Recent advancement on phytochemical and medicinal properties of *Tinospora cordifolia*: An Indian medicinal plant

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Abstract:

The usage of indigenous medicinal plants for novel drug discovery and as alternate therapeutics has been trending since the past few decades. *Tinospora cordifolia*, popularly called as Amruta, Guduchi or Giloya, is a therapeutic climber chiefly found in the Indian subcontinent. It belongs to the Menispermaceae family and has been widely used over the ages in Indian Ayurveda and folk medicine. A wide range of bioactive compounds from the categories of alkaloids, steroids, sesquiterpenoids, diterpenoids, phenolics, aliphatic compounds and polysaccharides etc. have been isolated from the plant making it an immensely popular choice among researchers. This resulted in the identification of a large number of pharmacological attributes of the plant including antioxidative, immunomodulatory, hepatoprotective, neuroprotective, hypoglycemic, and anticancer activity etc., making it a very important commercially important plant as well. In the present review, the therapeutic activities of Guduchi plant and its derivatives are discussed in relevance to their biological actions.

Keywords: Guduchi, *Tinospora cordifolia,*Giloya, Amruta, Ayurveda, pharmacological activity, bioactive compounds, immunomodulation.

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1. Introduction

Tinospora cordifolia (Tc) (Willd.) Miers. ex Hook. F. &Thoms., popularly recognized as Guduchi, Amruta or Giloya, is an herbaceous climber with broad leaves and is native to the tropical regions of India, Sri Lanka, Myanmar and other South Asian countries [1]. It is a large, glabrous, deciduous climbing shrub, usually found at an altitude of 300 m [2]. Propagation of this plant is performed during the months of May-June (suitable temperature ranges from 25 to 43 °C by stem cutting. It is flexible with the soil type and capable of growing under varying climatic conditions. Since it is a climber, it needs the support of trees like mango or neem and various other plants to climb [3]. Tc has been widely used in veterinary and Ayurvedic medicine for its immunomodulatory, anti-spasmodic, anti-inflammatory, anti-arthritic, anti-allergic, antidiabetic and hepatoprotective properties [4]. In Ayurvedic medicine, Tc is used to improve the immunity of the body and harbor resistance against several infections [5]. It has been used in folk or tribal medicine in various regions of India, including the Baigas, a tribe residing in the remote parts of Varanasi in Uttar Pradesh, who used it for fever and other diseases. The tribals of Khedbrahma region of North Gujarat used this plant to cure dysentery and diarrhea [6]. In the northern region of Gujarat, it's roots along with bark, are used to be administered with milk to treat cancer.

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According to the Ayurvedic Pharmacopoeia, all the parts of this plant are medicinally useful [1]. Table 1 summarizes the ethnobotanical uses of *Tinospora.*

In India around 400 tribal and various ethnic groups practice traditional medicine. Among them various groups have their own tradition, language and knowledge regarding the use of medicinal plants as medicines. Tc gain a special attention for its use in tribal medicine in various regions of the India. In traditional medicine, whole extract of plant, stem and root, juice of the stem, leaf and root of Tc are being used to treat several illnesses viz. fever, diarrhea, dysentery, jaundice, diabetes, cold, viral diseases, skin diseases, bone repair, eye infections, insects and snakes bite etc. This review highlighted the medicinal properties of Tc, its constituents from Ayurveda to modern medicine.

2. PHYTOCHEMICAL CONSTITUENTS

A variety of phytochemical constituents belonging to various classes such as: glycosides, alkaloids, steroids, phenolics, sesquiterpenoid, polysaccharides, aliphatic compounds and diterpenoid lactones have been obtained from Tc and their structures have been elucidated [7] (table 2). Proteins, calcium and phosphorus are also present in abundance in the leaves [8]. Several alkaloids have been obtained from Tc which showed significant pharmacological potential including immune-modulation, anti-viral, anti-diabetic, anti-cancer and anti-inflammatory actions [9, 10]. Callus and cell suspension cultures of Tc established the presence of protoberberine alkaloids like berberine and jatrorrhizine. Arabinogalactans were also purified from the dried stems of Tc [11]

Table 1: Ethno-botanical usage of *Tinospora*

Steroids such as: tinosporine, cordifolide, clerodane furano diterpene, tinosporide, tinosporaside, cordifol, heptacosanol, diterpenoid furanolactonetinosporidine, ecdysterone, δ and β-sitosterolcolumbin and hydroxyecdysone were also isolated from this plant [8, 9].

Glycosides isolated from Tc include 18-nonderodane glycoside, cordioside, tinocordiside, syringin, tinocordifoliside, syringinapiosylglycoside, cordifoliside - A, B, C, D, E, cordifolioside - A, B, C, D, palmatosides C and P [12, 13]. Four clerodane-furano-diterpene glucosides (amritosides-A, B, C and D) were purified in the form of their acetates from the stems of the plant [10]. Isolation, purification, and modification of glycosyl components of polysaccharides were performed by researchers using processes like methylation, hydrolysation, reduction, and acetylation which partially resulted in the production of methylated alditol acetate (PMAA) derivatives [14].

Lactones derived from the plant include diterpenoid lactone, furanolactone, columbin, tinosporide, tinosporoncolumbin, clerodane derivatives, tinosporon, tinosporisides, tinosporal. Rest includes tinocordifolin, cordifol, tinosporidin, giloincordifelone, and arabinogalactan giloinin etc. [12, 13]. Major groups and their components have been tabulated in Table 2.

Table 2: Phytochemical classes and their respective compounds

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Table 3: Pharmacological activity of Tc in various *in vivo* and *in vitro* against multiple diseases.

3. PHARMACOLOGICAL ACTIVITIES

Various pharmacological activities are associated with this plant. Aforementioned almost every part of this plant is pharmacologically active.

