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Review Article

Systematic Review of *Tinospora cordifolia* (Thunb.) Miers Phytoconstituents in Traditional Ayurvedic Medicine

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ABSTRACT

Tinospora cordifolia (Thunb.) Miers, a well-recognized herb in Ayurvedic medicine, has been extensively utilized for centuries due to its wide spectrum of therapeutic properties. The plant contains diverse phytoconstituents, including alkaloids (berberine, magnoflorine, palmatine), diterpenoid lactones (tinosporaside, giloin), glycosides (syringin, cordifolioside A), terpenoids, steroids, and polysaccharides. These bioactive compounds are responsible for their traditional use as a rasayana (rejuvenator) with immunomodulatory, anti-inflammatory, antioxidant, hepatoprotective, antidiabetic, antimicrobial, and anticancer activities. Recent pharmacological investigations support many of these traditional claims, with studies demonstrating that *T. cordifolia* phytoconstituents modulate key molecular pathways such as NF-κB, PI3K/Akt, MAPK, and apoptotic regulators. Moreover, *in silico* and *in vitro* studies have highlighted its potential in managing chronic diseases, including cancer, diabetes, arthritis, and infectious disorders. Despite promising results, limitations remain due to a lack of standardized extracts, variations in bioactive concentrations, and insufficient clinical validation. This systematic review aims to critically evaluate the role of *T. cordifolia* phytoconstituents in traditional Ayurvedic medicine, integrating evidence from ethnomedicinal uses, phytochemistry, pharmacology, and toxicity studies. A better understanding of its molecular targets and therapeutic relevance may pave the way for developing novel phytopharmaceuticals based on this traditional medicinal plant.

Keywords: Ayurveda, Immunomodulation, Pharmacology, Phytoconstituents, *Tinospora cordifolia*.

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INTRODUCTION

The growing global interest in traditional medicine and phytotherapy has spurred renewed scientific attention to medicinal plants as promising sources of novel therapeutically active compounds. Among the various medicinal plants identified in the Indian subcontinent, *Tinospora cordifolia*, a traditionally revered Ayurvedic herb, has gained considerable attention despite its relatively limited application in modern therapeutics. Commonly known as Guduchi or Giloy, *T. cordifolia* is recognized for its broad spectrum of pharmacological activities. It is a large, deciduous, climbing shrub that grows naturally in the tropical regions of India. For centuries, this plant has been widely used in traditional medicinal systems to treat numerous ailments, including fever, metabolic disorders, immune dysfunctions, and inflammatory conditions (Barabási *et al.*, 2011; Chandrasekaran *et al.*, 2009).

T. cordifolia has been described as a Rasayana plant in the Ayurvedic literature and possesses rejuvenating, life-prolonging, and disease resistance-building properties (Desai *et al.*, 2002). The pharmacological plethora of this plant is linked with its diverse bioactive phytochemicals profile, which includes: alkaloids (berberine, tinosporine), diterpenoid lactones (tinosporide, cordifolide), glycosides (cordifoliosides), steroidal, polysaccharides, and phenolics (Ghosh and Saha, 2012; Hopkins, 2008). These metabolites have been shown to exhibit various biological activities, including anti-inflammatory, antimicrobial, hepatoprotective, antidiabetic, and anticancer activities, which render the plant an important source of therapeutics.

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Various traditional claims of *T. cordifolia* have been pharmacologically proven in recent times. Alcoholic and aqueous extracts of the stem and leaves have shown significant immunomodulatory activity with their ability to potentiate both humoral and cell-mediated immunity through augmentation of macrophage function, leucocyte count, and modulation of cytokine (Kitano, 2002). The polysaccharide fraction of the plant has been described to enhance phagocytosis, nitric-oxide production, and lysosomal enzyme levels; such results suggest that the plant can elicit the participants of innate immune responses (Rege *et al*., 1999). Further, *T. cordifolia* is an adaptogen that provides resistance to stress-induced tissue damage and helps an organism to adapt to stress under normal and pathological circumstances (Saha and Ghosh, 2012). The present study aims to elucidate the various pharmacological and therapeutic potential of the *T. cordifolia* plant, with special emphasis given on its anticancer property.

Pharmacological and Therapeutic Role of the *T. cordifolia*

T. cordifolia, called guduchi or amrita, is a climbing shrub of the family Menispermaceae. This endemic tropical plant grows in the hot parts of the Indian subcontinent, and has been used in traditional medicine in Ayurveda and the Siddha system for many centuries. It has long been known as a Rasayana and is believed to slow down the aging process, enhance longevity, invigorate health, and provide resistance against disease. The pharmacological potential of *T. cordifolia* is thought to be mainly due to its rich phytochemical content, such as alkaloids, diterpenoids, glycosides, steroids, polysaccharides, and phenolics. These components manifest a wide range of biological activities (Gebrelibanos Hiben *et al*., 2019; Singh *et al*., 2003) (Figure 1). The stem, leaves, and roots are rich in bioactive compounds, including tinosporide, cordifolioside A, berberine, and magnoflorine, which are the main mediators of the plant's medicinally useful properties (Thatte and Dahanukar, 1997) (Table 1).

In the field of oncology, the plant has drawn significant interest because of its anti-proliferative, proapoptotic, and chemopreventive activity. Initial *in vitro* and *in vivo* experiments suggest that extracts and isolated compounds from *T. cordifolia* are able to suppress the growth of multiple cancer cell lines, regulate several signaling pathways, and induce apoptosis without adversely affecting normal cells (Kumar *et al*., 2018; Sharma and Singh, 2020). The plant's low toxicity side effects and its pleiotropic effects on biological systems qualify it to be a potential candidate for an integrative cancer therapy and as an adjunct therapy. Although the plant has high therapeutic potential but molecular basis of its actions has not been much explored. Phytochemical complexity and pleiotropic action represent a challenge to classical reductionist pharmacology (Yang *et al*., 2019). In this sense, systems biology becomes an attractive approach to understanding the integrative influence of phytochemicals on biological systems. Systems biology makes use of computational modeling, high-throughput screening, and network-centric approaches to elucidate how various bioactive compounds interact with the targets and pathways in cells to give an integrated understanding of the pharmacodynamics of the plant (Kumar *et al*., 2018; Yang *et al*., 2019).

