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TINOSPORA CORDIFOLIA CAN CURE SYSTEMIC LUPUS ERYTHEMATOSUS

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ABSTRACT: *Tinospora cordifolia* (T. col.), a plant which has great significance in the Ayurvedic system of medicine, has been tested according to modern medical techniques for numerous therapeutic effects like immunomodulation, reducing tumor cells, purification of blood, reducing fatty lipids from body, reduction of glucose and increasing glucose tolerance in case of diabetes and increasing body weight. T. col has been used even during various rheumatic diseases like rheumatoid arthritis and has shown positive therapeutic effects. T. col. reduces the unwanted lipids. It enhances the humoral immune response. It also cleans out the immune complexes from the body. T. col. acts as an adaptogen. It has been reported to both increase and decrease activities of substances in the body, so as to normalize its functionality. It enhances immunity, but on the other hand, it inhibits autoimmunity. This paper is a review of the findings of the medical benefits of T. col., and combining all the information to propose that this plant may be used in the treatment of another rheumatic disease, systemic lupus erythematosus (SLE).

INTRODUCTION: *Tinospora cordifolia* (T. col.) is a large, glabrous, perennial, deciduous, climbing shrub. It has a weak stem and is found throughout India. It is widely used in folk and Ayurvedic systems of medicine [1, 2]. The shrub of T. Col. has been reported to contain alkaloid, diterpenoid lactone, glycoside, steroid, sesquiterpenoid and phenolic molecules. It also contains aliphatic compounds and polysaccharides [3]. According to Upadhyay *et al*., 2010; Kulkarni, Kellaway, and Kotwal, 2005, [1, 2] major properties and uses of *Tinospora cordifolia* which are acquiring scientific validity are as follows T. col.:

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(1) acts as alleviator, (2) alleviates from severe fevers, (3) acts as moderator of vata, pitta, and kapha; medical situations related to air-related organs like the organs involved in respiratory systems, fluid organs like pancreas and gall bladder and organs related to cough, (4) acts as inhibitor of inflammation, (5) alleviates blockage in breathing, (6) alleviates jaundice, (7) alleviates skin diseases, jaundice and gout diseases, (8) acts as antipyretic, (9) treats parasites, (10) treats gonorrhea, (11) treats hemorrhoids, (12) alleviates heart situations.

Scientific research has reported that T. col. inhibits diabetic, pyretic, spasmodic, inflammatory, arthritic, oxidant, allergic, stress, leprotic, malarial, and neoplastic activities in the human body. It also shows hepato-protective, immuno-modulatory activities. T. col. also exhibits chemopreventive ability against immunological disorders and cancer and has a history of use against spasms, inflammation, arthritis, allergy, diabetes, cardio-

toxicity, and immunosuppression [4]. This paper is a review of the scientific findings of the therapeutic benefits of T. col. In section 3, its immunomodulatory effects are described, specifically the effects of T. col. on the immune system; section 2 describes the therapeutic effects of T. col. in all other organ systems and related diseases. In section 4, all the therapeutic benefits of T. Col. are summarized. In section 5, the findings of the characteristics of systemic lupus erythematosus (SLE) are described; the behavior of the body of the patients of SLE, along with the existing medication procedures and their side effects are discussed. Then in section 6, this paper advocates the use of T. col. to cure SLE. Finally, we conclude our findings discussing the future perspective of the use of T. col. in medical procedures.

Effect of administration of *T. cordifolia*:

A) Tumour Growth: Administration of T. col. has shown a reduction in tumor growth in various works. Mathew and Kuttan, 1999 showed that methanolic extract of stem of T. col. could reduce tumor cells in BALB/c mice (200 mg/kg, i.p., daily for 5 days). Mathew and Kuttan, 1999 have also reported that this extract synergistically acted with cyclophosphamide and reduced the animal tumors to 83% [5]. Jagetia and Rao, 2006 has reported a dose-dependent reduction in tumor cells in the mice transplanted with ehrlich ascites carcinoma [6]. Thatte *et al*., 1992 [7] showed that T. Col. reduces polymorph phagocytosis. Mittal and Singh, 2009 [4] reported that *Tinospora* exhibits anti-cancer properties. T. col. has shown to upregulate the antitumor activity of tumor-associated macrophages (TAM). It enhances differentiation of TAM to dendritic cells (DC) in response to granulocyte/macrophage-colony-stimulating factor, IL-4, and tumor necrosis factor. T. col. shows tumor cytotoxicity. It leads the production of tumouricidal soluble molecules like TNF, IL-1, and NO [8].

B) Bone Marrow: Mathew and Kuttan, 1999 [5] showed an increase in bone marrow cellularity 18.16×10^6 / femur along with α-esterase in bone marrow (1423/4000 cells). This indicated increased maturation of stem cells. Aher and Wahi, 2010 [9] has also reported an increase in bone marrow cells in treatment with T. col.

C) Cardiovascular System, Blood: Babu *et al.*, 2017 [10] has shown that T. col., used in combination with *Carica papaya*, leaf extract can increase the platelet count in case of dengue or other microbial infections, in cancer patients and thrombo-cytopenia. Nayampalli *et al.*, 1986 reported decreased capillary permeability (in rats) because of T. col [11].