Table 3 describes various major pharmacological activities associated with this plant followed by a brief description**.**

3.1 immunomodulatory activity

Researchers were able to show that Tc can modulate the immune system in CCL_4-intoxicated rats by increasing the number of macrophages in the peritoneal cavity along with protecting the liver at a dose of 100 mg/kg body weight for 15 days [15]. The dry stem crude extracts (DSCE) of Tc have been shown to have polyclonal B cell mitogen: G1-4A, as an active component that boosts the humoral immune response in mice and protects them from endotoxic shock generated by lipopolysaccharide. G1-4A was shown to have an affinity for macrophages and also induced IL-1 secretion. DSCE was able to overcome myelosuppression and stimulate resistance against endotoxic shock by the inflection of NO and cytokines [16].

Macrophages and other phagocytes contribute to modulate both humoral and cellular immune responses as well, and Tc is known to improve immune cell response including the neutrophil activity and this emphasizes it as a powerful prophylaxis agent against immunologically prone diseases [17].

Tc extracts and its compounds have shown promising results for immunomodulatory activities in experimental models as well as, in human clinical studies [1]. By improving immune functions in an intoxicated state, it can be a reasonable alternative to expensive allopathic medication and can easily complement allopathic drugs in a diseased condition [3].

Seven new immunomodulatory compounds were isolated by Sharma and Bala from Tc using ethyl acetate, hot water extracts and fractions of water. All the extracts already had demonstrated important immunomodulatory function, with an improvement in phagocytosis rate. A binary mixture was isolated upon further chromatographic purification of the above extracts and identified as: 11-hydroxymustakon and, N-methyl-2-pyrrolidon. Apart from these, five other compounds were found to improve phagocytic activity and augment in nitric oxide and production of ROS at concentration between 0.10-2.50 µg/ml [18]. The α-D-glucan compound obtained from Tc stimulates lymphocyte cells. Polymorphonuclear leukocyte (PMN) cells are essential components of the host immune network of protection. Extracts from Tc stimulated the PMN cells in phagocytosis [19]. Oral therapy of Tc Alcoholic Acid (100mg/kg) stimulates the count of white blood cells (WBC) and bone marrow cells displaying strong immunomodulating action [20]. Rangnekar et al. performed clinical trials in covid-19 patients and found that Tc improves innate immunity by modulating TH, NK cells, CD markers and Immunoglobulins [21]. Some recent studies also reported the role of Tc in modulation of the immune system and decreases the viral load [22].

In another similar study G1-4A isolated from Tc, enhanced the expression of CD-40, CD-80, C86, MHC-II in the lab and *in vivo* in murine splenic dendritic cells. There was also an improvement in the allostimulatory function of T-cells and production of IL-12 and TNFα by bone marrow derived dendritic cells (BDMC) was also enhanced. G1-4A therapy resulted in reduced phagocytosis and improved absorption of antigen which is typical of mature dendritic cells. G1-4A treated

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dendritic cells cross displayed exogenous antigens on the backdrop of Major Histocompatibility Complex- I which triggered cytotoxic T cells [23].

Guduchi compounds, including alkaloids and aliphatic substances, showed a strong immunoprotective function, in the rat model in preclinical studies [14]. The immunostimulatory function of the aqueous extract of Tc (AETC) and methanolic extract of Tc (METC) against *Salmonella typhimurium* was established by Sultan and Massod in 2017. Treatment of *S. typhimurium*-infected BALB/c rodents and macrophages established the antibacterial activity of aqueous extract of Tc as well as of methanolic extract of Tc. Aqueous or methanolic extract of Tc-treated macrophages produced higher levels of interferon-γ, tumour necrosis factor-α as well as, interleukin-1β. Methanolic extract of Tc exhibited higher activity against *S. typhimurium* infection in macrophages. METC therapy culminated in improved survival and a decrease of bacterial load in rodents tainted with *S. typhimurium*. Besides, treatment with aqueous or methanolic decreased hepatic inflammation and maintained the antioxidant enzyme levels in rodents tainted with *S. typhimurium*. The results of this research experiment indicate that the use of Tc can serve as a two-edged weapon in the battle against salmonellosis [25]. Beside its Antibacterial nature, a recent study in Covid-19 Patients suggested that Tc with other herbal drugs help in faster recovery, reduces the dispersal power of virus, modulates the level of inflammatory molecules without any side effects [25]. Overall this literature suggests that Tc have various bioactive compounds with strung immunomodulatory properties which help in combat against the various diseases.

3.2 Antioxidative activity

Oxidative stress is generated in response to the harmful effects of different radical and non-radical reactive oxygen species on the body tissues [27]. It plays a significant role in the pathophysiology of numerous diseases and accelerates the ageing process. Antioxidants may inhibit reactive oxygen species-induced damages and hence could possibly be used in the prevention as well as, remedy of diseases like cardiovascular disorders, persistent obstructive pulmonary disorder, persistent kidney disorders, neurodegenerative disorders and cancer etc. [28].

As depicted above, numerous samples of Tc have also exhibited antioxidative ability by scavenging the free radicals and other ROS. Tc greatly decreases lipid peroxidation control, therefore, reducing the amount of ROS in rats suffering from alloxan-induced diabetes and stimulates the production of antioxidant enzymes such as: catalase and glutathione that signify the antioxidative potential of Tc [29, 30].

Raman and his team analyzed Tc enzyme hydrolysates for antioxidant activity and found it to be highly effective. The protein hydrolysates were obtained after digesting the plant with enzymes trypsin, papain, pepsin, α-chymotrypsin, and pancreatin-pepsin. It was found that trypsin hydrolysate had the greatest $DPPH^{\bullet}$ free radical scavenging potential and that α-chymotrypsin hydrolysate had the greatest $ABTS^{+}$ scavenging activity and ferrous ion chelation. It was also found that undigested proteins can very strongly inhibit the gastrointestinal enzymes, which indicates that even after ingestion they can have a very prolonged antioxidant effect. A polysaccharide compound extracted from the plant called 'arabinogalactan' demonstrates defense against free radicals in rat models suggesting its antioxidant action. Tc is believed to alter the rates of various enzymatic systems which then regulate the release of these ROS, and in doing so, maintains oxidative load by

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controlling the lipid peroxidation cycle and the amount of glutathione [31-33].