Using systems biology methodologies, the synergistic, additive, or antagonistic combinatorial effects of *T. cordifolia* phytoconstituents can be predicted on molecular networks, novel therapeutic targets can be deciphered, and the traditional usage of the plant can be laid down in a data-driven manner. Cytoscape, STRING, SwissTarget Prediction, and KEGG pathway enrichment analysis are network pharmacology tools that visualize complex interactions between plant compounds and disease-associated genes/proteins (Sharma and Singh, 2020). These approaches are especially relevant for multi-ingredient, multitarget therapies, as in the case of herbal medicines such as *T. cordifolia*.

This plant has a wide range of phytochemicals involved in various therapeutic applications, which are, in turn, promising for further scientific evaluation. The combination of traditional medicine and modern systems biology approach provides a promising strategy to reveal the complete therapeutic potential of the ancient medicine plant. A systems-level perspective of the mechanisms of its action will facilitate drug discovery and the development of safe and effective phytomedicines for numerous chronic diseases (Park *et al*., 2019).

The immunomodulatory activity of *T. cordifolia* is the best studied and well-established. *T. cordifolia* extracts have been demonstrated to activate the macrophages, neutrophils, and Natural Killer (NK)-cell activity, which contribute to the activation of both innate and adaptive immune responses (Oliveros, 2007-15). The polysaccharides from *T. cordifolia* can stimulate cytokine production and increase phagocytic activity that could mediate infection containment and reestablishment of immunologic equilibrium (Stelzer *et al*., 2016). This immunostimulatory effect is especially advantageous for the treatment of immunosuppressive states, such as chronic infections and autoimmune diseases. Besides, the plant has been used for the cotreatment of cancer (adjuvant therapy) (Amberger, *et al*., 2019).

Apart from immunomodulation, *T. cordifolia* possesses strong antioxidant capacity attributed partly to its phenolics and flavonoids acting as free-radical scavengers, and blocking the generation of Reactive Oxygen Species (ROS) and mitigating lipid peroxidation as well as augmenting Endogenous antioxidant (EG) enzymes such as superoxide dismutase and catalase. These are important properties in the prevention of oxidative stress-associated diseases, such as neurodegenerative, cardiovascular diseases, and diabetes (Ge *et al*., 2020).

The hypoglycemic activity of *T. cordifolia* is one of the most important aspects of its pharmacological value. Daina, *et al*.,

(2019) confirmed that the herb improves glucose metabolism, insulin secretion, and peripheral glucose uptake via multimodal actions. Such mechanisms consist of inhibition of α-glucosidase activity, regulation of hepatic gluconeogenesis, and preservation of pancreatic beta cells from oxidative stress (Daina *et al.*, 2019). Bioactive compounds like tinosporide and berberine are the principal actors responsible for reducing hyperglycemia, insulin insensitivity, and control of lipids (Imanshahidi and Hosseinzadeh, 2008). *T. cordifolia* extracts also improve glycemic control in patients with type 2 diabetes mellitus and are used to reduce the requirement of synthetic oral antidiabetic agents (Keiser *et al.*, 2007). The anti-inflammatory activity of the plant correlated well with its antidiabetic effects, since chronic inflammation has been implicated in metabolic diseases.

In addition to its metabolic and immunologic effects, *T. cordifolia* also exhibits hepatoprotective activities according to animal and clinical studies. The antioxidant and detoxifying efficacy of the plant raises hepatic glutathione contents, maintains membrane stability of cells, and modulates serum liver injury biomarkers such as ALT, AST, and bilirubin (Kumar *et al.*, 2020). These effects have been shown in the models of CCl4 and paracetamol toxicity-induced liver damage. *T. cordifolia* also stimulates the regeneration of liver cells and is known to possess hepatoprotective effects and is used to treat ascites, jaundice, and alcoholic liver disease (Liu *et al.*, 2010).

T. cordifolia has gained interest in oncology as an adjuvant to standard cancer therapies. Though not directly cytotoxic, its potential to increase immunosurveillance, diminish oxidative stress, and alleviate side effects of chemotherapy has drawn it to be a potential candidate in integrative oncology (Patgiri *et al.*, 2020). Drugs including berberine and palmatine have been shown to have cytotoxic activities over a range of cancer cell lines, mainly through the induction of apoptotic pathways, cell cycle arrest, and inhibition of angiogenesis, among others, but more clinical trials are required to ascertain the real efficacy in humans.

In addition, *T. cordifolia* also has adaptogenic activity that assists the organism in countering stress, imbalances in hormones, fatigue, and neurological disorders commonly caused by it. Studies on its neuroprotective role have shown enhanced cognitive function and a decrease in neuroinflammation in models of neurodegeneration like Alzheimer's disease (Rathore *et al.*, 2021). The plant has also been demonstrated to penetrate the blood-brain barrier and exhibit effects on the central nervous system, validating the possible neuropharmacological status of the plant. Its customary application as a rejuvenating agent is consistent with its effects on quality-of-life indexes in general and aging in particular.

With respect to safety, *T. cordifolia* is usually safe in dosages within the established range. Toxicological studies published have high LD_{50} values (indicating a low acute toxicity), although isolated recent reports of hepatotoxicity emphasize the importance of dose standardization and formulation control during *T. procumbens* therapy (Bisht *et al.*, 2023). The long-term effects, interactions with other drugs and herbs, and standardization of bioactive components are the unresolved aspects. Phytochemical content variation by environment and processing has been reported to cause inconsistency of clinical effects and regulatory approval, indicating the significance of extraction standardization (Balasubramani *et al.*, 2011).

These diverse effects, namely immunomodulatory, antidiabetic, hepatoprotective, antimicrobial, neuroprotective, and so on, are due to the presence of a variety of phytochemicals. The interrelation between traditional uses and scientific data demonstrates the potential for future studies to advance *T. cordifolia* as an evidence-based integrative medicine. To fully exploit the therapeutic potential of this important plant, high-quality mechanistic studies, better delivery systems, and more rigorous clinical trials are needed (Bisht *et al.*, 2023).

