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A Mini Review on Pharmacological Effect of *Tinospora cordifolia* and its Inhibitory Activity on Covid-19

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Abstract

Herbal based produced with medicinal value are rapidly gaining prominence in clinical science due to their well-known properties with no adverse effects compared to synthetic medications. *Tinospora cordifolia* is one of the most widely recognized medicinal plants commonly known as Amrita and Guduchi belongs to the Menispermaceae family which is used to cure various disease in many traditional medicines. *Tinospora cordifolia* was found to be an essential medicinal plant among the *Tinospora* species used for the ethno-medical treatment of digestive order, headaches, colds, pharyngitis, flu, diarrhea, oral ulcer, diabetes and rheumatoid arthritis in the comprehensive literature survey. Their mode of action showed antidiabetic, antioxidant, antitumor, anti-inflammatory, antimicrobial and immunostimulation activities. Now a day we are trying to find out an alternative medicine to inhibit the transmission of Coronavirus disease 2019 (covid-19**,** a transmissible disease initiated and propagated through a new virus strain SARS-CoV-2) has been initiated and propagated from China since 31 December 2019 and the infection has affected millions of people globally. In addition, this herb's formulations have proven effective in improving immunity and providing resistance to infections with viruses. However, there are no complete studies available to examine bioactive compounds and their modes of action. The purpose of this analysis is to summaries current knowledge of the conventional uses, phytochemistry, biological activity and toxicity of the *Tinospora cordifolia* in order to reveal its therapeutic potential and how these molecules can function synergistically with other potential SARS-Cov-2 treatment drugs.

Keywords: *Tinospora cordifolia; Guduchi; Giloy; Covid-19; Anti-Viral*

Abbreviations

SARS CoV-2: Severe Acute Respiratory Syndrome Coronavirus-2; Covid-19: Corona Virus Disease-2019; SOP: Standard Operating Procedure; TNF-α: Tumour Necrosis-α; iNOS Genes: Inducible Nitric Oxide Synthases Gene; NF-kB: Nuclear Factor-Kappa Light Chain Enhancer of Activated B Cells; COX-2: Cyclooxygenase-2; IL: Interleukins; IFN: Interferon; MCP-1: Monocyte Chemoattractant Protein-1; NO: Nitric Oxide; RNA: Ribonucleic Acid; NSP: Non-Structural Proteins; CD4: Cluster of Differentiation 4; H1N1: Hemagglutinin-1 Neuraminidases-1

Introduction

Tinospora cordifolia (Guduchi or Giloy), is a medicinal plant which has been used for its remedial purpose for thousands of year in Ayurvedic system of medicine. *Tinospora cordifolia* (*T. cordifolia*) is a large, deciduous, glabrous, climbing shrub that belong family Menispermaceae. This herb is distributed throughout the Africa, China and India. In Hindu mythological, it is known with name *Giloy* that refers to the "heavenly elixir" or "soma" which saved old age celestial and kept them eternally young, mentioned in Rigved. It is also famous by several names amruthu, gillow, guduchi, guluchi and rasakinda [1]. This plant is known as Rasayana in Ayurveda because constituents of this plant can improve immune defense system and protect against microbial infections. Every parts of *T. cordifolia* are used therapeutically; however, the stem has been approved as human medicine and also listed in Ayurvedic Pharmacopoeia [2]. Standard Operating Procedure (SOP) is needed to for Ayurvedic Drug, which has been mention in figure 1 [3]. Traditionally, this plant has been used in treatment

of diabetes, fever, gout, jaundice and skin diseases. It is considered to be a nectar plant as it detoxifying, rejuvenating and immune boosting properties [4]. Its extracts have alkaloids, glycosides, steroids and polysaccharides. It is well known for its immunomodulatory, antimycobacterial, antidiabetic, antioxidant, antihepatotoxic and cytotoxic effects. Further, this plant has been considered as a main source of tonic, diuretic and anti-periodic by European practitioners in India. Some formulations prepared from Guduchi includes Guduchitaila, Sanjivanivati, Kanta-Kari avaleha, Guduchyadichurna, Chyavnaprasha, Guduchughrita, Guduchisatva, Brihatguduchitaila, Amrita guggulu, amritashtakachurna etc. for the treatment of human disorders [5]. Guduchi extract has been shown beneficial effects against many disorders as evidenced by various studies (Table 1).