Tc also confers protection to mice from gamma radiation due to its anti-oxidative activity via inhibition of the ferrous sulphate generated lipid peroxidation [34–36]. A clinical research study stated that Tc extract shows antioxidant impact by augmenting the amount of GSH and decreasing the expression of inducible nitric oxide synthase gene whereas, it is effective for the treatment of cataract by inhibiting the aldol reductase enzyme. Another report suggested that the samples of Tc bark in ethanol display a higher free radical scavenging activity and maximum phenolic content as opposed to the methanolic extracts [37].

In another study conducted on *Homo sapiens* acute monocytic leukemia cell line (THP-1), alcoholic and aqueous extracts of Tc were able to attenuate All-trans Arachidonic acid-induced reactive oxygen species generation by augmenting the activity of catalase enzyme thus, demonstrating significant antioxidant and anti-inflammatory potential [38].

3.3 Hepatoprotective activity

Liver diseases are a worldwide health problem and can be a result of modern drug usage, toxic chemicals, alcohol consumption, and lifestyle etc. Researchers found that at a dose of 100 mg/Kg of body weight for fifteen days, Tc extracts conferred hepatoprotection in carbon tetrachloride inebriated mice, as suggested by serum enzyme levels. Post CCl_4 overdose of Tc had shown a substantial decrease in serum levels of SGOT, SGPT, ALP and bilirubin [15].

The hepatoprotective activity of Tc aqueous extract was compared to the liver syrup Liv.52 and it was found that in the dose of 2 ml/100g/day for 30 days the extract gives the same result as that of Liv.52 syrup in 2 ml/kg for 20 days. However, since the Liv.52 is a hydroalcoholic extract, therefore, it is anticipated that Tc hydroalcoholic extract can also deliver similar results at smaller doses for less duration [39].

Priya et al (2017) had shown methanolic extract of Tc stem was able to inhibit Cadmium-induced toxicity in rats via down regulating oxidants and up-regulation of serum marker enzymes of the liver (Aspartate transaminase and Alanine transaminase), conferring hepato-protective benefits [40].

Serum enzymes like alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP) and total bilirubin (TBL) activities were assessed by many other researchers as well, to analyze the hepatoprotective potential of Tc. As a control, a group of rats was treated with paracetamol and it exhibited significantly increased levels of the serum enzymes. Another group that was pre-administered with Tc at the dosage of 200 mg/kg, exhibited 92.2%, 83.2% and 76.9% improvement of AST, ALT and total bilirubin, respectively. The sections of the liver of the paracetamol treated rat group showed macrophage infiltration and ballooning degeneration in liver parenchymal cells and at the same time nuclear degeneration, lesions of necrosis and pyknosis were clear. Tc treatment was effective in restoring the hepatic damage induced by paracetamol, as the Tc treated group was found to have near-normal cellular architecture in comparison with normal liver [41–43].

Tc could limit the free radicals production by inhibiting the microsomal enzymes and could prevent lipid peroxidation. It has been reported that Tc enhances glutathione (GSH) levels in cells thus, protecting hepatic cells from damages that can be highly toxic [15, 44].

Another study demonstrated that powdered stem extracts of Tc diminished obesity-induced weight gain, liver and kidney malfunctioning and amplified oxidative stress in mice models. The mice which received Tc

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extracts underwent a correction in their lipid profile by the promotion of lipolysis and suppression of lipogenesis [45].

In another research-study, the hepatoprotective potential of various extracts of Tc i.e. petroleum fraction, aqueous and ethanolic extracts made from different plant parts like the leaf, stem etc. were analyzed against the liver damage in rats induced by carbon tetrachloride. The extracts were tested at an oral dosage of 200mg/kg of body weight in rats of Wistar albino strain. Ethanolic extracts made from all the parts of Tc demonstrated significant liver-protective effect by decreasing the serum levels of the enzymes alanine ALT, AST, ALP and TBL in mice model; this was accompanied by aqueous extracts and petroleum ether. The overall experimental findings indicated that the considerable hepatoprotective function could be attributed to the biologically active phytoconstituents such as flavonoids, alkaloids found in ethanolic extracts of Tc. Therefore, results justify the use of Tc as a hepatoprotective agent [46–48]. Another study demonstrated that powdered stem extracts of Tc diminished obesity-induced weight gain, liver and kidney malfunctioning and amplified oxidative stress in mice models. The mice which received Tc extracts underwent a correction in their lipid profile by the promotion of lipolysis and suppression of lipogenesis [45].

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3.4 Anticancer Activity

Cancer is a category of diseases that includes an irregular development of cells with the ability to invade or spread to certain areas of the body. A normal cell turns into cancer cells when genes that govern cell development and differentiation are distorted or lose control [49]. Tc extracts have been found to show antitumor effects against glioblastoma, neuroblastoma, liver cancer, prostate cancer, cervical cancer and a range of other cancers.

Palmieri et al., (2019) isolated Berberine from the stem of Tc which was able to show time- and dose-dependent down regulation of thirty-three out of total forty-four genes in the cell line of human colon adenocarcinoma (HCA-7), implicated in the cell cycle, differentiation, and epithelial mesenchymal transformation [50]. This study suggested that the anti-cancer property of the plant can be credited to the presence of Berberine.

Berberine exhibited antineoplastic behavior in rats carrying Ehrlich ascites carcinoma as well at a dosage of 10 mg/kg body-weight and functioned as a type-2-topoisomerase inhibitor on the contrary, Columbine, a furanolactone diterpenoid, showed chemopreventive potential against human colon cancer [51, 52].

Intraperitoneal injection of Tc's alcoholic extract has been demonstrated to work against Dalton's lymphoma (DL) carrying mice, resulting in activation of macrophage activities such as phagocytosis, antigen-presentation, and production of IL-1, TNF,

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Reference Nutrient Intake (RNI) along with reduced tumour growth and improved lifespan of the tumour-bearing host [53].