Drug Likeness Score and Toxicity Prediction of Phytochemicals and Metabolites

Apparently, plant-based metabolites and phytochemicals have been known for a long time for their healing effects, and have constituted indispensable elements of the process of drug research and development. Nevertheless, a compound to be a potential drug must have good absorption, distribution, metabolism, and excretion, and toxicity behavior. One of the first and key evaluations along this pipeline is the drug-likeness analysis. Drug-likeness is a qualitative concept used in drug design to evaluate how "drug-like" a molecule is with respect to factors important for a molecule to have a chance of becoming an oral drug. This often includes application of the compound against several "standard" rules, including Lipinski's RO5, Veber rules, Ghose filter, and others (Ghosh *et al.*, 2011). In fact, according to Lipinski's Rule of Five, compounds will ultimately have good oral bioavailability if they have less than five hydrogen bond donors, less than 10 hydrogen bond acceptors, a molecular weight under 500 daltons, and a LogP less than five (Kapil and Sharma, 1997). A breach of more than one of them is often indicative of poor absorption and/or permeation (Kumar *et al.*, 2020). The number of rotatable bonds (≤10) and the polar surface area (TPSA ≤140 Å2) are both incorporated in Veber's rule to improve the oral bioavailability prediction (Yip *et al.*, 2021).

Recent *in silico* platforms, such as SwissADME, offer solutions with a friendly interface to consider these parameters, taking them into account simultaneously (Nair *et al.*, 2014). Multiple drug-likeness filters, such as those of Lipinski, Veber, Ghose, Egan, and Muegge, are calculated, along with pharmacokinetic parameters, such as gastrointestinal absorption, blood-brain barrier penetration, P-glycoprotein substrate, and cytochrome P_{450} inhibition. Such predictions are very important in determining if a natural

product would be significantly bioavailable in the human body and that can also be metabolically stable. Phytochemicals, for example, quercetin, kaempferol, and hydroxychavicol, typically have good SwissADME scores, which indicate their potential for oral bioavailability and permeability (Patgiri *et al.*, 2020; Rathore, *et al.*, 2021). In addition to these physicochemical evaluations, both bioavailability radar plots and the BOILED-Egg model by SwissADME assess the drug-likeness directly and predict the passive gastrointestinal absorption, and central nervous system penetration by considering WLOGP by TPSA.

Prediction of toxicity is one more very important aspect in the early drug discovery process. Bioactive products of natural origin, however, may display negative side effects, such as mutagenicity, hepatotoxicity, carcinogenicity, or cardiotoxicity, which are to be prescreened before clinical studies. Computational models, including ProTox-II, admetSAR, and pkCSM, predict these toxicity end points based on molecular structure and known toxicophores with the aid of machine learning and quantitative structure-activity relationship models (Saha *et al.*, 2011; Sharma *et al.*, 2012; Subilal *et al.*, 2020). For example, ProTox-II predicts the LD_{50} (lethal Dose 50), organ toxicity, immunotoxicity, cytotoxicity, and carcinogenicity classes. It divides compounds into 6 classes of toxicity (Class I, the most toxic, LD_{50} ≤5 mg/kg; Class VI, the least toxic, LD_{50} >5,000 mg/kg), by which they can be compared to one another in a safety context. AdmetSAR 2.0 further expands the toxicity prediction by adding the models of Ames mutagenicity, developmental toxicity, and hERG inhibition-a key indicator of cardiac risk (Zhang *et al.*, 2022).

It has been reported that certain phytochemicals derived from *Piper betle* (such as hydroxychavicol) are potential *in silico* toxicity screening candidates. Hydroxychavicol lies in Class IV and V in ProTox-II systems for moderate to low toxic characteristics with an LD_{50} of 2,000-3,000 mg/kg and is nonmutagenic and noncarcinogenic (Chen *et al.*, 2022). This may underlie its therapeutic utility in antimicrobial and anticancer contexts. Quercetin, a flavonoid, is also characterized by low hepatotoxicity and noncarcinogenicity, but few caveats were identified on its cytochrome P_{450} interactions (Su *et al.*, 2019). These evaluations are essential, particularly for chemotherapeutic applications where reducing off- target effects is important for patient safety. In addition, such tools assist in the ranking of compounds for *in vitro* and *in vivo* validation approaches, thus facilitating drug discovery pipelines.

Apart from toxicity, computational absorption, distribution, metabolism, and excretion, and toxicity can identify whether a compound is a substrate or inhibitor of major metabolic enzymes (such as CYP3A4, CYP2D6) or transporters (such as P-glycoprotein). This knowledge is critical in anticipating drug-drug interactions, more so if plant-derived compounds are proposed for combinations or adjuvant therapies. The cytochrome inhibitory potential of hydroxychavicol has also been investigated *in silico*, with the results showing minimal inhibition of the most important enzymes for drug metabolism, and is thus likely to be safe (Chowdhury, 2020; Das *et al.*, 2023) (Table 2).

Target Predictions of Phytochemicals of *T. cordifolia*

T. cordifolia contains a diverse range of bioactive secondary metabolites, which contribute to its therapeutic properties. With the growing emphasis on multitarget drug design, virtual target prediction of these phytoconstituents has emerged as an important strategy in phytopharmacological research (de Oliveira *et al.*, 2022).

Software packages such as SwissTarget Prediction, Similarity Ensemble Approach, PharmMapper, BindingDB, STITCH, and SuperPred are increasingly used to predict biotargets for phytochemicals based on the similarity principle, targeting-mapping ligand assay, pharmacophore mapping, and ligand-target interaction profiles (*"Clinical efficacy of Tinospora cordifolia extract in type 2 diabetic patients: A pilot study. IJPSR"*, 2022; Dilnashin *et al.*, 2023; Ranjan *et al.*, 2022). These methods assess the structural and physicochemical properties of small molecules and identify drug-like compounds similar to input molecules to predict the possible interactions with human protein targets. For *T. cordifolia*, these *in silico* approaches have recently predicted interactions between its active molecules and the key regulators and receptors in immune, inflammation, metabolism, and cellular proliferation signaling. With the current trend of drug discovery technologies shifting toward multitargeted

Table 1: Some common phytochemicals present in the *Tinospora cordifolia*.

