Review Article

www.ijrap.net

(ISSN Online:2229–3566, ISSN Print:2277–4343)

A REVIEW ON *TINOSPORA CORDIFOLIA* AS A POTENTIAL ANTI-ANGIOGENIC AGENT IN A RANGE OF ANGIOGENIC DISEASES

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Received on: 23/1/25 Accepted on: 05/3/25

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DOI: 10.7897/2277-4343.16278

ABSTRACT

*Tinospora cordifolia (*TC) has an impressive track record regarding its pharmacological potential in immunomodulatory, anti-inflammatory, and antioxidant activities in a range of diseases. The plant is acknowledged for having several other significant attributes. Angiogenesis plays a critical role in various developmental and pathological processes. TC is a significant medicinal important plant because of its variety of phytoconstituents including palmative, tinosporin, berberine, isocolumbin, and arabinogalactan, which play a critical role synergistically to tackle inflammation and oxidative stress, thus nominating itself as a potential anti-angiogenic agent in angiogenic diseases including cancer, rheumatoid arthritis, and psoriasis. Moreover, no significant adverse effects have been reported with its use. In this summary, author has reviewed the anti-angiogenic potential of TC, extrapolated TC's mechanism of action from some angiogenic diseases to other possible angiogenic ailments, suggesting a plant origin has been identified as promising adjuncts or may be a dietary agent to the anti-angiogenic pharmacotherapies.

Keywords: *Tinospora cordifolia*, cancer, angiogenesis, neovascularization, and anti-angiogenic.

INTRODUCTION

Tinospora cordifolia (TC), a deciduous climbing shrub indigenous to the Indian subcontinent, which belongs to the family *Menispermaceae*. TC has long held an esteemed position in Indian Ayurvedic traditional medicine (designated as "Rasayana" [means elixir or a medicine to bolstering immunity and preventing the diseases onset] which boosts the immune system) for its purported ability to modulate the immune system.[1] Extracts from this plant have demonstrated a variety of therapeutic effects, including functions as a general tonic [2], anti-inflammatory, anthelmintic, anti-arthritic, anti-periodic, anti-pyretic, anti-pruritic, aphrodisiac, cardiotonic, carminative [3], antiallergic [4], antidiabetic [5], hepato-protective [6], neuroprotective and neuroregenerative. [7] The plant has been identified as containing numerous chemical compounds, such as alkaloids, lignans, terpenoids, and steroids, which contribute to the vital phytochemical profile and crucial pharmacological properties of TC. In recent studies, TC has demonstrated its anti-angiogenic ability by inhibiting cell proliferation, reducing expression of vascular endothelial growth factors (VEGF), inhibiting angiogenesis-related enzymes, and supporting some other disease specific challenges. [8-11] The term 'angiogenesis' refers to the process of developing new blood vessels. This process is essential for handling various physiological functions, the menstrual cycle, including embryonic, wound healing, or recovering in injuries. The regulation of angiogenesis is governed by a complex interplay of stimulatory and inhibitory factors. An imbalance in these factors is associated with several diseases, such as cancer, cardiovascular and cerebrovascular disorders, age-related macular degeneration (AMD), rheumatoid arthritis (RA), multiple sclerosis, asthma, and psoriasis. Consequently, aiming for angiogenesis presents a convincing and promising strategy for treating these medical conditions.

This review article delves into all related angiogenic pathologies, where TC can show possible therapeutic opportunities as a treatment adjuvant, exploring its potential applications in complex angiogenic diseases.

Phytochemistry

A variety of constituents have been isolated from different parts of TC. The phytochemical classes of TC are remarkably diverse, encompassing a wide array of alkaloids, terpenoids, lignans, diterpenoid lactones, glycosides, steroids, sesquiterpenoid, and other bioactive compounds. [12] Table 1 shows phytochemical class and constituents of TC.