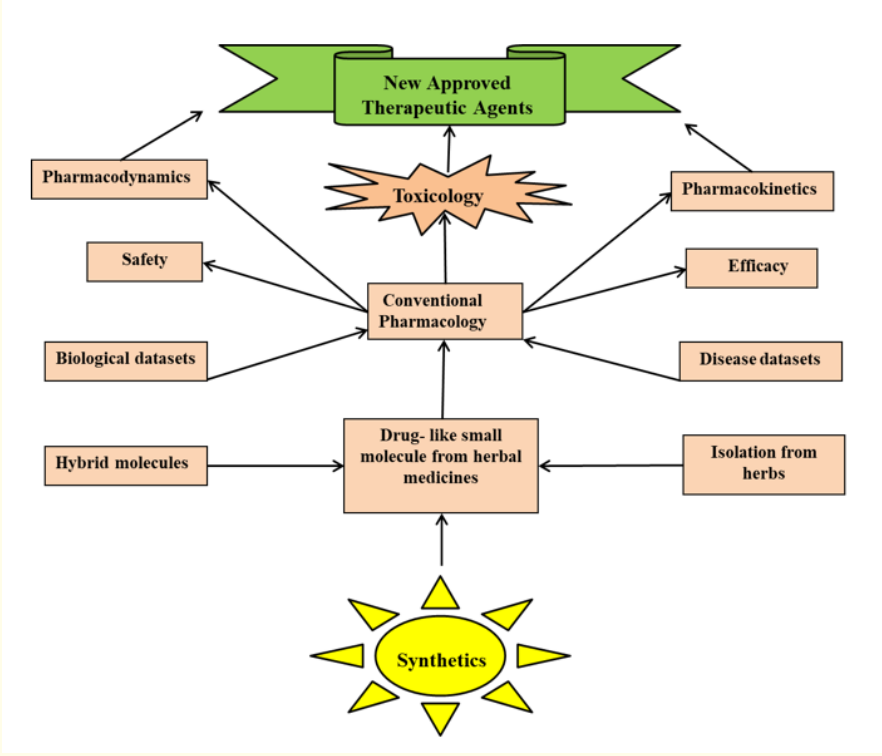

Figure1: *Standard operating procedure (SOP) for ayurvedic drug.*

Severe acute respiratory syndrome coronavirus 2 (SARS CoV-2) has spread at a tremendous rate, and vaccines are needed urgently to mass immunize the human race and antiviral drugs for the treatment of infected ones. Despite the world Health Organization's declaration that there is no effective vaccine or antiviral medication available to prevent or treat SARS-CoV-2, there is a rampant quest to find new antiviral molecules as evidenced by the growing published reports [6]. In the presented analysis, we reported some promising response that we obtained from some of *T. cordifolia* phyto-constituents tested in terms of inhibition potentials. We strongly consider that the outcomes of the present work will results in some valuable insights into the development of alternative drugs for COVID-19.

Pharmalogical actions of *Tinospora cordifolia* as an immunomodulation

It is found that *T. cordifolia* has several pharmacological activities as mentioned in table 1 below. Phytochemical experiments including *T. cordifolia* display various components that are shown in table 2. Many patents have been granted on therapeutic inventions on *T. cordi-*

difolia (Table 3). *T. cordifolia* influences the expression of cyclooxygenase-1, tumour necrosis-a (TNF-a), iNOS genes, cytokines and NF-kB activation and has the ability to decrease the expression of the COX-2 enzyme and thereby minimize the expression of TNF-a, IL-1B and IL-6 synthesis and other pro-inflammatory interleukins [7]. Phytosterol such as stigmasterol and β-sitosterol are found to be responsible for inhibiting cell-stimulated COX-2 synthesis and TNF-α adhesion molecule [8]. Stigmasterol inhibits E2 prostaglandin and other mediators of matrix degradation. In addition, dry stem crude extracts of *T. cordifolia* with poly B cell mitogen, macrophage-binding G1-4A have been reported to boost immune response in mice by including IL-1 secretion, together with macrophage activation [4]. Alpha-D-glucan isolated from *T. cordifolia*, is a polysaccharide that exhibits unusual immune stimulating properties. The definite prerequisite for biological activity consists of alpha-D-glucan (1-3) - β-glycosidic binding which help in proliferation of lymphocytes and production of antibody. Immune stimulating property of α-D-glucan activate different subsets of lymphocytes, syntheses of cytokines such as interleukin (IL)-1h, IL-2, IL-4, IL-6, IL-10, IL-12 p70 and p40, IL-18, interferon (IFN)-a and g, tumor necrosis factor (TNF)-α and-γ, monocyte chemoattractant protein (MCP)-1, synthesis of nitric oxide (NO) and the extent of oxidative stress elicited in human lymphocytes [9].