Chloroform and methanol fraction of Tc stem (TCCF) exhibits an anti-cancerous effect through ROS generation against human breast cancer cells. TCCF was shown to be an inducer of apoptosis by regulating pro and anti-apoptotic markers. Therefore, treatment of cells with TCCF and methanol extract showed reduced colony-forming capability and enhanced intracellular ROS production. The phyto-constituents identified of Tc extract were alkaloids, diterpenoid lactones, steroids, glycosides and aliphatics. Tc and its phytochemicals are reported as very potent anticancer drugs. [54–56].

Tc can be an alternative for chemotherapy or can also be used along with chemotherapy for the treatment of cancer. Presence of other active compounds i.e. Quercetin and Rutin were also reported to demonstrate anti-cancer activity giving the TcCF extract an overall potent preventive measure for breast cancer [57]. It possesses radio-protective activity, which helps to increase tissues as well as, body weight. Additionally, it protects against the sub-lethal range of gamma radiation being radiated on Swiss Albino mice [35, 58]. In one study, when mice with Ehrlich ascites tumor were treated with hexane extract of Guduchi, they showed inhibited proliferation of tumor cells in G1 phase which in turn increased Bax gene expression leading to caspase induced cell apoptosis [59].

In another study, a polysaccharide fraction isolated from Tc was administered intraperitoneally to mice which resulted in reduced metastatic colony formation to 72% in B16F-10 melanoma cells. Before inducing tumour, cells were pre-medicated with the extract resulting in maximum resistance and around 52% on simultaneous administration. Glutamyl Transpeptidase in serum is a proven marker for proliferation of the neoplasm. A drop in the rates of tumor markers in the treated population was also suggestive of decreased tumor growth in the given animal population. As the polysaccharide fraction is a particular B-cell mitogen, the tumor reduction observed may be mediated by B-cells or by non-specific immune cells like natural killer cells [60].

Tc extracts have shown anti-oxidative and anti-proliferative properties on human cervical cancer cells (HeLa). Phenolic content in ethanol extract was suggested to be responsible for the antioxidant activity. Prior studies have already proved the direct relationship between the total phenol content and antioxidant activity in various fruits, plants and vegetables. Therefore, Tc extract consumption may help scavenge free radicals causing cancer [35, 61].

Tc was proved to be effective in several other tumour models as well including Ehrlich ascites carcinoma (EAC) in mice. It induces proliferation and myeloid differentiation of bone marrow precursor cells in a tumour-bearing host and activates the tumour-associated macrophages derived dendritic cells. Tc in conjunction with gamma radiation may provide an effective remedial strategy for cancer because of its effectiveness against various cancers and inhibition of experimental metastasis [62].

This way we can state that the extracts from Tc were found to be preventive against radio-sensitization, DNA disruption, differentiation, senescence, and block the side population of cancer cells. A study showed that $CHCl_3$ and C_6H_{14} extracts of Tc slow down the proliferation rates, stimulate differentiation and suppress the migration of glioblastomas and neuroblastomas in humans and can, therefore, act as a probable plant-based therapeutic option in neural cancer treatment [64]; [65].

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Recent studies reported that Giloy extract has the potential to treat varioustypes of cancers like breast cancer [66, 67], lung cancer [68] oral cancerand neuroblastoma [63, 69].

3.5 Anti-inflammatory activity

Inflammation can be defined as a part of the body's immune response towards any injury caused to cells or via pathogenic infection. It is the local defense system response of the body to reduce the severity of the infection and even eliminate the foreign particle causing the spread of disease [70].

Guduchi Ghana synthesized by the classical method has been shown to produce significant suppression of carrageenan-induced edema indicating that it inhibits fluid exudation and thus, acute inflammation. When compared with the market sample, the market sample didn't show any significant suppression. The activity of Guduchi Ghana on inhibiting edema can also be linked to its contribution towards altering the role of the chemical mediators of inflammation like histamine and 5 HT [71].

Researchers carried out a study in which they evaluated analgesic and anti-inflammatory activity of aqueous extract of Tc (AECT) in rats, by using two different analgesic and anti-inflammatory models. Results from their study confirmed the anti-inflammatory and pain-relieving potential of AETC [72].

A research was performed to determine the *in-vitro* anti-inflammatory properties of different Tc stem extracts in combinations with *G. glabra* root powder [73]. By employing the maceration procedure, methanol and chloroform extracts were synthesized. Using Aspirin as standard, the anti-inflammatory potential of a range of concentrations of various extracts in combinations 2:1 and 1:2 was analyzed. The percent (%) inhibition of these extracts with different combinations of Tc was found to inhibit up to 79.45 ± 0.337 and 64.36 ± 0.27 at 25 µg/ml relative to the control, respectively. On the other hand, the percent inhibition values of methanolic extract in ratio of 1:2 and 2:1 showed inhibition up to 83.21 ± 0.024 and 71.28 ± 0.51 at 25 µg/ml, respectively. The results confirmed that both the plants in dosage ratios of 2:1 and 1:2 as well as their methanolic extracts possess enhanced anti-inflammatory activities [26].

Researchers assessed the potential of Tc against inflammation associated anaemia models *in vitro* as well as, *in vivo*, in Wistar rats suffering from HKBA induced anemia. Tc therapy was found to have resulted in a substantial reduction in gene expression of hepcidin and liver inflammatory biomarkers. Besides, researchers found that *in vitro* treatment with Tc in RAW 264.7 macrophages substantially decreased gene expression of inflammatory cytokines, hepcidin along with suppressed the release of nitric oxide radicals. The HPLC study confirmed the presence of tinosporaside and its anti-inflammatory ability is supported by decreased NO output in RAW 264.7 cells [74].