Table 1: Phytochemical Class and Constituents of *Tinospora cordifolia*

Phytochemical Class	Constituents	References
Alkaloids	Berberine, Palmatine, Magnoflorine, Choline, Tembetarine, Isocolumbin	13, 14
Diterpenoid Lactones	Tinosporide, Tinosporine, Cordifolide, Cordifol, Tinosporidine, Jateorine	15, 16
Glycosides	Tinocordifolioside, Tinocordifolin, Cordioside, Furanoid diterpine glucoside, Syringin.	17, 18
Steroids	β-Sitosterol, δ-sitosterol, Giloinsterol	19, 16
Sesquiterpenoids	Tinocordifolin	17, 20
Phenolics	Syringin	21, 22
Polysaccharides	Arabinogalactan, Glucan	23

Table 2: Pharmacological activities of *Tinospora cordifolia*

Activity	Pharmacological Effect	References
Immunomodulatory	Enhances immune response, increases lymphocyte count	24, 25, 26
Anti-inflammatory	Aqueous and methanolic extract of leaves possess anti-inflammatory properties and exhibited significant diphenyl picrylhydrazyl (DPPH) radical scavenging activity	27, 28
Antioxidant	Scavenges free radicals, reduces oxidative stress. The TC root extract additionally leads to elevated levels of glutathione and vitamin C in cases of alloxan-induced diabetes.	29, 30
Antidiabetic	Lowers blood glucose levels, improves insulin sensitivity.	31, 32
Antimicrobial	Ethanolic, methanolic and aqueous extracts of the leaf inhibited growth of *E. coli, Staphylococcus aureus, Streptococcus pyogenes, Bacillus subtilis and Proteus vulgaris*	33, 34
Wound healing	TC support in wound healing	35, 36
Hepatoprotective	Ethanolic extract of plant TC, showed significant hepatoprotective activity	37
Anti-cancer	Methanolic extract of TC illustrated to possess cytotoxic activity against human breast cancer cells	38
Antiviral	Exhibited activity against hepatitis-A virus	39
Anti-anxiety	Showed anxiolytic property in dose dependent manner.	40
Cardioprotective	Alcoholic extract of TC suggests the cardioprotective activity in limiting ischemia-reperfusion induced myocardial infarction	41
Neuroprotective effect	Ethanol extract possess significant neuroprotection in 6-hydroxy dopamine lesion rat model of Parkinson's disease.	42

TC has long been widely acknowledged as one of the extensively utilized plants in traditional medicine, primarily because of its spasmolytic, and anti-diabetic characteristics. This plant plays a vital role in enhancing the immune system. It is endowed with numerous beneficial pharmacological properties. The root is particularly noted for its ability to alleviate stress and combat malaria, while the stem is employed as a bitter stomachic and diuretic. Additionally, it enhances biliary secretion, improves the blood quality, and aids in the treatment of jaundice. Table 2 provides a snapshot of the diverse pharmacological activities of TC, supported by relevant research references.

These constituents are believed to contribute significantly to its pharmacological effects, particularly in regulating immune responses and enhancing the body's resilience against infections and diseases [1, 43]. Moreover, the immunomodulatory effects of TC have been demonstrated through various studies, indicating its potential to not only enhance immune function but also to ameliorate inflammation and oxidative stress, contributing to its reputation as a key player in general wellness. [1, 28, 43]

Numerous *in vitro* and *in vivo* studies have elucidated the mechanisms by which TC exerts its immunomodulatory influence. For instance, investigations have revealed that extract components can stimulate the proliferation of lymphocytes and enhance the production of cytokines, thereby promoting a balanced immune response essential for maintaining health and combating infections[1,43]. Additionally, the extract has shown promising results in clinical evaluations concerning its effects on viral infections, such as those associated with HIV, thereby positioning TC as a potential adjunctive treatment in managing immune-related conditions and infections[44]. Furthermore, the extensive research conducted on TC has not only highlighted its immunomodulatory effects but also its role in addressing various immune-related disorders, suggesting that this herbal remedy could be an invaluable asset in integrative medicine strategies aimed at enhancing overall health and well-being.

