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MINIREVIEW

Therapeutic Potential of the Medicinal Plant *Tinospora cordifolia*–Minireview

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ABSTRACT

For thousands of years, plant based herbal medicines have been utilized by millions of people all over the world. Plant materials or products are used in different folk/traditional medical systems, such as the Chinese, African and Indian medical systems, like Siddha, Ayurveda, Unani, and Homeopathy. *Tinospora cordifolia* (TC) is a medicinal plant belonging to the family Menispermaceae. It is a big deciduous, climbing shrub growing prevalently in the tropical part of Indian subcontinent regions such as India, Pakistan, Nepal, Bhutan, Bangladesh and Srilanka, and in Myanmar, and China. Guduchi, Giloy, Shindilkodi, and Amritha are all the common names for this plant. Extracts from different parts of this herbal plant have been used to treat many diseases. In Ayurvedic medicine, extract from this plant is used for preparing "rasayanas", which is known to cure diabetes, skin diseases, allergic conditions, jaundice, cardiovascular diseases, rheumatoid arthritis, poisoning, and microbial infections. *T. cordifolia* has a many bioactive phytochemicals that have been isolated from its aerial parts and roots. Many bioactive principles have been reported from this plant which belong to various classes like alkaloids, aliphatic compounds, diterpenoid lactones, phenolics, flavonoids, glycosides, sesquiterpenoids, lignans, steroids and polysaccharides. *T. cordifolia* possesses medicinal properties such as antioxidant, antiallergic, antiinflammatory, antimicrobial, antiviral, antidote, antitumor, antileprotic, antispasmodic, and antidiabetic properties. The present review will provide a comprehensive therapeutic potential of *T. cordifolia*.

KEYWORDS

Tinospora cordifolia; medicinal plant; alkaloid; phytomedicine; immunomodulatory

1 Introduction

Plants have always been a source of medicine. Scientists and the public have recently been acknowledging their usefulness as a source of novel and reliable medicinal products. Recent research outputs have highlighted the tremendous health benefits of plant-based compounds. The public's interest in medicinal plants has exploded in the last two decades, from the usage of herbal items as natural cosmetics and self-medication to scientific studies and dose standardization for their biological qualities in humans [1]. Medicinal plants are one of the key sources of new drugs and health-related products. The protective effects of plant-based compounds can be attributed to the presence of several components such as antioxidants, enzymes, proteins, vitamins, minerals [2], polysaccharides, fatty acids, carotenoids, terpenoids [3], curcuminoids, flavonoids [4] and phenolic compounds [5]. Traditional and alternative medicines are identified in India. Plants extracts of certain medicinal plants were able to possess intricate beneficial activities which includes antioxidant, antiinflammatory, antimicrobial, antiviral, antiparasitic, antibiotics, antitumor, antiaging, and antidiabetic properties. Researchers identified and distinguished medicinal plants with values of higher antioxidant capacity could exhibit major beneficial effects on human health and are being used as sources for alternative medicines [6].

Tinospora cordifolia (TC) belongs to the family Menispermaceae. It is a big deciduous, climbing shrub growing prevalently in the tropical part of Indian subcontinent regions such as India, Pakistan, Nepal, Bhutan, Bangladesh and Srilanka and in Myanmar and China. Commonly, *T. cordifolia* was called as Guduchi, Giloy, and Amritha. *T. cordifolia* in the form of 'Rasayanas' has been extensively used in the Ayurvedic medicine (i.e., an old Indian system of medicine) to treat jaundice, diabetes, rheumatoid arthritis, gout, general weakness, skin diseases, allergic conditions, and infections [7,8].