D) Diabetes: Rajalakshmi *et al*., 2009; Stanely *et al*., 2000; Stanely *et al.*, 2003 reported that T. col. shows potent anti-diabetic activity and reduces blood sugar. It reversed the reduction of glucokinase and increased glucose-6-phosphatase activity, which was stimulated when rats were induced with streptozotocin diabetes. T. col. also improves Insulin and C-peptide levels. They also reported that β-cells, which secrete insulin, were regenerated substantially [12, 13, 14]. T. col. has been used to treat diabetes mellitus [15, 16, 17]. T. col. reduces serum and tissue cholesterol, phospholipids and free fatty acids in alloxan diabetic rats. Stanely *et al.*, 1999, Stanely *et al.*, 2000 have shown T. col. to lower hepatic glucose-6-phosphatase and serum acid phosphatase, alkaline phosphatase, and lactate dehydrogenase in diabetic rats [18, 19]. T. col. reduces blood glucose level and increases glucose tolerance [19, 20]. Stanely *et al*., 2000 reported that T. col. reduced brain lipids in diabetic rats; its aqueous root extract caused an increase in their body weight [13].

E) White Blood Cells: Mathew and Kuttan, 1999 has shown that the total count of WBCs was increased in BALB/c mice [5]. Bishayi *et al.*, 2002 has reported that water extract of T. col. increases the WBC count in mice; *Tinospora sinensis* is even more effective [21]. Goel *et al.*, 2004 opined that T. col. treatment restored total lymphocyte counts (TLC) [22]. Aher and Wahi, 2010 has reported an increase in WBC count on treatment with T. col. alcohol extract [9]. T. col. enhances phagocytosis [23, 24, 25]. Ahmad *et al.*, 2015 reported that *Tinospora crispa* enhances the chemotactic activity of neutrophils. Ahmad *et al.*, 2015; Thatte *et al.*, 1992 reported that T. col. enhances the phagocytosis activity of neutrophils [26, 7]. T. col. activates / proliferates nuclear killer cells [27-32]. Gupta *et al*., reported a significant increase in the mean phagocytic index [33]. α-D-glucan, a polysaccharide derived from T. col., shows the activation of

nuclear killer (NK) cells [34]. Raghua *et al.,* 2009 has reported that treatment by G1-4A, a polysaccharide from *Tinospora cordifolia*, increased in the CD69 expression in lymphocytes [35].

F) Body Humor and Lipids: Mathew and Kuttan, 1999 has observed that T. col. has increased the plaque-forming cells in the spleen (1575 PFC/10^6 spleen cells) and circulating antibody titer (256) in BALB/c mice [5]. Raghua *et al.,* 2009 reported that G1-4A increased spleen cellularity and upregulated anti-apoptotic genes T. col. improves improve humoral immune response [35]. Kapil and Sharma, 1997 has reported an increase in humoral immunity dose-dependently [36]. Jagetia and Rao, 2006 has reported a drastic increase in lipid peroxidation to reduce tumor cells in mice [6]. Desai *et al.,* 2002 has reported that partially purified T. col. prevented lipid peroxidation to reduce thiobarbituric acid reactive substances in the liver when they were increased and increase the activities of superoxide dismutase and catalase when it was reduced in mice exposed to radiation [37]. Subramanian *et al.,* 2002 reported that T. col. showed good protection against iron-mediated lipid peroxidation of rat brain homogenate and provided protection to proteins against ɣ-ray induced damage [38].

G) Central Nervous System: *Tinospora cordifolia* Menispermaceae has been mentioned as an adaptogen [39, 40, 41]. Adaptogens have been associated with stimulating and stress-protective effects in the central nervous system (CNS) and vegetative nervous systems, the endocrine system, and the immune system comprising by definition the parts of a neuroendocrine immune complex stress system.

H) Other Organ Systems: CCl_4 is harmful to liver. Bishayi *et al.,* 2002 has reported that the liver of albino rats was protected by *T. cordifolia*, which were first administered with CCl_4 earlier [21]. Bairy *et al.,* 2004 has shown that T. col. has enhanced verbal learning and memory, and logical memory [42]. Agarwal *et al.,* 2002 reported that T. col. administration enhances cognition (learning and memory) in rats [43]. The stem of T. col. is useful in treating skin diseases. The root and stem of *T. cordifolia* are prescribed in combination with other drugs as an antidote to snakebite and scorpion sting [44, 45, 46, 47, 48]. Sannegowda *et al.,* 2015 showed that T. col. extract treatment limits bone damage. It shifts the balance of mediators of bone remodeling in favor of anti-osteoclastic activity to accomplish this. An example of such a mediator of bone remodeling is receptor activator of nuclear factor-kB ligand [RANKL] and MMP-9 [49]. T. col. inhibits the growth of Mycobacterium tuberculosis [50]. Nayampalli *et al.,* 1986 have reported that T. col. decreased the bronchospasm induced by 5% histamine aerosol [11].

Sushrut Samhita has suggested almost 50 drugs in different groups for the prevention of pregnancy loss. 11 ingredient herbs out of them were selected to make the combination of Torchnil. One of them is *Tinospora cordifolia*. This formulation combats the infections, immune complexes and stress of lipid peroxidation in placenta. It proved to be effective against HIV also [51]. T. col. causes protease inhibition [52, 53].