Angiogenesis is the physiological process through which new blood vessels form from the existing vasculature. It plays a critical role in various developmental and pathological processes. Precise regulation of angiogenesis is essential for maintaining a healthy vascular system. Any disruptions in this regulation may result in diseases like cancer and diabetic retinopathy. Table 3 illustrates angiogenesis mechanism of action (MoA) and role of medication in different diseases.

Table 3: Angiogenesis and Mechanism of Action (MoA) in Different Diseases

Disease	Angiogenesis Role	MoA of Anti-angiogenic Therapy	Example Therapies
Cancer	Essential for tumor growth and metastasis	Prevents VEGF signaling, starve tumors by blocking new blood vessel formation	Bevacizumab, Aflibercept
Diabetic Macular Edema (DME)	Abnormal blood vessel growth leakages fluid into the macula	Reduces VEGF signaling, prevent fluid leakage	Ranibizumab, Aflibercept
Age-related Macular Degeneration (AMD) (Wet Form)	Unusual blood vessel growth in the macula	Slows VEGF signaling, prevent fluid leakage and vision loss	Ranibizumab, Aflibercept
Rheumatoid Arthritis	Carries inflamed tissues by supplying nutrients	Target blood vessels supplying inflamed joints, reduce inflammation	Baricitinib (indirectly involves angiogenesis)
Psoriasis	Establishes rapid growth of skin cells	Inhibit blood vessel development in psoriatic lesions	Apremilast (indirectly influences angiogenesis)

Angiogenesis research has emerged as a highly appealing area in medicine for pharmaceutical scientists due to its extensive relevance to a range of diseases, including the most common and lethal diseases such as cancer, cardiovascular diseases, and ophthalmological diseases. Although the development of angiogenesis can be triggered by different and diverse angiogenic factors, a common mechanism that triggers the angiogenic process exists under several pathological settings.

The angiogenic cascade involves a complex interplay of various signaling molecules and cellular consequences. The angiogenesis process is explained in Figure 1. Here is a breakdown of the angiogenesis key steps:

Activators and Inhibitors: Numerous factors can stimulate or inhibit angiogenesis. Pro-angiogenic factors like VEGF are the primary initiators (stimulant), while anti-angiogenic factors like thrombospondin-1 (TSP-1) act as opposite regulators (inhibitors).

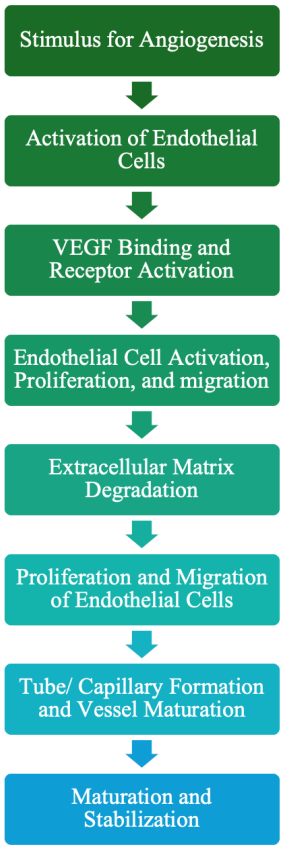

Figure 1: Angiogenesis Process

VEGF Binding and Receptor Activation: VEGF binds to specific endothelial cell surface receptors, primarily VEGFR-2. This binding triggers a signaling cascade within the endothelial cell.

Endothelial Cell Activation and Proliferation: VEGFR-2 activation leads to a sequence of intracellular signaling events encompassing molecules like protein kinase C (PKC), mitogen-activated protein kinase (MAPK), and Akt (Akt kinase). These pathways raise endothelial cell proliferation, relocation, and survival.

Extracellular Matrix Degradation: To migrate and form new blood vessels, endothelial cells need to break down the surrounding extracellular matrix (ECM). Proteases like matrix metalloproteinases (MMPs) are activated during this process.