In another study, conducted on human acute monocytic leukaemia cell line (THP-1), alcoholic and aqueous extracts of Tc were able to attenuate All-trans Arachidonic acid-induced reactive oxygen species generation by augmenting the activity of catalase enzyme thus, demonstrating significant antioxidant and anti-inflammatory potential (Reddi and Tetali, 2019). Recent study done by Philip et al suggested that chloroform extract of Tc suppresses the expression of pro-inflammatory like TNF-α, iNOS, COX-2, IL-1β, and IL-6 without altering the synthesis of COX-1 and finally reverse the inflammation induced by LPS in THP-1 macrophages cell line [75].

3.6 Anti-diabetic activity

Diabetes is a metabolic disorder which affects different organs in the body. Due to the irregular insulin secretion by β-cells of the pancreas or insulin resistance; organs like the

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kidney and liver are also damaged to a large extent. The increase in the glycogen catabolism results in low hepatic glycogen level and ultimately hepatic damage. Such conditions may result in elevation of liver marker enzymes like transaminase and phosphatase. The α-amylase is a key enzyme for the metabolism of starch which converts into maltose, maltotriose, various α-(1-6) and oligo glucans yielding glucose as the end product. Over-expression of α-amylase increases blood glucose level and finally leads to hyperglycemia [76, 77].

Researchers observed that aqueous Tc root extract (TCREt) upon being administered to alloxan diabetic rats induced substantial reductions in blood glucose rates and brain lipids. The extract induced weight gain, enhanced overall haemoglobin content, and hepatic hexokinase. In diabetic rats the root extract even decreased hepatic glucose-6-phosphatase, serum acid phosphatase, alkaline phosphatase, and lactate dehydrogenase. Thus, TCREt stimulates hypoglycaemia and hypolipidaemia [78].

High utilization of dietary fructose prompts a few antagonistic metabolic impacts. In a study, it was investigated whether the aqueous extract of Tc stem (TCAE) reduces high-fructose diet-incited insulin obstruction and oxidative worry in rodents. High-fructose diet (66% of fructose) and TCAE (400 mg/kg/day) were given at the same time for 60 days. Fructose fed rats showed hyperglycemia, hyper-insulinemia, hyper-triglyceridemia, debilitated glucose resilience and impeded insulin affectability. Treatment with TCAE forestalled the ascent in glucose levels by 21.3%, insulin by 51.5%, fatty oils by 54.12% and glucose-insulin profile by 59.8% of the fructose-fed rodents. Fructose fed rats demonstrated higher estimations of lipid peroxidation (91.3%), protein carbonyl groups (44%) and lowered GSH levels (42.1%) and, lowered activities of enzymatic antioxidants, while TCAE treatment showed to prevent all these observed abnormalities [79].

The potential of Tc was studied in Sprague Dawley rats for experimentally induced adult onset diabetes. A variation of high-fat diet (HFD) accompanied by an intraperitoneal streptozotocin injection for 10 weeks, caused diabetes in the rats. The animals underwent Tc oral therapy for 14 days which controlled their blood glucose levels, triggered insulin secretion and also blocked oxidative stress markers, thiobarbituric acid reactive substances (TBARS), and restored antioxidant cell protection markers like superoxide dismutase (SOD), glutathione peroxidase (GPx) and glutathione (GSH) in the liver [80].

Tc treatment (100 and 200 mg/kg) also blocked glucose-6-phosphatase and 1,6-diphosphatase fructose, and restored the liver glycogen content. Tc mediates its anti-diabetic ability by reducing oxidative stress, stimulating insulin release as well as by inhibiting gluconeogenesis and glycogenolysis, controlling blood glucose levels as a consequence [81].

In another study, researchers used rat insulinoma (RIN)-m5F cells and 3T3-L1 adipocytes to test the pancreatic β-cell defensive and glucose uptake augmenting activity of Tc stem aqueous extract. Increasing the dosage of stem extracts consistently improved cell viability and secretion of insulin in RIN)-m5F cells. Alternatively, stem extract enhances both the glucose uptake and the translocation of glucose transporter 4 in 3T3-L1 adipocytes through phosphatidylinositol 3-kinase pathway. Ultimately, in streptozotocin-induced diabetic rats, TCSE dramatically reduced the blood glucose and food consumption and raised body weight. Serum insulin and hepatic glycogen rates were increased, while serum triglyceride rates, total cholesterol, dipeptidyl peptidase-4, and reactive substances with thiobarbituric acid were reduced in TCSE-administered rats. TCSE

also improved glucose transporter 4 protein production of TCSE-fed diabetic rats in the adipose tissue and liver, conferring anti-diabetic benefits [82].

Further researchers found that even water extracts of Tc in 1:2 and 2:1 ratio inhibited α-amylase significantly with 53.69±2.14 and 52.89±1.40 %, respectively. In the case of methanolic extract, the 2:1 ratio produced significant inhibition of 53.95±0.66 % whereas, the 1:2 ratio of the same extract inhibited α-amylase by 48.12±1.40 % at 100 µg/mL concentrations. On increasing concentrations (75 and 100) µg/mL, α-amylase was found to show more significant inhibition. This plant also contains flavonoids, tri-terpenoids and alkaloids which are soluble in these solvents (water and methanol) thus, their higher activity can be correlated with the increased amount of phytochemicals in the solvents used [83].

3.7 Antimicrobial activity

Tc extracts in various solvents have shown anti-bacterial and anti-fungal activity against different microbes [84]. The stem extracts of Tc demonstrated antimicrobial action against gram positive and gram-negative bacterial species in the lab, showing therapeutic potential against bacterial infections. The acetone, water and ethanolic extracts of Tc inhibited the activity of pathogenic bacteria of the urinary tract infections including *P. aeruginosa* and *K. pneumonia* [85]. Researchers analyzed the antimicrobial potential of ethanolic extracts of Tc at various concentrations, against *Streptococcus mutans*. Their data revealed the highest antibacterial activity of Tc at a volume of forty microliters at 2% concentration with the 19 mm diameter of the zone of inhibition. Beside this Tc have a vast range of antimicrobial properties and could be considered as potent antimicrobial drug [86–88].