Key compounds	Function
β-sitosterol	antioxidant, anticancer, anti-inflammatory, and immunomodulatory (Afendi *et al.*, 2012)
Malabarolide	antioxidant, anti-inflammatory, cytotoxic potential (Mohanraj *et al.*, 2018)
Kaempferol	antioxidant, anti-inflammatory, cardioprotective, neuroprotective (Totrov *et al.*, 2011)
Tembetarine	antimicrobial, antioxidant, and neuroprotective (Banerjee *et al.*, 2018)
Berberine	anti-inflammatory, anticancer, antidiabetic (Daina *et al.*, 2017)
Magnoflorine	immunomodulatory, antioxidant, anti-viral, antidiabetic (Stelzer *et al.*, 2016)
Tinosporin	anti-inflammatory, multitarget activity, immunomodulatory (Amberger *et al.*, 2019)
Palmatine	antimicrobial, antidepressant, hepatoprotective action (Oliveros, 2007-15)
Jatrorrhizine	anti-inflammatory, antioxidant, neuroprotective (Stelzer *et al.*, 2016)

drugs, *in silico* target prediction methods are being employed to highlight the molecular targets of these phytoconstituents in phytopharmacology studies (Omori and Kotera, 2007; Suez Canal University Group, 2023).

Moreover, the multitarget binding potentials of the phytochemicals have also been explored through systems pharmacology analysis of *T. cordifolia*. Researchers have demonstrated that these phytochemicals globally influence several biological processes, since predicted targets were integrated with disease-specific genes and pathways from resources such as KEGG, DisGeNET, and GeneCards, such as regulation of apoptosis, response to oxidative stress, inhibition of angiogenesis, and immunity modulation (Savai *et al.*, 2010). For instance, genes TNF, IL6, AKT1, TP53, and epidermal growth factor receptor have been identified as hub nodes in network models obtained through tools like cytoscape, implying these nodes as important mediators of the pharmacological action of the *T. cordifolia* components. The pathway enrichment of such targets typically yields participation in important human pathways like the PI3K-Akt, MAPK, NF-κB, TLR, and JAK-STAT signaling pathways, essential for inflammation, cancer, and immune response (Thornalley, 2003; Turk *et al.*, 2012).

Furthermore, systems biology has provided insight into the possible polypharmacological activity of *T. cordifolia* phytoconstituents. For example, the compound cordifolioside A has been proposed to interact with proteins associated with glucose metabolism, such as glucokinase and insulin receptor Substrate-1, thereby showing antidiabetic potential, and was found to bind to TLR4, indicating immune modulatory activity. The multitargeted activities of these extracts make *T. cordifolia* an attractive source for the discovery of the lead compounds for the treatment of complex diseases like cancer, autoimmune and chronic inflammatory diseases, where single-target drugs have become futile (Kitano, 2002; Mohamed and Sloane, 2006).

Of great significance, binding affinity analyses and molecular docking simulations have supported a number of these predicted interactions. Docking studies via Autodock Vina indicated that berberine possessed binding energies lower than -8.0 kilocalorie/mol against COX-2, while magnoflorine displayed similar high affinities against acetylcholinesterase, suggesting practical pharmacological significance. Molecular dynamics simulations also demonstrated time-averaged structural stability of these bioactive-protein complexes at a nanosecond time scale and offered detailed insights into conformational fluctuation and modes of interactions (Banerjee *et al.*, 2018; Rathore *et al.*, 2021).

In therapeutic consequences, potential targets of *T. cordifolia* phytochemicals indicate drastic influences over infectious diseases, cancers, neurodegenerative diseases, metabolic syndrome, and autoimmunity (Table 3). For instance, their strong modulatory effects of IL-6 and NF-κB render these

Table 2: Drug-likeness and toxicity prediction of selected phytochemicals.

Phytochemical/metabolite	MW (da)	LogP	HBD/HBA	Lipinski's rule violations	Drug-likeness score	Predicted toxicity	Remarks
Eugenol	164	2.3	1/2	0	high	LD_{50} ~ 1,930 mg/kg (Oral rat, Cat. 4); Noncarcinogenic; No hepatotoxicity	safe at therapeutic doses
Curcumin	368	3.3	2/6	0	moderate	LD_{50} ~ 2,000 mg/kg (Cat. 4); Low mutagenicity risk; Possible hepatotoxicity	bioactive but poor bioavailability
Quercetin	302	1.5	5/7	1 (HBD > 5)	moderate	LD_{50} ~ 159 mg/kg (Cat. 3, more toxic); Possible mutagenicity; Low hepatotoxicity	potent antioxidant but limited drug-likeness
Resveratrol	228	2.8	3/3	0	high	LD_{50} ~ 1,560 mg/kg (Cat. 4); Noncarcinogenic; No hepatotoxicity	promising, but rapid metabolism
Berberine	336	1.5	0/4	0	moderate	LD_{50} ~ 713 mg/kg (Cat. 3); Predicted cardiotoxicity (hERG inhibition)	needs caution in dosing

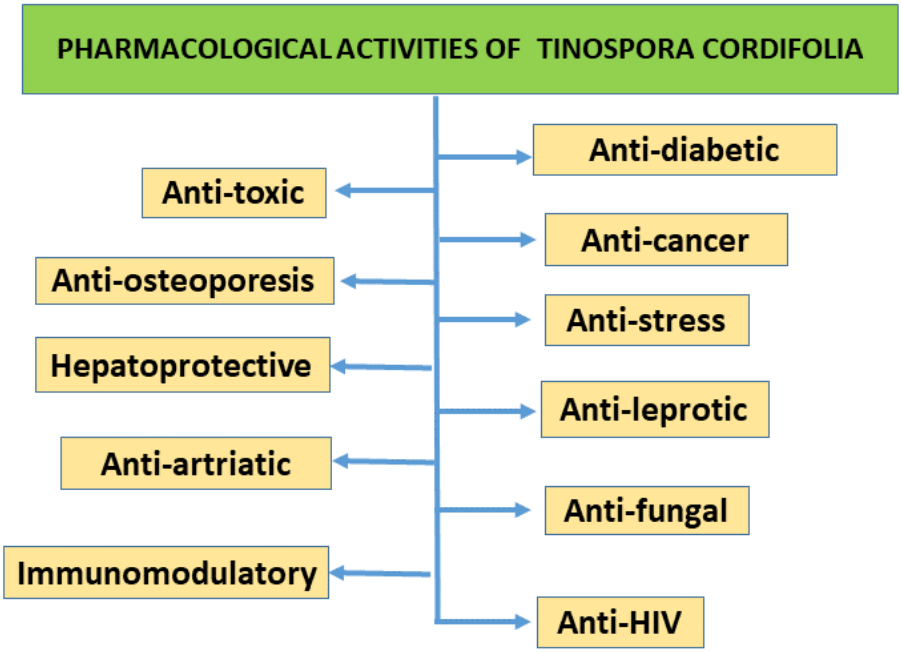

Figure 1: An insight into the pharmacological paradigms of *T. cordifolia*.