T. cordifolia was predominantly used in Indian ayurvedic medicine to boost the immune system and the body's immunity against infections. Moreover, in advanced medicine, it has also been used to treat general weakness, fever, dyspepsia, diarrhea, gonorrhea, urinary disorders, viral hepatitis and anemia. Recently, active compounds present in *T. cordifolia* have been reported to possess immunomodulatory and anticancer activities [9]. Many bioactive components like alkaloids, polysaccharides, steroids, glycosides, aliphatic compounds, and crystalline compounds like columibin, chasmanthin and palmarin, which is responsible for the bitter taste of the *T. cordifolia,* have been extracted from the whole plant. Plant leaves are rich in components like proteins, calcium, phosphorus, and alkaloids such as promoter brine, tinosporide, tinosporic acid and tinoporol. Phytochemical analysis suggested the presence of several diterpenoid furan lactones, phenolic ligands, phenyl propane glycoside and arbinogalactan [10].

Each part of *T. cordifolia* contains a wide range of pharmacological benefits. Extracts from different parts of the herb are used in different diseases. Bioactive compounds or extracts of *T. cordifolia* possesse medicinal uses such as antioxidant, antiallergic, antiinflammatory, antimicrobial, antiviral, antidote, antitumor, antileprotic, antispasmodic, and antidiabetic properties [11,12]. *T. cordifolia* root and stem parts are used as an antidote to snake bites and scorpion stings in conjunction with other medications. A decoction of the stem is used for washing sore eyes and syphilitic sores. *T. cordifolia* has many phytochemicals that have been isolated from its aerial parts and roots. It is known to have hepatoprotective, immunostimulatory, anti-diabetic, radio protective, anti-inflammatory, anti-cancer and free radical scavenging activities [8]. A variety of compounds have been reported from this plant which belong to various classes like alkaloids, aliphatic compounds, diterpenoid lactones, glycosides, sesquiterpenoids, lignans, steroids and polysaccharides [13].

Stems of *T. cordifolia* taste bitter, induce appetite, and helps digestion by inducing bile secretion, and are diuretic and used for treating jaundice [11]. The stem extract of this plant has been shown to decrease blood glucose in diabetic rats. The possible mechanism of hypoglycemic action is that it may potentiate the insulin effect of plasma by increasing the pancreatic secretion from the beta cells [8,14]. It has also been reported that

octacosanol from *T. cordifolia* may down regulate the VEGF gene expression, thus playing a major role in the prevention of diabetic retinopathy [14]. Ethanolic crude stem extract from *T. cordifolia* have been reported to boost the cellular immune response by increasing the leucocytes and phagocytic cells; further studies reveal that the aqueous extract from the stem is identified to have an α-glucosidase inhibitory activity [13].

2 Botanical Description

T. cordifolia is a large, fibrous, deciduous climbing shrub with a glabrous surface (Fig. 1). Transverse cut of the yellowish wood of *T. cordifolia* reveals radially-organized wedge-shaped wood bundles containing immense vessels divided by fine medullary rays. The stem has rosette-like lenticels, and the bark is creamy white to grey, spirally left. The leaves are cordate in form and membranous. Flowers are axillary and grow in a 2–9 cm long raceme on leaflet branches. They are unisexual, tiny, and yellow. Female flowers are normally solitary, while male flowers are grouped. The seeds have a curled shape. Fruits are fleshy and have only one seed [7]. In the summer, flowers bloom, and in the winter, fruits ripen [15].

Figure 1: *Tinospora cordifolia*

3 Chemical Composition

Various active compounds have been isolated from *T. cordifolia*, which belong to diverse classes such as alkaloids, aliphatic compounds, diterpenoid lactones, clerodane norditerpenoids, sesquiterpenoids, lignans, steroids, glycosides, polysaccharides, phenolics and flavonoids [16,17]. Table 1 describes the detailed chemical composition of *T. cordifolia*.