3.8 Wound healing property

Chronic wounds like leg ulcers and diabetic foot ulcers are considered quite complicated in terms of management. Even the drugs available for the same are expensive and possess side-effects. Therefore, herbal drugs are considered to be an alternative for these in terms of price as well as activity. The wound healing activity of Tc has been mentioned in Ayurvedic texts [82].

Barua and his colleagues evaluated the wound healing activity of methanolic extracts of Tc leaves using excision and incision wound model and found that the mean % of wound closure was remarkably enhanced in from day zero to day twenty-first to 77.02% in the Sprague Dawley rats that were administered with Tc extracts. By the end of the twenty-first day, the wounds were found to be entirely healed as compared to the standard group in which the wounds persisted even after twenty-one days [89].

In a study, the phytochemicals of Tc root extracts having astringent and antimicrobial properties were investigated. It confirmed the presence of triterpenoids, saponins, alkaloids and flavonoids which are known to help the process of wound healing by contraction of the wound and rise in the epithelialization rate. Flavonoids are known to reduce lipid peroxidation and it is believed that any drug that inhibits lipid peroxidation increases the viability of collagen fibrils by escalating the strength of collagen fibres, enhancing circulation, avoiding cell damage and stimulating DNA synthesis. Sesquiterpene lactones are considered to have antioxidative effects, and can also result in wound healing. It was revealed in the study that methanolic extract has remarkable wound healing promoting activity, evident with increased wound contracting rate; decreased epithelialization time, augmented collagen deposition and enhanced tensile strength in granulated tissue [46].

The findings of another study showed that Tc facilitates wound healing substantially in excision wound, re-sutured incision wound and dead space wound model in male Wistar rats by promoting amplified wound closure and reduced days for full epithelization in excision wound; augmented breakage pressure in re-sutured incision wound; enhanced dry granuloma and cellular infiltration in granulation tissue [90]. Similar results were obtained in re-sutured incision and dead space wound models in Albino rats indicating that perioperative application of Tc can facilitate surgical wound healing [91].

Studies also suggested that mice treated with methanolic extracts of Tc showed an improved count of monocytes with augmented collagenation relative to the control group.Collagen, an important protein of the extracellular matrix, adds to strength of the wound. When collagen breaks down, it releases free hydroxyproline which can be used as a collagen turnover indicator. In comparison with the control group, the hydroxyproline content of the granulation tissue of animals medicated with Tc showed a notable spike, suggesting an increase in collagen turnover. Increased breakage strength of granulation tissue of Tc medicated animals suggests improved collagen maturation by enhanced cross-linking. In comparison, an improvement in the weight of dry granulation tissue often suggested the existence of greater protein content. Tc potentially often reduces lipid peroxidation due to its antioxidant function, which in turn contributes to reduction or delay in the initiation of cell necrosis and increase in vascularity [92]. Therefore, Tc's wound-healing property may be attributed to the phytoconstituents present therein, which may be due either to their individual or additive effects that accelerate the wound healing process [93].

In another study researchers treated *E. coli* infected wounds using Tc extracts of chloroform and petroleum ether and found that the wound was cured within 5 days. Similarly, *Klebsiella pnemoniae* and *S. aureus* infected wounds of Wistar rats were treated with methanol and petroleum ether extract of Tc and observed that the wound healed within 4 days. [92, 94].

3.9 Cardioprotective activity

Tc is very well known for its cardio protective nature. Various scientists correlate this with its anti-oxidative property and cholesterol lowering ability.

Methanolic extract of Tc is also shown to significantly inhibit lipid peroxidation apart from reducing the artherogenic index and vascular wall injuries in rodents which can contribute to cardiovascular defects [95]. Extracts of Tc were shown to regulate lipid and FA biosynthesis by restraining cholesterol and glucuronide and providing protection against myocardial infarction due to its antioxidative qualities [96, 97].

Sharma and his colleagues demonstrated that alcoholic extracts of Tc were able to reduce calcium chloride-induced cardiac arrhythmia in mice indicating its efficiency in surgical antiarrhythmic environments and its potential use in atrial and ventricular fibrillation and flutter, and its recommendation for ventricular tachyarrhythmia. Their results suggested that the alcoholic extract of Tc confers cardioprotection in response to ischemia-reperfusion triggered myocardial damage, in a dose-dependent manner. They observed that cardioprotection can directly activated via free radical scavenging or indirectly via augmentation of endogenous levels of antioxidants or by shielding magnesium ions dependent Ca^{2+}-ATPase enzymes or by alienating free radical-mediated blocking of sodium-potassium ATPase sarcolemmal activity or via inhibition of the calcium ion channels [98].

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Priya and her colleagues were able to demonstrate that methanolic extracts from the stem of Tc acted as a putative therapeutic against cadmium-induced myocardial toxicity by decreasing the lipid peroxidation and protein carbonylation in mice [40]. The secondary metabolite Berberine from Tc confers cardioprotective benefits owing to its cholesterol-lowering and anti-hyperglycemic effects [99].

3.10 Bone strengthening activity

Indian traditional medicine acknowledges Tc as a bone toughening agent and prescribes it to treat bone fractures, gout and other inflammatory bone disorders like rheumatoid arthritis. Multiple studies have been conducted to date to confirm these claims; ethanolic extracts of the stem of Tc also prevent osteoporosis by significantly reducing the levels of serum osteocalcin and cross-lap [100].

Abiramasundari and his colleagues established that beta ecdysone, a steroid hormone usually produced by arthropods can also be extracted from Tc. Derivatives of Ecdysone have been widely documented in the literature as the remedy for various androgenic and oestrogenic diseases along with skin problems consistent with ageing [34]. It confers osteoprotective activity by exhibiting significant pro-stimulatory effects on MG-63 human osteoblasts like cell line and mice osteoblast cells, induces osteoblastic growth and differentiation in rodents, and promotes mineralization of bone matrix thus, conferring an anti-osteoporotic and anti-osteoarthritis benefits [35,101,102].