Table 3: Various phytochemicals and their targets.

Phytochemical	Predicted/reported targets	Biological role	Relevance in cancer/ disease
Tinosporaside (diterpenoid)	NF-κB, TNF-α, IL-6	anti-inflammatory, immune regulation	suppresses tumor-promoting inflammation
Berberine (alkaloid)	topoisomerase I/II, AMPK, PI3K/ Akt, MAPK	DNA intercalation, apoptosis induction, metabolic regulation	anti-proliferative, proapoptotic
Palmatine (alkaloid)	DNA minor groove, Bcl-2 family proteins	DNA binding, apoptosis modulation	inhibits tumor cell growth
Magnoflorine (alkaloid)	acetylcholinesterase, CYP450 enzymes	neuroprotection, metabolic modulation	may reduce drug resistance, enhance cytotoxicity
Cordifolioside A (glycoside)	COX-2, iNOS, NF-κB	anti-inflammatory, antioxidant	prevents inflammation-driven carcinogenesis
Tinocordifolin (sesquiterpene)	caspases, p53 pathway	apoptosis regulation	induces cancer cell apoptosis
Syringin (glycoside)	IL-2, IFN-γ, T-cell receptors	immunostimulatory	enhances immune surveillance against cancer
Giloin and Giloiside (diterpenes)	VEGF, HIF-1α	angiogenesis regulation	inhibits tumor angiogenesis

Abbreviations: VEGF: Vascular Endothelial Growth Factor.

compounds as being suitable candidates for the treatment of chronic inflammatory disorders, including rheumatoid arthritis and ulcerative colitis. Moreover, the interaction with enzymes like DPP-IV and PPARs could justify the usual antidiabetic uses of the plant. In addition, regulation of oxidative stress mediators, including Nrf2 and superoxide dismutase by some agents may underlie antioxidant-related therapeutic benefits (Afendi *et al.*, 2012; Kitano, 2002; Saha *et al.*, 2011).

In silico target prediction techniques for the phytochemicals of *T. cordifolia* have revealed an extensive pharmacophore of

multitarget and multipathway interactions. These models do not just support the time-honored records of multiutility potentials of *T. cordifolia* but also provide a molecular view of how it exerts its effects. Facilitating a dialogue between ancient wisdom and modern computer technology, they can systematically investigate and confirm the medicinal potential of these phytochemicals (Park *et al.*, 2019).

Anticancer Mechanism of *T. cordifolia*

One important anticancer mode of action of *T. cordifolia* is via selective induction of apoptosis (programmed cell death) in cancerous cells (Figure 2). It has been suggested that compounds such as berberine and columbin act through regulation of the intrinsic mitochondrial apoptotic pathway, as they increase the expression of proapoptotic Bax and Bak, and also of p53, and decrease the levels of anti-apoptotic Bcl-2 and Bcl-xL. Modulations of protein expressions result in depolarization of mitochondrial membrane, loss of cytochrome c, and activation of caspases-3, -7, -9, which finally leads to DNA fragmentation and cell death in cancer cells (Ranjan, *et al.*, 2022; Singh *et al.*, 2003). Significantly, this apoptosis induction is without damaging noncancerous cells, implying selective cytotoxicity, a very important feature for a candidate anticancer therapy.

In addition, *T. cordifolia* also suppresses the growth of cancer cells via the blockage of the cell cycle at G0/G1 or G2/M phase (Figure 3). This is mediated by the inhibition of cell cycle-promoting proteins cyclins (cyclin D1, cyclin E) and cyclin-dependent kinases and upregulation of cyclin-dependent kinases inhibitors like p21 and p27 (Sharma and Singh, 2020). This arrest leads to the blockage of DNA synthesis and entry into mitosis, thus stopping cancer development. As observed in *in vitro* model studies using MCF-7 (breast cancer) and HeLa (cervical cancer) cell lines, the ethanolic and aqueous extracts of *T. cordifolia* substantially decreased the cell viability in a dose- and time-dependent manner (Daina *et al.*, 2017).

Angiogenesis, the generation of new blood vessels to feed nutrients and oxygen to tumors, is a key hallmark of tumor progression. *T. cordifolia* phytochemicals are anti-angiogenic by inhibition of VEGF, basic fibroblast growth factor, and matrix-metalloproteinases (MMP-2 and MMP-9), key regulators of angiogenesis and degradation of extracellular matrix (74) (Figure 4). The inhibition of angiogenesis deprives cancer cells of oxygen and nutrients and inhibits metastases and tumor growth (Amberger *et al.*, 2019; Kumar *et al.*, 2018).

Another mechanism by which *T. cordifolia* exhibits its antitumor activity is by regulating oxidative stress. Although a fine equilibrium between ROS production and the antioxidant system exists in healthy cells, cancer cells experience a higher oxidative pressure. Several phytochemicals from *T. cordifolia* play a dual role; they act as antioxidants in normal cells by scavenging free radicals and augmenting antioxidant enzymes such as superoxide dismutase, catalase, and glutathione peroxidase, whereas in cancer cells, they can induce excessive ROS formation that causes oxidative stress to mitochondria and DNA and results in apoptosis (Hopkins, 2008; Sharma *et al.*, 2012; Yang *et al.*, 2019). This ROS activation selectivity is essential to selectively hit the cancer cells and spare the normal tissues. Just as crucial is *T. cordifolia's* immunomodulatory role in enabling the host to recognize and kill cancer cells. Polysaccharides and glycoside constituents of *T. cordifolia* enhance the immune effector cells, such as NK cells, macrophages, and cytotoxic T lymphocytes. These chemicals also promote cytokines such as IL-2, IFN-γ, and TNF-α, which are necessary for the induction of antitumour immunity (Sharma *et al.*, 2012; Stelzer *et al.*, 2016) (Figure 5). It is interesting to note that *T. cordifolia* extracts exhibit adjuvant activity, improve the therapeutic potential of conventional chemotherapeutic agents, and ameliorate the overall immune status of patients.