Table 1: Chemical composition of *T. cordifolia*

Chemical group	Compounds	References
Alkaloids	Tinosporin, magnoflorine, berberine, palmitine, tetrahydropalmatine, isocolumbin, jatrorrhizine, and isocorydine, tembeterine, choline, 1, 2-Substituted pyrrolidine, N-formylasimilobine 2-O-β-D-glucopyranosyl-(1→2)-β-D-glucopyranoside (tinoscorside A, 1), N-acetylasimilobine 2-O-β-D-glucopyranosyl-(1→2)-β-D-glucopyranoside (tinocordiside B, 2)	[16,18–20]
Aliphatic compounds	Octacosanol, heptacosanol, nonacosan-15-one	[21–23]
Diterpenoid lactones	Clerodane derivatives, [(5R, 10R)-4R-8R-dihydroxy-2S-3R: 15, 16-diepoxy-cleroda-13 (16), 14-dieno-17, 12S: 18, 1S-dilactone], furanolactones, jateorine, tinosporal, tinosporides, columbin, Tinosporon	[22,24,25]
Sesquiterpenoids	Tinocordifolin, einocordifolin and 11-hydroxymustakone	[16,22,25]

(Continued)

Table 1 (continued)

Chemical group	Compounds	References
Lignans	3 (a, 4-dihydroxy-3-methoxybenzyl)-4-(4-hydroxy-3-methoxybenzyl)	[20]
Steroids	δ-sitosterol, nonacosan-15-one, tetrahydrofuran, giloinsterol, 20a-hydroxyecdysone, ecdysterone, and makisterone A	[21–22,26]
Glycosides	Furanoid diterpene glycoside, 18-norclerodane glycoside, tinocordifoliside, cordioside, syringin, syringinapiosylglycoside, palmatosides C and F and cordifoliside A, B, C, D & E	[16,18,24,25]
Other compounds	Tinosporic acid, tinosporidin, cordifol, cordifelone, giloin, gilenin, giloinin and arabinogalactan polysaccharide, chasmanthin, palmarin, amritosides, tinosponone, glucan polysaccharide, N-trans-feruloyl tyramine, N-formylanonaine and N-methyl-2-pyrrolidone	[16,21,25,27–29]

4 Therapeutic Properties *T. cordifolia*

T. cordifolia has been reported to have antioxidant, anticancer, radio protective, antidiabetic, antidote, antimicrobial, antiallergic, antihyperglycemic, antileprotic, anti-inflammatory, antihyperlipidemic and immunomodulatory properties [30].

4.1 Antioxidant Activity

Reactive oxygen species (ROS) are highly reactive free radicals inducing oxidative stress and causing cellular damage which leads to organ dysfunction. Hypergenerated ROS contribute to the development of various diseases and disorders including diabetes, cancer, and neurodegenerative- and inflammation-mediated diseases. Antioxidants contribute for the major defense against free radicals inducing oxidative damage. These antioxidants can be abundant in medicinal plants in the form of natural antioxidants. Antioxidants play an important role in counterbalancing such free radicals by hindering in the mechanism of free radical production, and thereby play a key role in inactivating them [31]. The strong antioxidant or free radical scavenging potential of medicinal plants can be attributed to the presence of different classes of phytochemicals such as carotenoids, tocopherols, ascorbates, and polyphenols present in them, leading to play a significant role in the health care system [32]. Polyphenols, a major class with strong antioxidant properties, constitute subclasses such as phenolic acids, flavonoids, bioflavonoids, and anthocyanins, which are reported to prevent many types of cancer, neurodegenerative diseases, diabetes and cardiovascular diseases [33].