I) Irradiation: *Tinospora* exhibits radioprotective properties [4]. Mice were administered with T. Col. before full-body gamma irradiation; Goel *et al*., 2004 reported 76.3% survival. Goel *et al.,* 2004 has also opined that because of its radioprotective manifestation, T. col. can be exploited for human applications [22]. Radiation produced reactive oxygen and nitrogen species (ROS/RNS) were generated by photosensitization/peroxynitrite in mice. Photosensitization caused a significant increase in thiobarbituric acid reactive substances in liver. The activities of superoxide dismutase and catalase were reduced. T. col. restored activities of both these enzymes. Oxidative damage caused by peroxynitrite was inhibited by T. col. The degradation of proteins due to photosensitization was significantly reduced [37].

Immunomodulatory Effects of *Tinospora cordifolia*:

A) Immune System and Antibodies: Bishayi *et al.,* 2002 has reported that the immunosuppressive effect of CCl_4 in albino rats was inhibited by *T. cordifolia* [21]. Manjrekar *et al*., 2000 has reported that T. col., because of its immunomodulatory properties, inhibited cyclophosphamide induced anemia [54]. Aher and Wahi, 2010 has opined that T. col. shows potent immunomodulatory activity [9]. Kapil and Sharma, 1997 reported a dose-dependently increase in cell-mediated immunity [36].

T. col promotes the production of antibodies [55] and also enhances lysozyme activity and antibody responses [29, 30, 31]. Sudhakaran *et al.*, 2006 reported that ether and petroleum extracts of T. col. enhanced the secondary antibody response. T. col. also enhances neutrophil activity, provides protection against *A. hydrophila* [56]. Ranjith *et al.*, 2008 reported that T. Cordifolia aqueous and ethanolic extracts enhanced antibody production when sheep red blood cells were used as antigens [23]. T. Col. provides protection against sepsis and cecal ligation. It also provides protection against *E. coli* induced peritonitis in mice and *E. coli* induced cholera in humans [57-63].

More and Pai 2011; Panossian and Wikman 2005 also reported the protection provided by T. col. from *E. coli*. Administration of T. col. resulted in a significant increase ($P<0.05$) of total serum immunoglobulin [64, 7, 33]. Dry barks of *T. cordifolia* has anti-spasmodic, anti-pyretic [65, 66, 67], anti-allergic [68], anti-inflammatory [69, 70, 52, 53] and anti-leprotic properties [71]. T Col. has been observed effective against acute inflammation and has been functional as non-steroidal anti-inflammatory agent [72]. Nayampalli *et al.*, 1986 reported that T. col. reduced the number of disrupted mast cells (in rats) [11]. Nair *et al*., 2006 reported that (1,4)-α-d-glucan inhibited the binding and internalization of opsonized zymosan A bioparticles. The anti-CD11b mAb inhibits the zymosan A-induced tumor necrosis factor (TNF)-α synthesis [73].

B) Complement System: Kapil and Sharma, 1997 reported that when antibody-coated sheep erythrocytes by guinea pig serum are treated with T. col., Syringin (T. col.-4) and cordiol (T. col.-7) inhibit the in vitro immunohaemolysis. This inhibition was found to be due to inhibition of the C3-convertase of the classical complement pathway [36]. T. Col. has also shown to activate the complement system [27-32, 24, 25, 55, 74, 75, 34], when required by the body in cases like chronic tonsillitis, gamma irradiation.

C) Macrophage: T. col stimulates the secretion/ proliferation of macrophages [55]. Raghua *et al*., 2009 reported that G1-4A has resulted in an increase in macrophage count [35]. Mathew and Kuttan 1999 has reported a significant enhancement in macrophage activation [5].

Kapil and Sharma, 1997 has reported that macrophage activation was reported for various polysaccharides of *Tinospora cordifolia*, such as cordioside (T. col.-2), cordiofolioside A (T. col.-5) and cordiol (T. col.-7); with increasing incubation times, this activation was more pronounced [36]. Abood *et al.*, 2014 showed that *T. crispa* crude extract significantly stimulates RAW 264.7 cells [76]. More and Pai, 2011 reported that *T. col*. enhanced secretion of lysozyme by macrophage cell line J774A [64].

D) T and B Cells: T. col. activates / proliferates T and B cells [32, 55, 74, 35]. Desai *et al.*, 2002 reported that dry stem crude extract (DSCE) of *Tinospora cordifolia* contained a polyclonal, G1-4A, which is a B cell mitogen [37]. Nair *et al.*, 2006 reported that (1, 4)-α-d-glucan activated NF-κB, an enhancer of activated B cells, time and dose-dependently [73]. This modulation of nuclear NF-κB activity is associated with the degradation of I-κBα thus facilitating the translocation of NF-κB into the nucleus; I-κBα inhibits the NF-κB transcription factor. G1-4A activated Akt, ERK and JNK, which finally activated IKK, degraded IκB-α and translocated NF-κB to the nucleus. Also, an increase in macrophage count [35].