Table 4: Various phytochemicals and their role as anticancer molecules.

Mechanism	Biological action	Outcome in cancer
Induction of apoptosis	activation of caspases, upregulation of Bax, downregulation of Bcl-2	triggers programmed cell death of cancer cells
Cell cycle arrest	arrest at G0/G1 or G2/M phases	prevents uncontrolled proliferation
Antioxidant activity	scavenging of ROS and free radicals	reduces DNA damage and mutagenesis
Immunomodulation	activation of macrophages, NK cells, and cytokines (IL-2, IFN-γ)	enhances immune-mediated destruction of tumor cells
Inhibition of angiogenesis	suppression of VEGF and angiogenic signaling	restricts tumor blood supply and growth
Anti-inflammatory effects	downregulation of NF-κB, TNF-α, IL-6, and COX-2	reduces inflammation-driven cancer progression
Modulation of signaling pathways	influences PI3K/Akt, MAPK, and p53 pathways	suppresses proliferation and enhances apoptosis

Abbreviations: NK: Natural Killer
ROS: Reactive Oxygen Species
VEGF: Vascular Endothelial Growth Factor.

Recent *in silico* and network pharmacology investigations have also disclosed the molecular targets and pathways modulated by *T. cordifolia* phytoconstituents. The computational docking models have provided evidence for the high-affinity binding of berberine, magnoflorine, and columbin with the major oncogenic proteins epidermal growth factor receptor, tumor protein p53, Nuclear Factor-Kappa B (NF-κB), Cyclooxygenase 2 (COX-2), and AKT1 (Afendi *et al.*, 2012; Kumar, *et al.*, 2020). These interactions disrupt cell signaling, such as PI3K/Akt/mTOR, MAPK, and NF-κB, which are crucial for the survival, proliferation, and resistance to apoptosis in cancer cells. For example, inhibition of the PI3K/Akt pathway decreases glucose metabolism in cancer cells and increases susceptibility to apoptosis, whereas suppression of NF-κB diminishes the inflammatory milieu that nurtures tumor growth (Bisht *et al.*, 2023; Su *et al.*, 2019).

Also, *T. cordifolia* has demonstrated potential in overcoming chemoresistance, one of the main problems in cancer therapy. Its phytochemical constituents are reportedly capable of downregulating expression of multidrug resistance proteins, including P-glycoprotein (P-gp), which actively extrude anticancer drugs from cancer cells (Omori and Kotera, 2007; Patgiri *et al.*, 2020) (Table 4). Through the downregulation of such efflux transporters and simultaneous modulation of apoptosis-related genes, it can resensitize the drug resistance to drugs such as

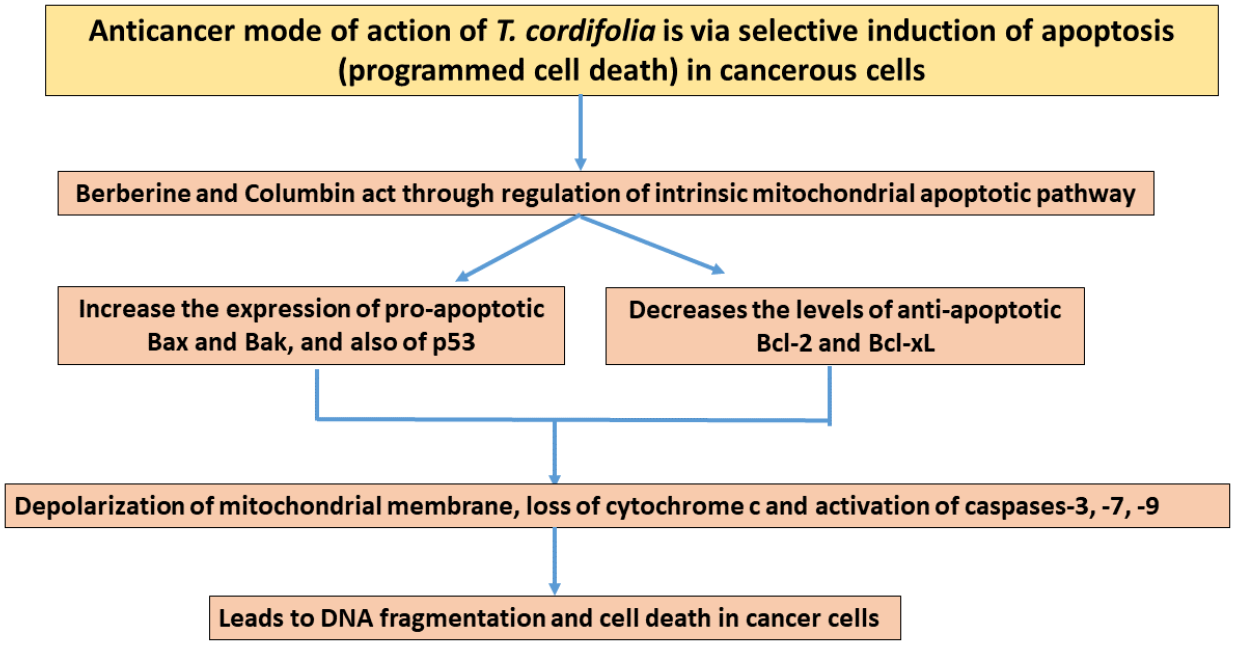

Figure 2: Anticancer mode of *T. cordifolia*.