Tube Formation and Vessel Maturation: Endothelial cells migrate, proliferate, and construct hollow tubular structure. Additional signaling molecules like angiopoietins and Tie receptors play a role in vessel maturation, stabilization, and recruitment of perivascular cells.

Targeting angiogenesis has provided an effective therapeutic method of treatment of some diseases. An example here, anti-VEGF drugs show significantly beneficial effects in terms of improvement in patients with wet type of AMD.

Unfortunately, the current therapies struggle with varieties of adverse effects including high blood pressure, nosebleeds, and gastrointestinal perforations in cancer patients, and eye pain and increased eye pressure in DME/AMD patients, hence there are limitations treating such patients [45]. Also, despite considerable progress in the management of all such listed disease during the past few decades, there remains a significant population of patients who are not served well by current treatment approaches. Cost effectiveness and adverse effects are predominant causes among all these reasons. Anti-angiogenic therapy with plant extracts may offer benefits of safety and cost effectivity over conventional VEGF inhibitors used in therapy.

***Tinospora cordifolia* as a potential Anti-angiogenic agent**

Antiangiogenic activity of TC in Cancer

The predictable number of new cancer cases in India for the year 2022 was determined to be 1,461,427, linking to a crude rate of 100.4 per 100,000 individuals. In India, Sathishkumar *et al.* predicted that one in nine individuals will be diagnosed with cancer at some point in their lives. [46] Phytochemicals and their constituents found in plants represent promising alternatives for enhancing treatment efficacy in cancer patients while reducing adverse effects. Many of these phytochemicals are naturally occurring biologically active substances that exhibit considerable anticancer properties.[47] TC derived phytocompounds demonstrated remarkable anti-carcinogenic properties, including palmative, berberine, a novel clerodane furanoditerene glycoside, phenolic compounds, arabinogalactan, and epoxy clerodane diterpene. [48-50] Malabadi *et al*. highlighted its anti-carcinogenic properties, including the existence of phytocompounds such as berberine that exhibit significant antitumor activity. [51]

Ali *et al*. evaluated anticancer potential of palmatine alkaloid of TC in 7,12-Dimethylbenz(a)anthracene (DMBA) induced skin cancer model in mice, concluding oral administration of palmatine in the daily dietary to achieve some protection against skin cancer. [14] TC stem extract was evaluated against human breast cancer cell line MDA-MB-231 cell line and extracts of TC showed cytotoxic activity against human breast cancer cells. [38, 52.] Cancer development and metastasis are dependent on the formation of new blood vessels. [53] Many studies have highlighted the relationship between the expression of angiogenic factors and the occurrence of metastasis in cancer patients. VEGF plays a critical role as a growth factor in the processes of tumor development and metastasis. It is synthesized by various tumor cells, which may enable tumor progression through the promotion of neo-vascularization. According to Nagaraj *et al*. VEGF-mediated proliferation, migration, and invasion are crucial to the process of cancer formation and should be suppressed to cease it from proceeding. [54] TC is a potent inhibitor of metastatic events which are trigged by VEGF and metastasis associated 1-like protein and demonstrated as an antiangiogenic molecule. Additionally, Mishra *et al*. provided evidence of TC's anti-proliferative, differentiation-inducing, and anti-migratory/anti-metastatic potential in glioma cells, which could be indirectly related to anti-angiogenic effects, as these processes are often associated with the angiogenic pathways in cancer progression. [55] TC is potent anti-inflammatory agents; it has been shown to exert its anti-angiogenic potential in cancer through different possible mechanisms. Some possible key anti-angiogenic MoA are discussed in the following steps;

Down regulation of pro-angiogenic factors: The in *vivo* angiogenesis assay has proved that octacosanol, a long-chain aliphatic alcohol derived from the plant TC, down regulates the expression of the VEGF gene. This effect is attributed to the inhibition of matrix metalloproteinases activity and the translocation of the transcription factor nuclear factor kappa B into the nucleus. [9.]