E) Cytokines: T. col activates Th1 pathway cytokines [34]. Abood *et al.*, 2014 showed that T. Crispa crude extracts significantly stimulate intracellular expression of cytokines INF-γ, IL-6, and IL-8 [76]. Raj *et al.*, 2016; Debnath *et al.*, 2014 have reported that T. col. activates Th1 pathway cytokines, coupled with low nitric oxide synthesis [27, 28]. Sannegowda *et al.*, 2015 showed that *T. cordifolia* reduces pro-inflammatory cytokines such as: IL-1β, TNF-α, IL-6, and IL-17; the frequency of IL-17-producing T cells; and the production of chemokines such as RANTES. Ahmad *et al.*, 2015 reported that T. col. enhanced the proliferation of splenocytes and a significant increase in Th1 (TNF-α, IL-2, and IFN-γ) and Th2 (IL-4) cytokines [49]. Castillo *et al.*, 2014 reported that Tinospora lotion significantly reduces IL-1 and IL-6 in scabies patients and thus inhibits hyperkeratosis and infiltration of inflammatory cells into scabietic lesion [77]. Raghua *et al.*, 2009 reported that G1-4A has protected mice against septic shock by modulating the pro-inflammatory cytokines [35].

F) Autoimmune Diseases: Aiyer and Kolammal 1963 has opined that *T. crispa* possesses the immunostimulatory activity and has therapeutic potential for the prevention of immune diseases [44]. Sannegowda *et al.,* 2015 reported that *T. cordifolia* has shown anti-arthritic activity using the rat adjuvant-induced arthritis model of human rheumatoid arthritis [49]. Choubey *et al.,* 2013 reported that T. col. significantly reduces pain in rheumatoid arthritis patients [78]. Sudhakaran *et al.,* 2006 reported that T. col. acts as an immunoprophylactic [56]. *Tinospora cordifolia* is one of the ingredients of the Rasna saptak kashaya. *Piper longum* Linn. is one of the ingredients of the Pippali Vardhamana Rasayana. Both these *rasayanas* are suggested in amavata, whose symptoms are similar to rheumatoid arthritis. Pippali Vardhamana Rasayana acts against autoantibody, decreases the immune complex, and provides symptomatic relief with decrease the erythrocyte sedimentation rate [79].

G) Immune Complex: T. col. is a disease-modifying drug and inhibits the immune complex formation. T. col. is used in the treatment of rheumatic diseases [80]. Palep 2015 presented a formulation called Torchnil which contained T. col.; this has been effective in combat with immune complex, also HIV [51].

Discussion on Therapeutic Properties of *Tinospora cordifolia*: *Tinospora cordifolia* has shown modulatory activities in various organ systems and modulates the body contents to normalize them for normal functioning. T. col. has shown anticancer and antitumour properties. It has shown maturation of stem cells and an increase in bone marrow cellularity.

In combination with *Carica papaya*, it has shown an increase in blood platelet count in patients with cancer, dengue and thrombocytopenia. T. col decreases blood capillary permeability. It has shown to reduce serum, tissue cholesterol, phospholipids and free fatty acids in case of diabetes. It reduces blood sugar and increases body weight. It also increases blood insulin levels and glucose tolerance. T. col. has been reported to increase WBC count; also, it restores total lymphocyte count (TLC). It proliferates/ activates/ increases the activity of neutrophils, nuclear killer cells, other lymphocytes. T. col. improves the humoral immune response. It increases the plaque-forming cells in the spleen. It has shown to increase lipid peroxidation to reduce tumor cells. On the other hand, it has shown to prevent lipid peroxidation to provide protection in various cases when the subject was exposed to gamma radiation.

It has also been opined that T. col. provides protection to CNS. It has also been reported to enhance memory. T. col. been reported to show positive effects in the treatment of various skin diseases like scabies. It has been used as an antidote to snakebite and scorpion sting. It has also shown anti-osteoclastic activity and protection against bone damage. It has also been used against tuberculosis and even HIV and shown positive therapeutic effects. It has shown an increase in spleen cellularity and upregulation of anti-apoptotic genes.

T. col. exhibits radioprotective properties and has especially shown protection against gamma irradiation; it has reduced protein degeneration. T. col. has provided protection against immuno-suppression caused by CCl_4, cyclophosphamide induced anemia. It has shown to enhance the production and response of immunoglobulin and other antibodies. It has shown antipyretic, anti-allergic, and anti-leprotic. It has also shown protection against *E. coli* and reduced the number of disrupted mast cells. T. col. has been reported to inhibit the complement system in order to provide protection against immunohaemolysis. In other various cases, it has shown to enhance the complement system where required by the subject's body. T. col. has shown to stimulate the secretion/ proliferation of macrophages. T. col. activates and proliferates T and B cells. On the other hand, T. col. has also shown anti-inflammatory properties.

In various cases, T. Col. has been reported to significantly increase the Th1 and Th2 cytokines. On the other hand, it has shown to reduce IL-1 and IL-6 to provide protection against hyperkeratosis and scabies. It has also shown protection against pro-inflammatory cytokines. It has also provided protection against various autoimmune diseases such as rheumatoid arthritis; it has reduced pain in RA patients significantly.

Piper longum Linn. (PLL), an ingredient of the Pippali Vardhamana Rasayana, has shown protection against autoantibody and Erythrocyte Sedimentation Rate. PLL and T. col. have shown protection against immune complexes and have been used against a number of rheumatic diseases. The experimental results and reviews of papers on the medicinal benefits of *Tinospora cordifolia* are summarized in **Table 1**. The table cells where *target* is not given are from the references where it is not discussed explicitly. The target here is considered to be human. The table cells where *administration* is not discussed are from the references where the particular administration is not discussed. Here, the administration is considered to be the combination of all three excerpts of the T. col. plant, *i.e.*, root, stem, and leaves in powder, or aqueous extract from.