Excellent antioxidant properties were reported with the ethanolic and n-butanol fractions of *T. cordifolia* extracts [34]. They have been shown to stabilize the antioxidant status of heart [35], liver and kidney [30,36,37] and inhibit the superoxide, hydroxyl radicals and lipid peroxidation. Studies showed that the methanolic extracts of *T. cordifolia*-stems prevented cadmium-induced cardiotoxicity, hepatotoxicity and nephrotoxicity by their antioxidant activity via modulation on the cellular antioxidant status of antioxidant enzymes such as superoxide dismutase, catalase, glutathione-s-transferase, glutathione peroxidase and GSH levels [30,35,37]. Electron paramagnetic resonance spectroscopy studies exposed the strong free radical scavenging properties of *T. cordifolia* against reactive oxygen and nitrogen species [38]. The arabinogalactan polysaccharide (TSP) isolated from *T. cordifolia* offered good protection against iron-mediated lipid peroxidation of rat brain homogenates. Further, TSP also protects rat brains from γ-ray radiation through antioxidant activity by scavenging hydroxyl radicals [39]. Reddi et al. [40] reported that pre-treatment with *T. cordifolia* aqueous and hydroalcoholic extracts attenuated arachidonic acid-mediated ROS generation through enhanced enzymic activity of catalase in human monocytic (THP-1) cells. Oral administration of *T. cordifolia* extract protected against ochratoxin-induced toxicity through increased expression of SOD activity, decreased Asc• and NO• radicals and ROS productions, and Malondialdehyde (MDA) formation in the spleen and serum of mice [41].

4.2 Anti-Hyperglycemic Activity

Hyperglycemia often associated with metabolic disorders such as obesity and diabetes cause serious side effects. The alkaloid fraction of *T. cordifolia* stems has been shown to have hyperglycemic activity. It has been determined in rat models which are fed with the alkaloid fraction of *T. cordifolia* (AFTC) where it stimulates the insulin secretion [13]. The anti-hyperlipidemic activity of the methanolic extract of the stem was studied for its possible activity on high cholesterol fed rats. The *T. cordifolia* stem methanolic extract reduced cholesterol, triglycerides, HDL, LDL and VLDL levels in the cholesterol fed rats [42]. The α-glucosidase inhibitory activity of *T. cordifolia* stems has been reported in animal models which are involved in the anti-hyperglycemic activity [13].

Sivakumar [43] reported that daily oral administration of micropropagated *T. cordifolia* methanolic extract in alloxan-induced diabetic rats significantly decreased blood glucose, glycosylated hemoglobin, cholesterol, glucose 6-phosphatase, fructose 1, 6-bisphosphatase and urea levels with increased hepatic enzyme hexokinase, body weight and total protein levels. Oral administration of *T. cordifolia* loaded poly (D, L-lactide) (PLA) nanoparticles (NPs) for 28 successive days showed significant anti-hyperglycemic activities comparable to the present anti-diabetic drug glibenclamide in streptozotocin-induced type 2 diabetic rats [44]. Stems of *T. cordifolia* showed strong α-amylase, α-glucosidase inhibitory activities *in vitro,* and remarkable anti-hyperglycemic activities *in vivo*, with blood glucose levels at a normal range in the overnight fasted animals when prepared in different dosage formulations using the Ayurvedic pharmaceutical process of Bhavana (levigation) [45]. Another study by Cherku revealed the antidiabetic efficacy of the *T. cordifolia* leaf extract and its component alkaloid magnoflorine with decreased serum glucose, prevention in weight loss and aldose reductase inhibitory activity. This was comparable to the drug metformin on streptozotocin-induced diabetic rats, suggesting that the component alkaloid magnoflorine can be developed into a potent antidiabetic drug with additional trials [46]. Co-administration of the TC aqueous extract (TCE) with the commonly prescribed oral hypoglycemic drugs (metformin, sitagliptin, and glibenclamide) in the therapeutic management of diabetes mellitus showed no significant pharmacokinetic interaction. Instead, it offered a significant improvement in the glycemic control and the conditions associated with diabetes mellitus in streptozotocin-induced diabetic male albino rats, proving safety and efficacy for the combination therapy of TCE with the above standard drugs in the management of diabetes and associated conditions [47]. Improved wound healing efficacy was observed with a combination of the oral TC methanolic extract and the local insulin therapy in alloxan-induced diabetic rats [48].