Inhibition of angiogenesis-related enzymes: TC inhibit Matrix metalloproteinase (MMP) activity. MMPs are enzyme involved in breaking down the extracellular matrix to allow new blood vessel formation, which is an important step in angiogenesis. [9]

Modulation of signal pathway: TC can interfere with signalling pathways that advances angiogenesis and offers protection in neurodegeneration, such as the phosphatidylinositol-3-kinase PI3K/AKT/ mammalian target of the rapamycin (mTOR) and MAPK pathways. [56, 57]

Antiangiogenic activity of TC in Age-related Macular Degeneration (AMD)

AMD with neovascularization is a frequent cause of vision loss in the elderly characterised by the degeneration of the macula the central part of the retina one of the key pathological processes in AMD is abnormal angiogenesis or the growth of new blood vessels. This can lead to leakage of blood and fluid into the retina causing damage. [58] Immune mediators (proinflammatory cytokines IL-1β, IL-6, IL-8, IL-18, TNF-α, and MCP-1) play a critical role in pathophysiology of AMD. [59]

TC a traditional Ayurvedic herb has been studied for its potential therapeutic properties in various diseases recent research has suggested that they have antiangiogenic effects. [8-10] Furthermore, TC has already demonstrated its important role in prevention and management of diabetic retinopathy by inhibiting overexpression of angiogenic and inflammatory mediators, which are distinct markers of diabetic retinopathy making it a promising candidate for the treatment of AMD. [60]

Potential possible anti-angiogenic MoA of TC in prevention of AMD:

Inhibition of VEGF is a key player of angiogenesis: TC has been shown to reduce VEGF levels potentially inhibiting the formation of new blood vessels. [8-11]

Modulation of inflammatory pathways: inflammation plays a crucial role in AMD. TC has anti-inflammatory properties that may help reduce inflammation by inhibiting proinflammatory mediator release (cytokines like tumour necrosis factor-α, interleukin-1β) and associated angiogenesis [16, 61-63.]

Antioxidant activity: Oxidative stress is another contributing factor to AMD. TC contains antioxidants that may help protect the retina from oxidative damage and reduce angiogenesis. [27-29] Arunachalam *et al*. specified that, phytoconstituents of TC may trigger antioxidant transcription factor (Nrf2), which leads to the overexpression of antioxidant enzymes such as glutathione peroxidase (GPx), and catalase (CAT), and thereby induces the adaptive response to oxidative stress. [64]

Antiangiogenic activity of TC in Rheumatoid Arthritis (RA)

Rheumatoid arthritis (RA) is an autoimmune inflammatory condition that manifests as symmetrical polyarthritis, marked by joint discomfort, swelling, and stiffness. It is projected that by the year 2050, approximately 31.7 million (ranging from 25.8 to 39.0 million) individuals will be affected by RA globally. [65] The presence of effective medications, such as biologics, has not ensured that all patients experience positive outcomes; some do not respond to these treatments, while others encounter adverse effects from prolonged usage. Subsequently, there has been a notable increase in the utilization of natural herbal products among RA patients in recent years. There are strong literature supports available which suggests that plant extracts or polyherbal compounds effectively regulate the immune system to alleviate RA by inhibiting pro-inflammatory cytokines. [66-69] Flavonoids, phenolic acids, alkaloids and triterpenes of traditional herbal medicines are identified as the main components to ameliorate RA. [70] The development of new blood vessels, known as 'angiogenesis,' is increasingly acknowledged as a crucial factor in the formation and sustenance of the pannus in RA. This pannus displays a high degree of vascularization, indicating that affecting blood vessels in RA could represent a promising therapeutic target.[71] Furthermore, it is well understood now that VEGF and its receptors are the best characterized system in the regulation of rheumatoid arthritis (RA) by angiogenesis. Anti-VEGF drugs have generated promising clinical data in patients with RA, pharmacologic alterations targeting VEGF, or its receptor may offer new therapeutic tactics. [72.] Berberine successfully attenuates arthritic scores and suppresses collagen–specific immune responses in collagen-induced arthritis (CIA) rats, reversing pathological changes. Berberine treated group also showed improvement in inflammatory infiltration and synovial hyperplasia as compared to the untreated CIA group. Moreover, serum sample post berberine treatment pointed significantly lower expression levels of VEGF, interleukin (IL)-1β, IL-6, IL-17, and tumor necrosis factor (TNF)-α (all $P < 0.05$). [73]