TABLE 1: EXPERIMENTAL RESULTS AND REVIEWS OF PAPERS ON MEDICINAL BENEFITS OF *TINOSPORA CORDIFOLIA*

S. no.	Subject in body / Abnormality	Target	Administration	Effect
1	Tumour Growth	BALB/c mice	Stem methanolic extract, 200 mg/kg, i.p, daily for 5 days	Acted with cyclophosphamide and reduced the animal tumors to 83%[5]
2		Mice Transplanted with Ehrlich Ascites Carcinoma	Stem dichloromethane extract, doses of various strengths	Dose-dependent reduction in tumor cells [6]
3		Adults Swiss Albino Mice injected with 1 x 10^8 *E. coli*	Stem aqueous extract 100mg/kg/d	Polymorph phagocytosis reduced[7]
4				Anticancer Properties[4]
5				Upregulate antitumor activity of tumor-associated macrophages[8]
6	Bone Marrow	BALB/c mice	Stem methanolic extract, 200 mg/kg, i.p, daily for 5 days	Increase in bone marrow cellularity 18.16 ×10^6 / femur along with α-esterase in bone marrow (1423/4000 cells) [5]
7		Rats	Stem alcohol extract, 100 mg/kg/d, oral	Increase in bone marrow cellularity along with α-esterase [9]
8	Cardiovascular system, blood	Humans with dengue thrombocytopenia and cancer	Leaf extract [with *Carica papaya*], 5ml, twice daily	Platelet count was increased [10]
9		Rats	Stem aqueous extract	Decreased the capillary permeability [11]
10	Diabetes	Rats induced with hyperglycemia	Stem hexane, ethyl acetate, methanol extracts 250mg/kg/d	Anti-diabetic activity [12]
11		Diabetic rats	Root extract	Anti-diabetic activity [14-17]
12		*Tinospora cordifolia*		reduces blood glucose level and increases glucose tolerance [19, 20]
13		Alloxan diabetic rats	Root extract	reduces serum and tissue cholesterol, phospholipids and free fatty acids [18]
14		Diabetic Rats	Root aqueous extract, doses of various strengths	Anti-diabetic activity, reduction in brain lipids, increase in body weight [13]
15	White Blood Corpuscles	BALB/c mice	Stem methanolic extract, 200 mg/kg, i.p, daily for 5 days	WBC count increases [5]
16		CCl4 intoxicated albino rats	Water extract, 100mg/kg/d	WBC count increases [21]
17		Male mice, Various doses of gamma irradiation	Stem extract, 200 mg/kg before irradiation	Restored total lymphocyte counts [22]
18		Rats	Stem alcohol extract, 100 mg/kg/d, oral	WBC count increases [9]
19		Wistar rats	Stem aqueous, ethanol, ethyl acetate, chloroform extract, different doses	WBC count increases [23]
20		Wistar Kyoto rats	Stem ethanol extract, doses of various strengths	Chemotactic activity and phagocytosis activity of neutrophils enhanced; nuclear killer cells proliferated [26]
21		Humans with chronic tonsillitis	Kumarabharana rasa (tablet), 500 mg once daily	Nuclear killer cells activated/proliferated [27]
22		Fish	Water-soluble fraction, doses of various strengths	Nuclear killer cells activated/proliferated [31]
23		Gamma irradiated swiss albino mice	Alcohol-water extract, 5mg/kg/d	Nuclear killer cells activated / proliferated [32]