4.3 Cardioprotective Activity

Rao et al. [49] studied the beneficial effects of the alcoholic extract of *T. cordifolia* in preventing the in ischemia/reperfusion (I/R)-induced myocardial infraction rat model. The *T. cordifolia* alcoholic extract treatment in I/R rats reduced lipid peroxidation and infract size. The methanolic extract of *T. cordifolia* is one of the key ingredients in the ayurvedic herbal preparation “Caps HT2”, which exerts cardioprotective effects. These effects are through an antioxidant activity by inhibition of lipid peroxidation, scavenging of superoxide and hydroxyl radicals, and decreasing the levels of total cholesterol, LDL cholesterol, and triglycerides [50].

T. cordifolia contains the alkaloid berberine. It has been reported to reduce endothelial inflammation, resulting in cardioprotective effects [51]. Supplementing with *T. cordifolia* stem juice decreases the glucuronide and cholesterol synthesis by intervening the lipid metabolism in humans [52]. *T. cordifolia* stem methanolic extract protects heavy metal-induced cardiotoxicity in male wistar rats through its antioxidant activity. The methanolic extract from the *T. cordifolia* stem decreases lipid peroxidation, increases myocardial antioxidant enzyme levels, and prevent histological abnormalities induced by cadmium [35]. The aqueous extract of *T. cordifolia* and vitamin C administration for 14 days significantly

reduced cisplatin-induced histopathological and myocardial degenerative changes, with less number of inflammatory cell infiltrations in the cardiac tissues of male Wistar rats [53]. The cardioprotective effects of *T. cordifolia* may be attributed to its interaction with Adrenoceptor Beta 1 (ADRB1) and a neuroactive ligand-receptor interaction. The compound in TCE responsible for this interaction was identified as tembetarine [54].

4.4 Immunomodulatory Activity

Aqueous extracts of *T. cordifolia* stems were shown to reduce mortality rates of chickens experimentally infected with very virulent infectious bursal disease virus (IBDV) through increased levels of IL-1, IL-2, IL-4, and IFN-γ in the peripheral blood mononuclear cells (PBMCs). In addition, TC treatment also leads to the augmentation of vaccine response in terms of a greater antibody titer after administration of commercially existing IBDV vaccine [55]. Methanolic fraction of TC offers effective inhibition of lipoxygenase and cyclooxygenase enzymes with modest NO scavenging, indicating the free radical scavenging-independent mechanism of immunomodulation by TC [56]. Oral administration of alcoholic stem extract of TC induced increased percentile adhesion of neutrophil to nylon fibers with increased antibody titre dose dependently. In addition, the treatment potentiated a delayed type hypersensitivity reaction induced by sheep red blood cells resulting into a conclusion that TCE increased humoral as well as cell mediated immunity [57].

4.5 Anti-Cancer Activity

The isolated compounds and solvent extracted from *T. cordifolia* have been used to treat various cancer types. Hexane extract from the *T. cordifolia* stem induces apoptosis mediated cell death in ehrlich ascites tumor (EAT) in mouse model. TC hexane extract treatment in EAT cells inhibits the cell cycle progression by arresting the cell cycle at the G1 phase, decreasing Bcl2 expression and increasing Bax expression and DNA fragmentation. TC stem ethanol and dichloromethane extracts have many alkaloids such as berberine, palmatine and tembetarine which are responsible for the anti-cancer activity [58]. The methanolic extract (750 mg/kg body weight) from *T. cordifolia* stem treatment for 30 days in melanoma tumor xenografted C57 Bl mice increased the life span and decreased the micronucleus formation and tumor size [17]. Methanolic stem extracts of *T. cordifolia* have anticancer activity against human breast cancer cell line MDA-MB-231. TC methanolic extract treatment in MDA-MB-231 cells decreases the cell viability and affects the cell morphology [59]. Aqueous extract from stem and arabinogalactan polysaccharide isolated from *T. cordifolia* proved to have anticancer effect against benzo (a) pyrene-induced lung cancer in mice through its antioxidant activity. Both methanolic extract and arabinogalactan from *T. cordifolia* decreased the tumor markers such as carcinoembryonic antigen, circulating tumor DNA, lactate dehydrogenase and TNF-α. Further they also reduced the TUNEL positive cells in benzo (a) pyrene treated mice [60]. Chloroform and hexane extracts from *T. cordifolia* stems inhibit the cell proliferation in Human U87MG glioma and IMR-32 neuroblastoma cell lines. They also prevent the cell migration and inhibit the expression of Neural cell adhesion molecule (NCAM). Diterpeniod lactones such as tinocordin, columbin, 8-hydroxycolumbin, and 10-hydroxycolumbin are reported to be in the chloroform extracts from *T. cordifolia* stems [61]. The methanol extract and berberine isolated from *T. cordifolia* exert potential antitumor activity against HCA-7 cells (human colon adenocarcinoma cell line). Both methanolic extract and berberine decreased the cell viability of HCA-7 cells in a dose-dependent manner. Computational analysis revealed that berberine could regulate the genes involved in the proliferation, differentiation, cell motility, and EMT of the colon cancer cells [62].