George *et al*. successfully evaluated anti-arthritic effect of TC (150 mg/kg) in the CIA model. Additionally, in the same study TC extract effectively downregulated the level of pro-inflammatory mediators (IL-6, TNF-α, PGE2, and NO) in LPS-stimulated RAW 264.7 cells. [63] In another study, Sannegowda *et al.* demonstrated that TC extract treatment suppressed arthritic inflammation and bone and cartilage damage, using the rat adjuvant-induced arthritis model of human RA. [74]

Furthermore, Sannegowda *et al*. attributed anti-inflammatory effect of TC extract was mediated *via* reduction of the pro-inflammatory cytokines and the production of chemokines. TC extract and its isolated compounds demonstrated to possess immunomodulatory, anti-proliferative, and anti-angiogenic effects in various *in vitro* models. [74] So, TC contains various bioactive compounds including alkaloid glycosides and terpenoids which have been shown to possess anti-inflammatory and antioxidant properties several studies have investigated the effect of TC on RA.

Possible anti-angiogenic MoA of TC in prevention of Rheumatoid Arthritis (RA) is as follows,

Inhibition of pro-inflammatory cytokines and upstream kinases of the JAK/STAT pathway: TC has found to reduce the level of IL-6, IL-1β, PGE2 and TNF-α. Furthermore, TC extract exert anti-inflammatory and anti-arthritic effect via modulation of JAK/STAT pathway. [74, 63, 75.]

Modulation of VEGF expression: VEGF is a key promote pro angiogenic factor TC has been shown to down regulate VEGF expression potentially inhibiting angiogenesis. [63]

Direct effect on endothelial cell: some studies suggest that TC may direct inhibit the proliferation and migration of endothelial cells which are essential for angiogenesis. [55]

Effect on bone re-modelling: TC extract exerted pro-stimulatory effects on human osteoblast-like cells and promoted mineralization of bone-like matrix on two *in vitro* model systems of bone diseases. [76]

Antiangiogenic activity of TC in Psoriasis

Psoriasis is a prevalent and persistent autoimmune skin disorder marked by ongoing inflammation. It affects approximately 2–5% of the worldwide population. Psoriasis is characterized by hyper-proliferation and inflammation of the skin. The pathogenesis of psoriasis involves dysregulated immune responses characterized by increased levels of proinflammatory cytokines, increase in dermal vascularity and proliferation of keratinocytes. Oxidative stress is regarded as one of the underlying pathological factors contributing to the progression and exacerbation of psoriasis. Between all factors, vascular modifications and angiogenesis seems to have a critical role in giving rise to psoriasis phenotype.[77]

Recently, the field of herbal product development has gained attention as a valuable complement to conventional treatment methods in psoriasis management. Specifically, some natural solutions display characteristics that may help alleviate the symptoms of psoriasis. [78] Immunomodulation and controlling inflammation have emerged as a hopeful therapeutic approach for dealing psoriasis. TC can play crucial role in immunomodulation because this plant contains pharmacologically active compounds that can boost the production of antibodies [79], nitric oxide, and supports many other immune system-modifying processes. [80] Aqueous and alcoholic extract of TC have been tested and reported successfully as immunomodulatory activity. The TC product demonstrated peak activation (viability) in J774A macrophage cells at a concentration of 80 µg/ml. [26]

In skin repair, Arora *et al*. reported a curative effect of polyherbal formulation including TC in a preclinical mice model of imiquimod-induced psoriasis [81.] In another study, TC extract was reported to have chemopreventive ability on skin carcinogenesis in mice [82] suggested beneficial role in skin repair. TC is also reported for its significant wound healing abilities in many articles. [83] Furthermore, TC extract notably diminished the erythema and swelling in DNFB-induced allergic contact dermatitis mouse model. [84]

In psoriasis abnormal angiogenesis contributes to the development of thickened, scaly patches on the skin. TC is thought to exit its anti-psoriatic effects at least in part by regulating this process. The complex interplay of factors including its potential to modulate angiogenesis by different mechanism action.