24		Shrimp hemocyanin		Antiviral activity against phagocytosis, WBC count increase [24]
25		Fish		Antiviral activity against phagocytosis, WBC count increase[25]
26		Cows	Dry stem powder, 100 mg/kg/d	Mean phagocytic index significantly increased [33]
27		Mice	G1-4A	CD69 expression in lymphocytes increased [35]
28	Body Humour and Lipids	BALB/c mice	Stem methanolic extract, 200 mg/kg, i.p, daily for 5 days	Increase in plaque-forming cells in the spleen (1575 PFC/106 spleen cells)and circulating antibody titre (256) [5]
29		Sheep infected with guinea pig serum	Cordioside (TC-2), Syringin (TC-4), cordiofolioside A (TC-5) and cordiol (TC-7)	A dose-dependent increase in humoral immunity [36]
30		Mice Transplanted with Ehrlich Ascites Carcinoma	Stem dichloromethane extract, doses of various strengths	Drastic increase in lipid per-oxidation to reduce tumour cells [6]
31		Photosensitized C3H mice Liver Homogenate treated with peroxynitrite	G1-4A	Prevented lipid peroxidation to reduce thiobarbituric acid reactive substances in liver [37]
32		Lipid peroxidation of rat brain homogenate	An arabinogalactan polysaccharide TSP from stem methanol extract	Protection against iron-mediated lipid peroxidation of rat brain homogenate [38]
33		Mice	G1-4A	Spleen cellularity increased, anti-apoptotic genes upregulated [35]
34	Central Nervous System		As an adaptogen	Stimulation and stress-protective effects in the central nervous system [39-41]
35	Other Organ Systems	CCl4 intoxicated albino rats	Water extract, 100mg/kg/d	Liver was protected [21]
36		Humans, age 18-30 years	500mg tablets daily	Enhanced verbal learning and memory, and logical memory [42]
37		Adjuvant Arthritis induced male Lewis rats	Aerial part methanol extract, 1g/kg/d	Limiting of bone damage, shifting the balance of mediators of bone remodeling in favour of anti-osteoclastic activity [49]
38		Humans	Stem	Therapeutic effect in skin diseases [44, 45]
39		Humans	Root and stem	Therapeutic effect in snake bite and scorpion stings [46, 47, 48]
40		Humans with Mycobacterium tuberculosis	Alcohol extract	Inhibition of the growth of Mycobacterium tuberculosis [50]
41		Wistar Albino rats	Alcohol extract (100 and 200 mg/kg/d) and aqueous extract (100mg/kg/d)	Enhanced cognition [43]
42		Bronchospasm induced guinea pigs by 5% histamine aerosol	Stem aqueous extract	Decreased bronchospasm [11]
43		Humans with HIV		Anti-HIV activity [51]
44		Humans	Alcohol extract	Protease inhibition [52]
45	Irradiation	Male mice, Various doses of gamma irradiation	Stem extract, 200 mg/kg before irradiation	76.3% survival (30 days) [22]
46		Photosensitized C3H mice Liver Homogenate treated with peroxynitrite	G1-4A	Degradation of proteins due to photosensitization was significantly reduced [37]
47				Radioprotective properties [4]
48	Immune System and Antibodies	CCl4 intoxicated albino rats	Water extract, 100mg/kg/d	Immunosuppressive effect of CCl_4 was inhibited [21]
49		Humans	Stem water and ethanol extract (and *T. sinesis*)	Inhibition of cyclophosphamide-induced anemia [54]
50		Sheep infected with guinea pig serum	Cordioside (TC-2), Syringin (TC-4), cordiofolioside A (TC-5) and cordiol (TC-7)	A dose-dependent increase in cell-mediated immunity [36]
51		Rats	Stem alcohol extract, 100 mg/kg/d, oral	Potent immunomodulatory activity showed [9]
52		Wistar rats	Stem aqueous, ethanol, ethyl acetate, chloroform extract,	Aqueous and ethanolic extracts enhanced antibody production

			different doses	against injected sheep red blood cells [23]
53		Mice, Humans		Protection against peritonitis, cholera. Immunomodulation [57, 58, 60, 61, 62, 63]
54		Mice infected with E Coli	Water extract 100gm/kg/d	Cellular immune function improved, mortality reduced [59]
55		Infected albino rats	Stem powder, 50mg/kg/d	Effective against acute inflammation; functional as non-steroidal anti-inflammatory agent [72]
56		*Oreochromis mossambicus*	Leaf petroleum ether extracts, doses of various strengths	Enhanced the secondary antibody response [56]
57		Rats		Reduced the number of disrupted mast cells [11]
58		Bronchospasm induced guinea pigs by 5% histamine aerosol	Stem aqueous extract	Decreased bronchospasm [11]
59		Humans		Promotion of antibodies [55]
60		Fish	Water-soluble fraction, doses of various strengths	Enhanced lysozyme activity and antibody responses [31]
61		Adults Swiss Albino Mice injected with 1 x 10(8) E. coli	Stem aqueous extract 100mg/kg/d	Protection from *E. coli* [7]
62			(1,4)-alpha-D-glucan	inhibition of binding and internalization of opsonized zymosan A bioparticles [73]
63		Cows	Dry stem powder, 100 mg/kg/d	Total serum immunoglobulin significantly increased [33]
64	Complement System	Sheep infected with guinea pig serum	Cordioside (TC-2), Syringin (TC-4), cordiofolioside A (TC-5) and cordiol (TC-7)	Inhibition of the C3-convertase resulting in inhibition of *in-vitro* immune haemolysis [36]
65		Humans with chronic tonsillitis	Kumarabharana rasa (tablet), 500 mg once daily	Activation of complement system [27]
66				Activation of complement system [28-30, 34, 75]
67		Fish	Water-soluble fraction, doses of various strengths	Activation of complement system [31]
68		Gamma irradiated Swiss albino mice	Alcohol-water extract, 5mg/kg/d	Activation of complement system [32]
69		Shrimp hemocyanin		Activation of complement system [24]
70		Fish		Activation of complement system [25]
71		Humans		Activation of complement system [55]
72	Macrophage	BALB/c mice	Stem methanolic extract, 200 mg/kg, i.p, daily for 5 days	Signiphicant enhancement in macrophage activation [5]
73		Sheep infected with guinea pig serum	cordioside (TC-2), Syringin (TC-4), cordiofolioside A (TC-5) and cordiol (TC-7)	Macrophage activation [36]
74			T Crispa ethanol extracts, doses of various strengths	Stimulation of RAW 264.7 cells [76]
75		Macrophage J774A.1 cell line	5ul of 80ug/ml daily	Macrophage activation enhancement; protection from *E. coli* [64]
76		Humans		Stimulates of secretion / proliferation of macrophages [55]
77		Mice	G1-4A	Macrophage count increased [35]
78	T and B Cells	Photosensitized C3H mice Liver Homogenate treated with peroxynitrite	G1-4A	B Cell mitosis [37]
79		Gamma irradiated swiss albino mice	Alcohol-water extract, 5mg/kg/d	Activation / proliferation T and B Cells [32]
80		Humans		Activation / proliferation T and B Cells [55]
81			(1,4)-alpha-D-glucan	Activation of NF-κB time and dose-dependently [73]
82		Mice	G1-4A	Akt, ERK and JNK activated, which finally activated IKK; IκB-α degradated and NF-κB translocated to the nucleus [35]
83	Cytokines		*T. crispa* ethanol extracts, doses	Stimulation of intracellular