3.11 Anti-HIV activity

Tc extracts were able to cause a decline in the recurrent resistance of the human immunodeficiency virus thus, improving the therapeutic result in patients suffering from AIDS. The anti-human immunodeficiency virus effects of Tc extracts were established by reduction of the eosinophil population, stimulation of B cells, macrophages and the percentage of PMNL and haemoglobin, thereby disclosing its putative therapeutic activity in management and control of AIDS [103, 104].

Another study demonstrated the therapeutic benefits of Shilajatu (Mineral pitch) treated with extracts of Tc and two other medicinal plants in patients undergoing antiretroviral therapy for AIDS. The patients who were administered Shilajatu responded better to antiretroviral therapy than the control group, indicating Shilajatu decreases the recurrent resistance of the human immunodeficiency virus to antiretroviral therapy and enhances the therapeutic result [105, 106].

3.12 Neuroprotective and pro-cognitive activity

Tc has been known to possess anti-oxidative and anti-stress properties due to which it has been used synergistically with other Ayurvedic herbs in Indian System of medicine against Alzheimer's, cerebrovascular ischemia, ADHD, Parkinson's Disease and oxidative stress-induced damage. The traditional usage of Tc roots has been documented for their anti-stress activity. It has been observed that the water extract of Tc roots improves oral learning and analytical memory in normal rats and also reverses the memory deficit induced by cyclosporine [107–109].

Its mode of action is by regulating cytokine production, augmentation of memory by impeding amine reabsorption in the brain as well as, elevated levels of noradrenaline, serotonin, dopamine and reduced amounts of GABA has been established in various studies [8, 13]. The antidepressant activity of Tc is due to its high free radical scavenging properties against superoxide anion, hydroxyl radicals, nitric oxide, and peroxynitrite anions [110].

Ethanolic extracts of Tc demonstrated a decrease in sleep deprivation-induced anxiety, cognitive malfunction and motor

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coordination disablement in rats, relative to the control groups. The animals which received TCE showed suppressed expression of inflammatory markers like CD11b/c, major histocompatibility complex 1 and cytokines together with the repression of apoptotic markers 111]. Additionally, a study established that butanolic extracts of Tc can improve cognitive defects related to glutamate-induced excitotoxicity in rodents via protection of neurons in the hippocampus region of the brain from excessive glutamate related neurodegeneration and impairment of synaptic plasticity; thus, conferring neuroprotection [112]. Ethanolic extracts of Tc enhanced the cognitive performance of mice suffering from scopolamine-induced amnesia. The rats which received synergistic doses of TCE along with extracts from other Ayurvedic herbs showed better performance in MWM test and passive avoidance test [113].

The pro-cognitive and memory-enhancing properties Tc have been well studied in the past and made Tc a potential candidate for management of neurodegenerative disorders such as Alzheimer's disorder and Parkinson's disease [114]. Aqueous extract of Tc suppresses the MPTP i.e. 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine induced activation of nuclear factor kappa-B, its related pro-inflammatory cytokines (IL-12 and IL-1 β) and TNF-α in parkinsonism mice models, which resulted in reduced symptoms in the animals that were administered with the Tc aqueous extract in comparison to control groups [30, 115]. Onoja and colleagues established that compounds like Oxoglaucine, Liriodenine and N-formyl anonaine isolated from Tc were successful in the inhibition of acetylhydrolase thus, showing promise as putative therapeutic agents for controlling the symptoms of Alzheimer's disease [116]. Additionally, a recent study Suggested that Tc supplementation protects from anxiety and loco-motor dysfunctions induced due to obesity. This study also reported that Tc restores brain function by suppressing oxidative stress and inflammation in HFD-induced obese rats [45].

3.13 Other pharmacological activities

3.13.1 Differentiation of myocytes

Other than the above-mentioned qualities many other activities are also reported for Tc. A brief description of all these is given below.

Aqueous extract of Tc was demonstrated to stimulate *in vitro* differentiation of myocytes in C2C12 cell lines and the mice which received TCE supplements showed reduced inflammation and oxidative stress as TCE significantly modulated catalase, GPx, lipid peroxidase, SOD, and beta-glucuronidase activities apart from enhancing the production of MF-20c and augmented muscle protein degradation by repressing MuRF-1 and calpain function. These studies showed the therapeutic potential of Tc against muscular atrophy [112, 120].

3.13.2 Anti-stress activity

Stress is a biological response produced by the brain as a reaction to challenging stimulations of physical or emotional nature. In Indian Ayurveda, it serves as MedhyaRasayana or brain tonic which enhances the intellectual capacities such as memory, awareness and recollection [117]. In a study conducted by Salve and his colleagues, evaluated the impact of aqueous extract of Tc on physical performance and sympathetic activity in thirty healthy participants upon being subjected to physical stress, and it was observed that aqueous extract of Tc enhanced physical performance and inhibited the over-stimulation of the sympathetic nervous system demonstrating its adaptogenic properties. Tc enhances the body 's resilience to emotional, chemical and biological tension, and creates strength and vitality in general [118].

Researchers conducted another randomized double-blind placebo study conducted on sixty-three patients clinically diagnosed with stress, administration of Tc extracts along with yoga practice demonstrated substantial anti-stress activity similar to that caused by the common adaptogen Diazepam 119].

3.13.3 Against respiratory disease

Earlier this plant was used to treat asthma and chronic cough. In a study it was shown that 83% of the total patients had 100% relief from sneezing, 69%, 61% and 71% had relief from nasal discharge, nasal obstructions, and nasal pruritus, respectively therefore, decreasing the allergic rhinitis symptoms 121].