Here's the proposed possible anti-angiogenic step by step MoA of TC:

Immunomodulation: TC is one of the important plants with proven immunomodulatory activities, it has seven immunomodulatory active compounds which synergistically provide immunomodulatory activity. [25]

Handling of inflammation, angiogenesis and cell signalling pathways:

- Nuclear factor kappa B (NF-κB): which is a key regulatory parameter in a variety of immune and inflammatory pathways in cellular proliferation [85]. Octacosanol isolated from the plant TC as a new antiangiogenic compound markedly inhibits translocation of NF-κB to nucleus[9].
- Signal Transducer and Activator of Transcription (STAT) 3 and Janus kinase (JAK) STAT pathway is also actively involved in pathogenesis of psoriasis promoting inflammation [86,87] and TC plays important role in downregulation of overexpression downregulation of overexpressed cytokines in mice. [81,63]
- Mitogen activated protein kinase (MAPK) and phosphatidylinositol 3-kinase (PI3K)/Akt plays critical role in pathogenesis and progression of psoriasis by increasing and activating psoriatic lesions. [88] TC has showed reduced phosphorylated p38 MAPK levels in a preclinical study [64,89] may be by reducing cell proliferation and promoting apoptosis in psoriatic keratinocytes.
- Anti-inflammation action: TC has been shown to reduce the levels of pro inflammatory cytokines such as TNF-α, PGE2, IL-1, IL-6 and IL-8 that contribute to angiogenesis. [63]

Inhibition of VEGF expression: TC can supress VEGF levels which is potential proangiogenic factors.

Improve skin repair function: TC plays a vital role in wound healing may be by promoting angiogenesis, fibroblast activity leading to collagen production improving overall skin function [90]. The anti-inflammatory properties of TC can help restore skin barrier functions.

There is enough non-clinical and clinical literature available where TC has been evaluated and confirmed as a safe supportive alternative. [91,92]

CONCLUSION

Tinospora cordifolia (local name Guduchi), a renowned medicinal plant in Ayurveda, being a potent anti-inflammatory and antioxidant exhibits significant anti-angiogenic properties, making it a hopeful therapeutic representative for various conditions such as cancer, AMD, RA, and psoriasis.

The anti-angiogenic mechanism of TC primarily involves anti-inflammatory action, down regulation of pro-angiogenic factors (MMP), modulation of signalling pathway, a key mediator of angiogenesis. In cancer, this inhibition can reduce tumor growth and metastasis by limiting the blood supply to the tumor. For AMD, the suppression of VEGF can help in preventing abnormal blood vessel formation in the retina, thereby preserving vision. In RA, TC remarkably reduces inflammation and joint damage by downregulating pro-inflammatory cytokines and mediators such as IL-6, IL-1β, TNF-α, and PGE2, which are also involved in angiogenesis. Similarly, in psoriasis, the anti-inflammatory and anti-angiogenic effects help in repairing skin barrier function, reducing the proliferation of keratinocytes and thus reducing the neovascularization in psoriatic lesions. Overall, the multi-faceted action of TC makes it an effective supporting agent in managing these angiogenesis-related diseases. Further, research needs to be conducted in this area to understand beneficial and effective doses of TC in angiogenic diseases.

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Cite this article as:

Pawar Amit Vikram, Anil Kumar Middha and Basavraj Chivade. A review on *Tinospora cordifolia* as a potential anti-angiogenic agent in a range of angiogenic diseases. Int. J. Res. Ayurveda Pharm. 2025;16(2):234-241
DOI: http://dx.doi.org/10.7897/2277-4343.16278

Source of support: Nil, Conflict of interest: None Declared