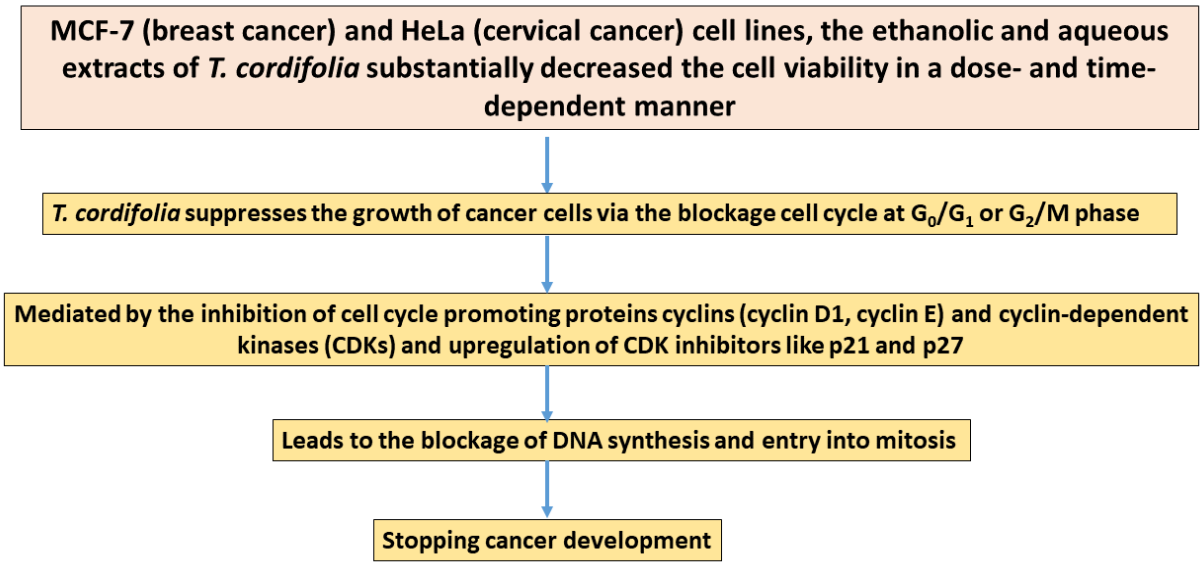

Figure 3: Regulation of the cell cycle by *T. cordifolia*.

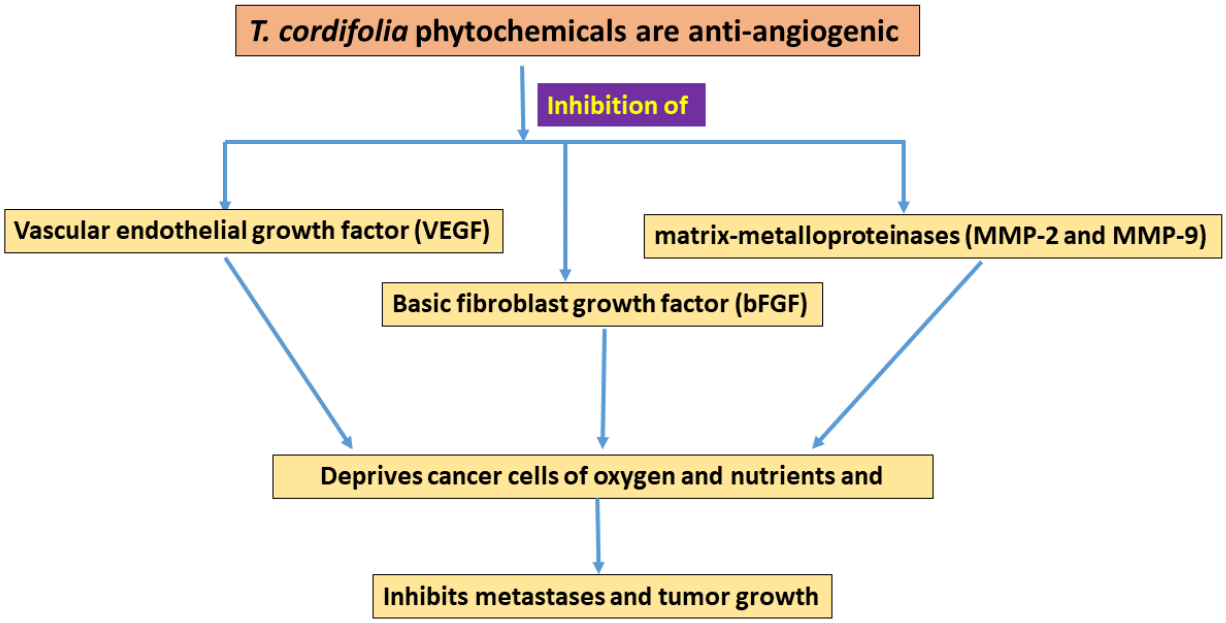

Figure 4: Anti-angiogenic mode of *T. cordifolia*.

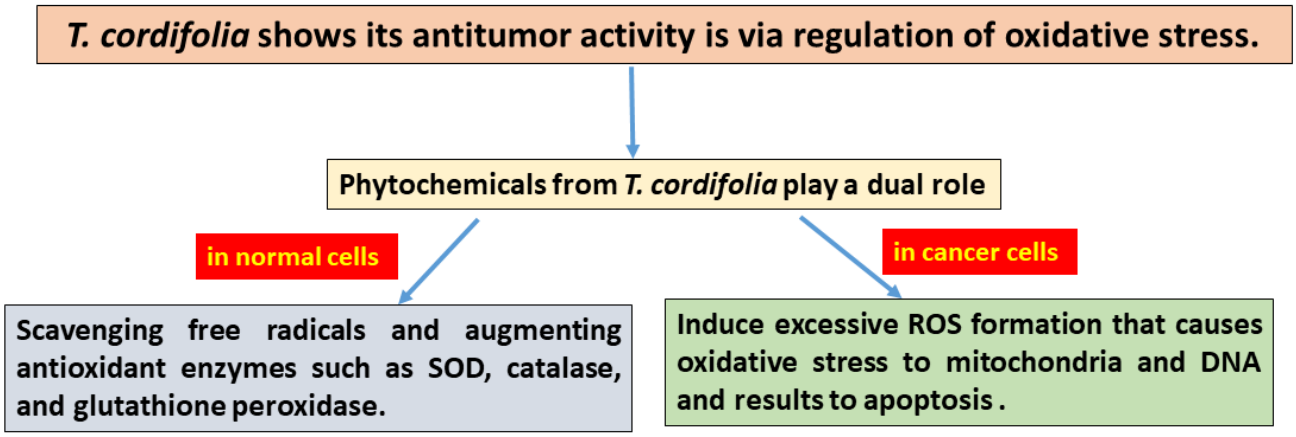

Figure 5: Antitumour activity of *T. cordifolia* by regulation of oxidative stress.