4.6 Antimicrobial Activity

T. cordifolia extracts show antibacterial activity against various infectious bacteria such as *Mycobacterium tuberculosis* [63]. *T. cordifolia* stem extracts show antimicrobial activity against both gram-positive and gram-negative bacteria *in-vitro.* They were found to be effective in treating infectious

diseases; methanolic extract of *T. cordifolia* was used against both gram-positive and gram-negative bacteria [64]. Different solvent extracts (aqueous, ethanol and acetone) strongly inhibit growth of the pathogens *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* isolated from clinical isolates of urinary samples [65]. In H_2O_2 scavenging and hydroxyl free radical scavenging assays, *T. cordifolia* ethanolic extracts had the highest free radical scavenging activity of 87.2% and 91.0%, respectively. Phenolic extracts from stems and roots of *T. cordifolia* exert antimicrobial properties [66]. Commercially available *Tinospora* powder shows antimicrobial activity against *Streptococcus mutans* at 2% concentration [67]. Dichloromethane and ethanolic extracts of *T. cordifolia* have antimycobacterial activity against H37Rv INH-sensitive and resistant INH strains of *Mycobacterium tuberculosis* [68].

4.7 Against SARS-CoV-2 (COVID-19)

Six constituents (1a, 1e, 2a, 2b, 4a, 4g and 5a) present in *T. cordifolia* could effectively inhibit the binding of SARS-CoV-2 spike protein with the human receptor ACE2 protein in molecular docking and ADME/T studies, suggesting these 6 constituents as potential drug candidates for COVID-19 [69]. *In silico* studies using tools of network pharmacology, molecular docking reveals that berberine from *T. cordifolia* can inhibit the main protease $3CL^{pro}$ protein function, thereby preventing the SARS-CoV-2 virus replication [70]. Phytoconstituents from *T. cordifolia* have a high binding efficiency to the SARS-CoV-2 main protease enzyme and prevent COVID-19 virus replication. Compounds like Amritoside C, Amritoside B, Amritoside A, Tinocordifolin, Palmatoside G, Palmatoside F, and Maslinic acids from *T. cordifolia* have a docking score between −5.02 to −5.72 on *in silico* molecular docking studies [71]. Another molecular docking and molecular dynamic simulation studies reveal that the compound Tinocordiside present in *T. cordifolia* has a high affinity towards the SARS-CoV-2 main protease [72]. Phytochemical compounds, namely tinosponone, xanosporic acid, cardiofolioside B, tembetarine and berberine of *T. cordifolia* strongly inhibit the main protease $3CL^{pro}$ protein in molecular docking studies [28].