3.13.4 Blood tonic

In a study, to evaluate the *in vivo* protective role of aqueous extract of stem and leaves of Tc (Tc) on the toxic effects of lead on the haematological values it was found that the lead-treated male albino mice concurrently received either Tc stem or leaves extracts for 30 days. The animals exposed to lead showed a significant decrease in RBC, Hb level, WBC, DLC, and PCV. These effects of lead were prevented by concurrent daily administration of Tc stem and leaf extract thus, protecting against lead intoxication [78].

3.13.5 Antiviral potential against SARS-CoV-2

The ongoing Covid 19 pandemic has been caused by the novel Corona-Virus 2 (SARS-CoV-2) Severe Acute Respiratory Syndrome. The World Health Organization has declared COVID-19 a pandemic disease which has seriously affected the health of the people all around the globe.

Researchers in India performed in silico docking studies on thirty-seven phytochemical constituents of KabasuraKudineerChooranam and JACOM against spike protein SARS-CoV-2. Out of thirty-seven phytochemicals, six candidates with high binding abilities were selected; Tinosponone which was isolated from Tc showed the third-highest binding capacity in docking studies suggesting its potential therapeutic effect against SARS-CoV-2 spike protein [122]. Another *in silico* studies done by Jena and colleagues in which they performed molecular docking and ADME/T have reported that variousphytochemicals could be a potent drug candidate that can stop the attachment of SARS-CoV-2 spike with Human ACE2 receptor [123]. A related study also performed by Chowdhury et al and revealed that with other phytochemicals, berberine is the most suitable drug candidate against the COVID-19 and other viral infections [124].

In another study, researchers tried to isolate natural compounds from *T. cordifolia* having antiviral activity against SARS-CoV-2 targets. In addition to binding with all four main SARS-CoV-2 targets, Tinocordiside and Isocolumbin demonstrated record IC_{50} values below 1 µM compared to 6Y84 and 6VSB respectively, indicating that they could potentially become therapeutic agents against SARS-CoV-2[125].

4. TINOSPORA AND GREEN NANOTECHNOLOGY

Nanotechnology is an evolving area of interdisciplinary science, particularly in biotechnology, and nanoparticles are generally known as particles with a maximum size of 100 nanometers. Currently, nano-science is anticipated not only for its application but also through nano-material synthesis [126]. Developing gold or silver nanoparticles (noble metals) from plants like Tc which possess medicinal properties is the latest approach against numerous biological problems including antimicrobial resistance and cancer.

Ali and his colleagues were able to synthesize gold nanoparticles from the stem of Tc against the biofilm of *P. aeruginosa*. The spherical AuNPs having a diameter of approximately

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sixteen nanometers were able to significantly affect the biofilm creation capacity of *Pseudomonas aeruginosa* as indicated in the scanning electron microscopy and crystal violet assay, demonstrating a decline in the amount of biofilm-producing cells with a higher concentration of AuNPs. Confocal laser scanning microscopy showed abnormalities in the biofilm structure at a sub-minimum inhibitory concentration of gold nanoparticles. This research indicated that green-synthesized gold nanoparticles from Tc may be used as putative nano-antibiotics against *Pseudomonas aeruginosa*-associated biofilm infections in future [127, 128]. A recent study reported that phytochemicals like flavonoid, alkaloids, glycosides and tannin help in stabilizing nanoparticles during synthesis and are used as a strong antibacterial and antifungal agent [24].

Singh and her colleagues evaluated the antibacterial activity of silver nanoparticles of Tc stem in response to multidrug resistant strains of *P. aeruginosa,* which had been collected from patients suffering from burns. Zone of inhibition of Ag nanoparticles of Tc ranged from 10 ± 0.58 to 21 ± 0.25mm. The minimum inhibitory concentration of AgNPs against different strains of *P. aeruginosa* was found to be 6.25 to 200 µg/ml. The researchers concluded that AgNPs developed from Tc possess high-quality antibacterial activity making them a great source of antimicrobial agents [129].

Mittal and his colleagues synthesized silver nanoparticles from aqueous leaf extracts of Tc, having a diameter within the range of twenty-five to fifty nanometers. AgNPs were then assessed against *Homo sapiens* lung adeno-carcinoma cell line A549 by trypan blue and MTT assay; apoptotic morphological variations with the help of Detection Kit ab14085 and Propidium iodide, nuclear morphological variations with DAPI (4, 6-diamidino-2-phenylindole) staining, generation of reactive oxygen species and mitochondrial membrane determination potential. The test analysis supported that the silver nanoparticles developed using leaves of Tc are extremely toxic to lung adenocarcinoma cell line A549 of Homo sapiens, elucidating the anti-cancerous therapeutic potential of Tc nanoparticles [68].

5. CONCLUSION

Documentation of research through various field analysis shows that Tc has been considerably investigated for the quantification of pharmacological activity of its crude form (whole plant or extracts) and various bioactive compounds isolated from the plant. All these forms of *Tinospora* exhibit a broad spectrum of pharmacological activity. It seems if this plant (appropriate formulation) may be included in daily life it can act as a nutraceutical as it can deal with many such conditions such as: lifestyle disorders, stress related issues, respiratory issues and cancer etc. One of the finest technology-nanotechnology also has also started using this herb for preparing nano structures/formulations which would further enhance its pharmacological activities, efficacies and targeting efficiencies. It is abundantly found in South Asian countries, which render it to be a relatively economical and effective alternative herbal remedy for several health conditions in comparison to allopathic drugs and formulations (Fig 1). In fact, it can also assist modern day medicines in various conditions to work in a better way. Many phytoconstituents of these herbs have been explored for their mechanism of action but, still there are many molecules for which the probable mechanisms of action still need to be elucidated, along with more clinical trials and toxicology studies in humans. In brief it can be concluded that *Tinospora* has high potential to be used for old, present days

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and emerging diseases without having side effects.

CONFLICT OF INTEREST

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SUPPLEMENTARY MATERIAL

Table 1: Ethno-botanical usage of Tinospora.

Table 2: Phytochemical classes and their respective compounds

Table 3: Pharmacological activity of Tc in various in vivo and in vitro against multiple diseases.

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