Tinospora cordifolia as potential ligand drugs: berberine ($C_{20}H_{18}NO_4$), choline ($C_5H_{14}NO$) and tetrahydropalmatine ($C_{21}H_{25}NO_4$) from the group of alkaloids, β-sitosterol ($C_{29}H_{50}O$) from steroids, octacosanol ($C_{28}H_{58}O$) from aliphatic group gives positive responses target proteases enzymes suggest by *in silico* studies in which berberine can regulate protein's function due to its easy inhibition and can control viral replication [10].

Activity	Animal model	References
Ameliorative	Exposure of aflatoxin B1	[11]
Analgesic	Hot plate and writhing test	[12]
Antidepressant	Forced swim test and Tail suspension test	[13]
Antidyslipidemic	Alloxan induced diabetic male adult rats of charles foster strain	[14]
Anti-inflammatory	Carrageenan induced paw edema model in rats.	[15]
Antimalarial	Microorganism used Plasmodium berghei on mice models.	[16]
Antioxidant	N-nitrosodiethylamine induced liver cancer	[17]
Antipsychotic	Amphetamine challenged mice model	[18]
Antiulcer	Pylorus ligation induced ulcer	[19]
Cardioprotective	Calcium chloride produced arrhythmia	[20]
Diabetic-neuropathy	Streptozotocin induced wistar albino diabetic rats	[21]
Gastroprotective	Indomethacin induced gastric ulcer	[22]
Hepatoprotective	Bile duct ligation induced jaundice in rats	[23]
Neuroprotective	6-hydroxy dopamine lesion model	[24]
Nootropic	Radial arm maze task performance	[25]
Radio protective and Cytoprotective	4 Gy-γ radiation and cyclophosphamide induced genotoxicity	[26]

Table 1: *Preclinical evaluation on Tinospora cordifolia extract.*

Chemical Constituents	Part of Plant	Compound isolated	References
Alkaloids	Stem, root	Berberine, Palmatine, Tetrahydropalmintine, Isocolumbin, Columbin, Tembetamine, Magnoflorine, Choline, Aprophine, Jatrinhizine, Tinosporin, corydine	[27]
Bitter	Stem and leaves	Tinosporin, tinosporic acid, tinosporol, tinosporide and cordifolide	[28]

Carbohydrates	Stem	(1-4)Alpha-D-glucan (RR1), glucose, arabinose, rhamnose, xylose, mannose and galactose units	[29]
Flavonoids	Stem	Quercetin, (−)-Epicatechin	[29]
Glycosides	Stem	Tinocordiside, tinocordifolioside, cordioside, syringing, syringing-apiosylglycoside, pregnane, glycoside palmatosides	[29]
Lignans	Stem	3 (a, 4-dihydroxy-3-methoxybenzyl)-4-(4-hydroxy-3-methoxybenzyl)	[29]
Protein/amino acid	Leaves and stem	ImP (acidic protein lacking hemagglutination activity)	[30]
Steroids	Aerial part of stem	β-sitosterol, δ-sitosterol, 20 β-hydroxyecdysone, Ecdysterone, Makisterone A, Giloinsterol	[31]
Terpenoids	Whole plant	Tinosporide, Furanolactone diterpene, Furanolactone clerodane diterpene, furanoid diterpene, *Tinospora*side, ecdysterone makisterone and several glucosides isolated as poly acetate, phenylpropene disaccharides cordifolioside A, B and C, cordifoliside D and E, Tinocordioside, cordioside, palmatosides C and F, Sesquiterpene glucoside tinocordifolioside, Sesquiterpene tinocordifolin	[32]
Volatile oil	Leaves	Hydroquinone, 2-hexenal, palmitic acid, 2-hexen-1-ol, phytol and 2,2-diphenyl-1-picrylhydrazyl (DPPH)	[29]