4.8 Other Activities

In vitro acetylcholinesterase inhibitory action of *T. cordifolia* supports its usage as a cognitive enhancer. Allergic rhinitis is the most common atopic disease, which has symptoms such as sneezing, runny nose, nasal congestion, and itchy nose and eyes. Tablets containing TC (Tinofend)® prepared from aqueous stem extracts were used in clinical trials in patients with allergic rhinitis. TC treatment decreased eosinophil and neutrophil counts in allergic rhinitis patients [73]. Methanolic stem extracts of TC have been shown to have male antifertility activity [74]. Ovariectomized rats treated with TC showed an osteo protective effect [75]. The radio protective activity of *T. cordifolia* extracts was proved in mice when they were irradiated with gamma radiation. The free radical formed during irradiation was scavenged by the compounds present in the extract [76]. Fig. 2 illustrate the mechanisms of *T. cordifolia* in preventing different disease conditions.

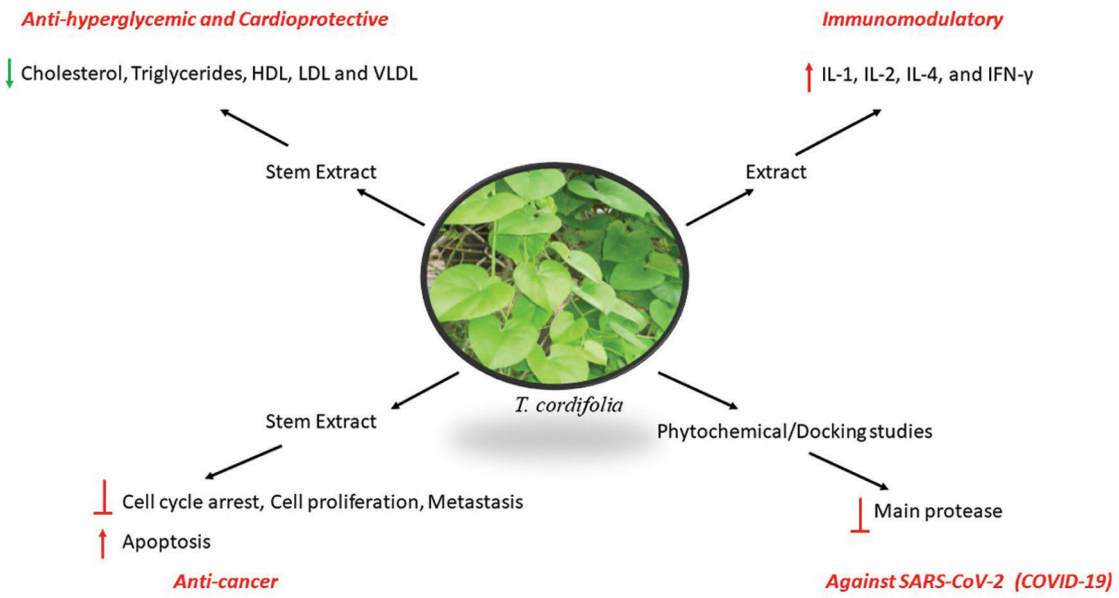

Figure 2: Summary of mechanisms of *T. cordifolia* under various disease conditions

5 Conclusions

T. cordifolia is a medicinal plant that contains several different chemicals including alkaloids, steroids, glycosides, sesquiterpenoids, and other bioactive chemicals. This review highlighted different medicinal properties like antioxidant, anti-hyperglycemic, cardioprotective, immunomodulatory, anti-cancer, and antimicrobial activities of different compounds and extracts of *T. cordifolia*. It has been effectively used in different Indian systems of medicine for a time, and its products are employed for a better economic and therapeutic application. The present review provides a comprehensive therapeutic potential of *T. cordifolia*. It mostly presents the effect of the crude extract, which is one of the limitations of the review. Further studies with active principles from *T. cordifolia* and their molecular mechanisms need to be explored. The review's future focus will be on using the biochemical and signaling pathways of active components in *T. cordifolia* to enable an efficient disease targeting.

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