, making it a subject of continued interest in the fields of traditional medicine and modern pharmacology. Researchers are increasingly uncovering the mechanisms behind its therapeutic effects, which may lead to the development of novel treatments and therapies in the future.

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