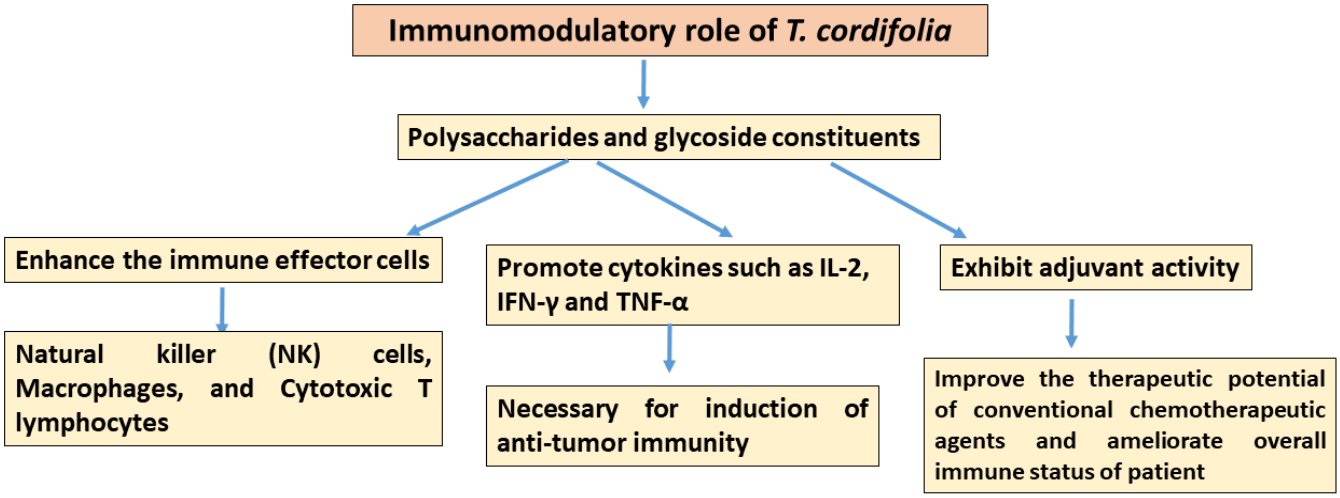

Figure 6: Immunomodulatory role of *T. cordifolia*.

doxorubicin or cisplatin, thus providing a promising adjunct therapy source (Figure 6).

CONCLUSION

T. cordifolia holds a significant place in traditional Ayurvedic medicine owing to its diverse phytoconstituents and wide-ranging therapeutic applications. The available evidence highlights its strong immunomodulatory, antioxidant, anti-inflammatory, hepatoprotective, and anticancer activities, which are mediated through multiple bioactive molecules such as alkaloids, diterpenoid lactones, glycosides, and polysaccharides. These compounds act on key molecular targets and signaling pathways, including NF-κB, PI3K/Akt, MAPK, VEGF, and apoptotic regulators, underscoring their multitargeted mechanism of action. While preclinical and *in silico* studies provide encouraging insights into its pharmacological potential, clinical evidence remains limited and heterogeneous, necessitating well-designed trials to validate its safety, efficacy, and therapeutic standardization. Future research should focus on isolation, structural characterization, bioavailability enhancement, and mechanistic elucidation of individual phytoconstituents, alongside the development of standardized formulations. Overall, *T. cordifolia* remains a promising plant-derived therapeutic candidate that bridges traditional Ayurvedic wisdom with modern pharmacological science, holding potential for integration into evidence-based phytomedicine and novel drug discovery.

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ABBREVIATIONS

AKT: Protein Kinase B; **ALT:** Alanine Aminotransferase; **AMPK:** AMP-Activated Protein Kinase; **AST:** Aspartate Aminotransferase; **Bcl-2:** B-Cell Lymphoma 2; **Bcl-xL:** B-Cell Lymphoma-extra Large; **COX-2:** Cyclooxygenase-2; **CYP450:** Cytochrome P450; **DNA:** Deoxyribonucleic Acid; **DPP-IV:** Dipeptidyl Peptidase-IV; **EG:** Endogenous Antioxidant; **hERG:** Human Ether-à-go-go-Related Gene; **HIF-1α:** Hypoxia-Inducible Factor-1 Alpha; **HBA:** Hydrogen Bond Acceptors; **HBD:** Hydrogen Bond Donors; **IFN-γ:** Interferon Gamma; **IL:** Interleukin; **iNOS:** Inducible Nitric Oxide Synthase; **JAK-STAT:** Janus Kinase–Signal Transducer and Activator of Transcription; **KEGG:** Kyoto Encyclopedia of Genes and Genomes; **LD_{50}:** Median Lethal Dose; **LogP:** Octanol-Water Partition Coefficient; **MAPK:** Mitogen-Activated Protein Kinase; **MCF-7:** Michigan Cancer Foundation-7 Cell Line; **MMP:** Matrix Metalloproteinase; **MW:** Molecular Weight; **NF-κB:** Nuclear Factor Kappa B; **NK:** Natural Killer; **OMIM:** Online Mendelian Inheritance in Man; **P-gp:** P-Glycoprotein; **PDE:** Phosphodiesterase; **PI3K:** Phosphoinositide 3-Kinase; **PPAR:** Peroxisome Proliferator-Activated Receptor; **PTSD:** Post-Traumatic Stress Disorder; **ROS:** Reactive Oxygen Species; **STRING:** Search Tool for the Retrieval of Interacting Genes/Proteins; **TLR:** Toll-Like Receptor; **TLR4:** Toll-Like Receptor 4; **TNF-α:** Tumor Necrosis Factor Alpha; **TPSA:** Topological Polar Surface Area; **VEGF:** Vascular Endothelial Growth Factor.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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