			of various strengths	expression of cytokines [76]
84		Adjuvant Arthritis induced male Lewis rats	Aerial part methanol extract, 1g/kg/d	Reduced pro-inflammatory cytokines, the frequency of IL-17-producing T cells, production of chemokines such as RANTES [49]
85		Wistar Kyoto rats	Stem ethanol extract, doses of various strengths	Splenocytes proliferated; Th1 (TNF-α, IL-2, and IFN-γ) and Th2 (IL-4) cytokines significantly increased [26]
86		Humans with scabies	*Tinospora* lotion on the skin	IL-1 and IL-6 significantly reduced, thus hyperkeratosis and infiltration of inflammatory cells into scabietic lesion inhibited [77]
87		Humans with chronic tonsillitis	Kumarabharana rasa (tablet), 500 mg once daily	Activation of Th1 pathway cytokines, coupled with low nitric oxide synthesis [27]
88		Mice	G1-4A	protected mice against septic shock by modulating the proinflammatory cytokines [35]
89	Autoimmune diseases	Adjuvant Arthritis induced male Lewis rats	Aerial part methanol extract, 1g/kg/d	an anti-arthritic activity using the rat adjuvant-induced arthritis model of human Rheumatoid Arthritis [49]
90		Humans	Stem	Immunostimulatory activity. Therapeutic for the prevention of immune diseases [44]
91		Humans with arthritis		Significant reduction of pain in rheumatoid arthritis patients [78]
92		Oreochromis mossambicus	Leaf petroleum ether extracts, doses of various strengths	Immunoprophylactic [55]
93		Humans with Juvenile Rheumatoid Arthritis	Rasna saptak kashaya	Symptomatic relief with decrease the erythrocyte sedimentation rate [79]
94	Immune Complexes	Humans with rheumatic diseases		Modifies disease. Inhibits immune complex formation [80]

Systemic Lupus Erythematosus (SLE):

A) SLE: The Disease: In SLE, different cytokines and other mediators of inflammation are released and hence contribute to its progression. This systemic disease results in hyperactivated leukocytes as well as the pathogenic autoantibodies and immune complexes, which cause local autoimmunity and end-organ disease [81]. In SLE, all pathways lead to the production of interferon α (IFNα) mediated by endogenous nucleic acids. SLE autoimmune response is initiated by increased production of autoantigens during apoptosis, decreased disposal, deregulated handling [82].

Activation of DCs and B cells is promoted by nucleosomes that contain endogenous danger ligands, that can bind to pathogen-associated molecular pattern receptors, are incorporated in apoptotic blebs. Activation of DCs causes the production of interferons (IFN) and the activation of B cells causes the production of autoantibodies [82]. In SLE Maintenance mechanisms of T- and B-cell tolerance is broken down; removal autoreactive B cells are depleted, leading to cell death induced by FcgRIIb, inhibition of migration and control plasma cell survival, which contribute to autoimmunity and infection; phagocytosis is depleted, along with depletion of clearance of apoptotic blebs, impaired nitroblue tetrazolium reduction, and reduced production of IL–8 and IL-12 by polymorph nuclear cells; toll-like receptor (TLR) for self-antigens are inappropriately activated, along with TLR3 ds-RNA, TLR7 ss-RNA, and TLR9; complement- and Fc-mediated uptake is reduced, leading to delay in clearance of IgG-coated erythrocytes and soluble IC [83].

According to Cuchacovich *et al*., 2009, the following microorganisms are found in patients with SLE most frequently. The patient might contain bacteria, *Staphylococcus aureus*, non-typhoidal *Salmonella*, *Escherichia coli*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Klebsiella spp*, *Acinetobacter spp*, *Pseudomonas spp*, *Mycoplasma spp*. The patient might also contain Virus, Parvovirus B19, Cytomegalovirus, Epstein-Barr virus, Herpes simplex/varicella zoster, Human papillomavirus, Hepatitis A. A patient might also be affected with Fungus, *Candida spp*, *Aspergillus spp*, *Nocardia*

spp, *Cryptococcus neoformans*, *Mycobacterium*, non-tuberculous mycobacterium, or otherwise *Mycobacterium chelonae*, *M. tuberculosis*, *M. avium* complex, *M. haemophilum*, *M. fortuitum*, *M. marinum*. A patient may contain many or any of the discussed cells which might degrade the medical condition [83].

B) Fatalness of SLE: The major cause of death in patients with SLE is renal failure. The renal autoimmunity is initiated when immunoglobulin and complement start to deposit on the glomerular basement membrane. This follows engagement of activating Fc receptors by circulating monocytes, endothelial activation, chemokine secretion, recruitment of activated lymphocytes and finally release of proapoptotic factors that result in renal cell death, which is irreversible [84]. Similarly, all other organ systems are affected, majorly by the deposition of these immune complexes on the tissues of organs followed by the destructive action of immune system, like the renal system [84, 85], integumentary system (especially the skin), skeletal system (especially bone joints), central nervous system, lymphatic system and spleen [86], cardiovascular system, gastrointestinal system [87, 88], reproductive system (especially in females during pregnancy) [82].