Table 2: *Qualitative analysis of various parts of Tinospora cordifolia.*

Patent No.	Title	References
US8936817	Preparation for weight loss management	[33]
US6780441	Composition of eleven herbals for treating cancer	[34]
US7914824	Herbal extract for renal disorders	[35]
US5529778	Ayurvedic composition for the prophylaxis and treatment of AIDS, flu, TB and other immuno- deficiencies and the process for preparing the same	[36]
EP1781708	Materials and methods for immune system stimulation	[37]
EP1732579	Herbal extract for renal disorders	[38]
US7344739	Anti-allergic herbal formulation	[39]
US7247322	Herbal nutritious chocolate formulation and process for preparation thereof	[40]
US6251383	Method for *ex vivo* expansion of hematopoietic cells	[41]
US6759061	Liver function improvement formulation	[42]
US7550163	Herbal soft drink	[43]

Table 3*: Patents granted on Tinospora cordifolia for its potential medicinal properties.*

Efficacy and activity of natural constituents from *Tinospora cordifolia* against SARS-cov-2

Coronaviruses are positive-sense RNA viruses with non-segmented genomes. The polyproteins are processed into non-structural proteins (NSP) and structural proteins [44]. After infecting host cells, coronaviruses undergo recombination periodically. Novel coronavirus

proteases share a high percentage of sequence and structure similarity to SARS coronavirus, which plays a major role in viral polyprotein production. Such proteins strip ubiquitin to assist in preventing the host's immune response [45].

Antimicrobial properties of *T. cordifolia* are reported mainly from the leaf extract as broad spectrum (both for gram positive and gram negative bacteria). The leaf extract also relevant for fungal infection and malarial parasites [46]. *T. cordifolia* extract show antiviral properties as the silver nano particles of *T. cordifolia* were reported to be effective against Chikungunya virus and H1N1 viral protein. Shilajatic Rasayana is a ayurvedic preparation shows synergistically improve efficacy of antiretroviral therapy in HIV positive patients [47]. *In silico* screening of TC extract shows pharmalogical activity against COVID-19. Analysis of *in-silico* tools against the use of four primary SARS-CoV-2 targets i.e., 1) surface glycoprotein (6VSB), 2) Receptor binding domain both responsible for attachment of the virus to host cell, 3) RNA dependent RNA polymerase and 4) main protease, responsible for virus attachment and replication of the virus in the host cell [48]. Berberine, Isocolumbin, Magnoflorine and Tinocordiside showed superior binding affinity against all the four SARS-CoV-2 targets. Tinocordiside and Isocolumbin shows high efficacy in preventing SARSCoV- 2 attachment to host cells and replication [49].

To protect the host system, small molecules and drug inhibitors can be engineered to block the pathways of cascade signaling. There are several functional domains of viral protein, such as the largest NSP-3 protein, and polyprotein processing includes proteases such as protease and papain like protease (3CLpro and PLpro) [50]. Novel infection with coronavirus leads to over activation of CD4 effector T-cells resulting in excessive amounts of immune cells at infection site and decrease tissue potential that contributes to organ failure [51]. Plant-based immunomodulatory agents would decrease the intensity of inflammatory response hyper-activation and decrease the cytokines storm [52]. Many medicinal plants extracts and their immunomodulatory constituents have shown their ability to reduce the over-inflammatory response of cytokines. The phytochemical compounds, namely tinosponone, xanosporic acid, cardiofolioside B, tembetarine and berberine of *T. cordifolia* were identified by computational analysis as potential lead molecules to combat SARS-Cov-2 [53]. *In-silico* study demonstrated that tinosponone is a potent, selective and nontoxic inhibitor of SARS-CoV-2 3CL protease [9].

Conclusion

T. cordifolia is a medicinal plant with numerous bioactive compounds that have been discussed, including alkaloids, steroids, glycosides, etc. All these active compounds have various forms of immunomodulatory and physiological functions, thus demonstrating the plant's complex versatility. Studies must be done with aspects of how the active compounds actually communicate with the living systems and influence the relationships between structure and function. Present analysis spotlights that the *in-silico* research supports *T. cordifolia* inhibitory activity on covid-19. The future reach of analysis will remain the analysis of biochemical and signaling pathways of the active components of *Tinospora* thus, enabling effective disease targeting.

Conflict of Interest

None declared.

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