C) Medications: The drugs that are used in the treatment process of SLE patients in present medical procedures are shown in **Table 2**.

TABLE 2: DRUGS BEING USED TO TREAT SLE

S. no.	Treatment procedures / Drugs	Effects against
1	Antimalarials	Articular and mucocutaneous manifestations of SLE; Fatigue and serositis; Improvement of lipid profile; Flares [89, 90, 91, 92, 93, 94, 95]
2	Azathioprine	Diffuse proliferative glomerulonephritis; lupus nephritis [85, 96, 97, 98, 99, 100]
3	Cyclophosphamide	Lupus nephritis [93, 99, 101, 102, 103, 104, 105]
4	Cyclosporin A	T-cell mediated responses; thrombocytopenia; proteinuria; histological lesions; reduces steroid requirements [106-114]
5	Methotrexate	Serositis [105]
6	Mycophenolate mofetil	LN and proteinuria; Suppresses autoimmunity [115-120]
7	Autologous bone marrow transplantation	Good disease control and survival [121-127]
8	Dapsone	Vasculitic lesions, bullous LE, sub-acute cutaneous lupus, oral ulcers, severe leukopenia, thrombocytopenia [128-131]
9	Thalidomide	Cutaneous lupus; discoid lupus [132-133]
10	Dehydroepiandrosterone	Disease activity, flares [134, 135]
11	Bromocriptine	Disease activity [105]
12	Nucleoside analog (fludarabine and cladribine - 2-chloro-2'-deoxy-adenosine)	LN (fludarabine and cladribine); SLE (fludarabine) [136-140]
13	Tacrolimus	Similar to Cyclosporin A [141]
14	Anti-CD40 ligand antibodies	CD40:CD40L interaction, CD40:B cell interaction, renal disease [142]
15	DNase	Antigenic load, immune complexes [84]
16	LJP 394	anti-dsDNA antibody [143]
17	Bindarit	Disease development, proteinuria, renal disease, anti-dsDNA and antinuclear antibodies; urinary albumin, urinary IL-6 [144, 145]
18	Belimumab	Functioning of B-Cell, B-lymphocyte stimulator [145]
19	Micro-antibodies	B-Cell (ultimate target) [146]
20	Anti-cytokines	Inflammation response (by inhibiting one or more of the cytokines) [146]

D) Side Effects of Medications: The major issue in the medication of systemic lupus erythematosus is the management of side effects that arise from the drugs administered to the patients.

Anti-malarials have shown side effects when the drug is discontinued [147]. Long-term use of Cyclophosphamide has shown major infections, premature ovarian failure, amenorrhea, malignancy, cervical dysplasia [106, 99, 104, 105, 148].

Cyclosporin A has caused hypertension, hypertrichosis, gingival hypertrophy in patients [81, 84]. Methotrexate causes dyspepsia and increase in

hepatic-enzyme serum levels [149]. Mycophenolate mofetil has caused pancreatitis and severe febrile pancytopenia in a few patients. Dapsone may cause hematological hemolysis and neurological polyneuritis [106]. Thalidomide may cause neuropathy, which may be irreversible; and may also induce nerve damage, which is dose-dependent [150]. In case of treatment with autologous bone marrow transplantation, it is required to identify the patients who are suitable for this treatment. The risks involved are relatively high which include fatality in suitable cases [151].

Dehydroepiandrosterone may result in acne, hirsutism and irregular menses. The main side effects of bromocriptine are headaches and nausea [106]. Treatment with anti-CD40 ligand antibodies may cause asthenia, dizziness, nausea and headache [152]. LJP 394 has adverse effects including headache and insomnia [106]. No medical procedure being used has shown complete cure for SLE.

***Tinospora* over the Existing Drugs to Cure SLE:**

A) Current research scenario on modern medicine, SLE and T. Col.: In spite of the strict side effects of the drugs being currently used in the therapy of SLE, they are being used in the treatment process. *Tinospora cordifolia* has numerous benefits and can be used in the SLE treatment process. The only side effect of *Tinospora* recorded so far is that it results in constipation. SLE is a dysfunction of the immune system, majorly the B-cells. T. col. has been recorded to show immunomodulatory properties and properties of modulation of T and B-cells, along with cytokines and antibodies. It purifies blood and cleans out the unwanted lipids and enhances the humoral immune response. It has also been reported to clean out the immune complexes from the body.

B) T. Col. as a Strong Hope towards Successful Treatment of SLE: The strange, but best activity was shown by T. col. is that it acts as a moderator. It has shown to both increase and decrease activities of substances in the body, as required according to the medical state and requirements to normalize the functionality of numerous systems by the body. These substances include T and B cells, antibodies (and autoantibodies) and cytokines. These therapeutic properties of T. col. are potent, which advocate its exploitation in the treatment of systemic lupus erythematosus.

CONCLUSION: There are numerous benefits of *Tinospora cordifolia* stated in the Indian Ayurvedic texts. Many of them have been tested according to modern testing techniques for medicine and it has started to be used to treat a large variety of abnormalities in the human body. Because of the immunomodulatory and antitumor properties, and numerous others, along with no major side effect, T. col. can be used in the treatment of systemic lupus erythematosus, a rheumatoid autoimmune disease. *Tinospora cordifolia* may be administered along with *Piper longum* Linn., *Carica papaya*, *Tinospora sinensis* as well as *Tinospora crispa*.

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