REVIEW ARTICLE

Antiviral Efficacy of *Tinospora cordifolia* – A Review

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Abstract

Since ages, plants have had a pivotal role as medicine due to their therapeutic value. *Tinospora cordifolia* is a well-known plant with versatile medicinal properties including hypoglycemic, anti-inflammatory, antioxidant, immunomodulatory, and antimicrobial, which can be attributed to its secondary metabolites. Viral infections constitute a major faction of human diseases. Developing efficient and novel therapeutic agents to combat viral diseases is an ongoing process, wherein plant-derived natural products are a potential source. *T. cordifolia* has been explored for its use in viral infections as an immunomodulatory and antiviral agent. Bioactive components of the plant, such as berberine, tinosponone, tinocordiside, isocolumbin, magnoflorine, tinosporin, and cordiofoliside have been reported to exhibit antiviral efficacy. The present review summarizes the efficacy of *T. cordifolia* as an anti-viral agent and its role in combating viral infections.

Key words: Antiviral activity, immunomodulatory activity, phytocomponents, secondary metabolites, *Tinospora cordifolia*

INTRODUCTION

The term "Traditional medicine" refers to the time-tested and indigenous systems of medicine. The World Health Organization defines traditional medicine as therapeutic practices developed and used hundreds of years before the onset of modern medicine.[1] India is renowned for its traditional system of medicine Ayurveda, which was conceptualized between 2500 and 500 BC.[2] A significant proportion of components used in Ayurveda include medicines derived from plants, also known as herbal medicines. Herbal medicines are used worldwide for their lesser side effects, easy availability, and effectiveness. Extensive research on herbs has proven their efficacy in many communicable and non-communicable diseases. One such plant with highly valued medicinal properties and widely used in Ayurvedic preparation is *Tinospora cordifolia.*

T. cordifolia belongs to the *Menispermaceae* family, which is a vibrant source of alkaloids and terpenes.[3] It is a climbing shrub with dense foliage [Figure 1]. It is frequently found in dry and deciduous forests. *T. cordifolia* stems are fleshy and have many twining branches. It produces flowers and fruits in summer and winter, respectively.[4] The plant is native to India, Myanmar, Sri Lanka, and China. In India, it is found in tropical and subtropical regions and known by many names such as Amritbel, Guduchi, Giloy, and Amarlata.[5] Ayurveda pharmacopeia of India recommends the use of *T. cordifolia* as a therapeutic agent in various ailments such as fever, anemia, leprosy, symptoms of obesity, diabetes mellitus, and jaundice.[6]

Different parts of *T. cordifolia* such as leaves, stems, roots, and the whole plant in itself are widely used by indigenous tribes in India for the treatment of many health disorders. It also finds an important place in commercial herbal formulations. Giloy juice and powdered plant material are available as ready-for-consumption products. Reportedly, the plant is a rich source of several biologically active compounds such as flavonoids, alkaloids, diterpenoid lactones, glycosides, steroids, sesquiterpenoids, phenolics, aliphatic compounds, and polysaccharides.[7] Such a varied array of bioactive components make it an important medicinal plant with a versatile range of applications.

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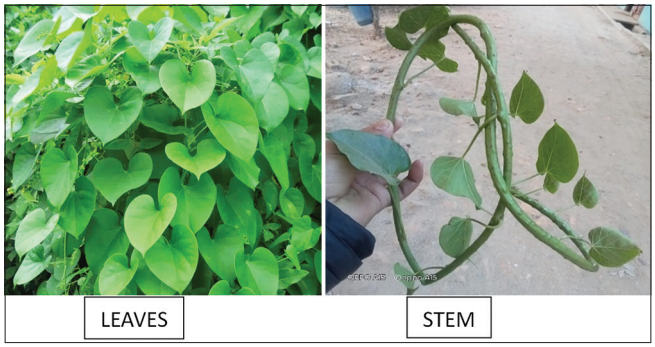


Figure 1: (a and b) Morphology of *Tinospora cordifolia*

USES OF *T. CORDIFOLIA* AS FOLK MEDICINE

T. cordifolia extract is used either by itself or in combination with other herbs to treat many common ailments. Some of its important medicinal properties are hypoglycemic, anti-inflammatory, anti-arthritic, antioxidant, anti-allergic, anti-malarial, anti-cancer, hepatoprotective, and immunomodulatory. Listed below are some of the common, documented applications of *T. cordifolia* especially among tribals throughout India [Table 1].

Table 1: Uses of *T. cordifolia* in the management of common ailments[7]

Ailments	Mode of application of *T. cordifolia*
Fever	Combined paste of *T. cordifolia* stems and roots of *Solanum surattense* roots in a specific proportion. Root extract is taken orally. Mature stems' decoction taken orally
Cancer	Powdered root and stem of *T. cordifolia* consumed with milk
Dysentery, diarrhea	Oral consumption of root concoction
General debility	Around 4 g of *T. cordifolia* stem is boiled in water and the decoction is consumed on an empty stomach
Cough	The combined powder of *T. cordifolia*, *Terminalia chebula*, and *Trachyspermum ammi* in equal proportions is consumed with salt, once a day, early morning
Leucorrhea	The paste of *T. cordifolia* and seeds of Piper nigrum is eaten every morning
Asthma	The juice expressed from the stems of *T. cordifolia* is mixed with honey and consumed
Skin disease	*T. cordifolia* stem extract prepared by boiling in hot water is consumed.

T. cordifolia: Tinospora cordifolia

PHYTOCOMPONENTS OF *T. CORDIFOLIA*

Extensive research has revealed that *T. cordifolia* extract contains many biologically active phytocomponents, some of which are listed in Table 2.

ROLE OF *T. CORDIFOLIA* IN COMBATING VIRAL INFECTIONS

T. cordifolia has been widely investigated for its application in viral diseases and antiviral effectiveness. Many reports have been published wherein *T. cordifolia* extracts have been studied for their *in vitro, in vivo,* and *in silico* proficiency against viruses. *In vitro* experiments demonstrate the antiviral efficacy of the test material in terms of reduction in viral titer and give a fair idea of its mode of action. In experiments involving animal models, the antiviral efficacy is measured based on physiological and immunological parameters, and clinical symptoms.

Stimulation of the immune system is an important aspect of combating infections.[30] During viral invasion, a wide array of host mechanisms come into play. The innate immune responses function with the major objectives of inhibiting the infection and protecting the spread of the virus to other cells by killing virus-infected cells before adaptive immunity sets in.[31] Toll-like receptors (TLRs) are a family of pathogen recognition receptor proteins expressed by many immune system cells such as the phagocytes and dendritic cells. TLRs identify pathogen-associated molecular patterns and initiate expression of type I α or β interferons (IFN) and IFN-stimulated genes, and other cytokines, all of which lead to antiviral activity through a network of mechanisms.[32] In addition, the non-specific response of natural killer (NK) cells which destroy virus-infected cells, and virus-specific T-cell responses also play a major role in defense against viruses.[33]

One of the significant properties of *T. cordifolia* is its immunomodulatory effect which could enhance the immune system in fighting against viral infections. *T. cordifolia* extracts prepared in alcoholic solvents and water were beneficial for the immune system[34,35] and have shown good immunomodulatory activity.[36,37] Among the many phytocomponents of *T. cordifolia*, phenylpropanoid glycosides including cordifoliosides A and B and syringin have been documented as the primary immunomodulatory components.[25,38] The plant-derived glycopeptide (1,4)-alpha-D-glucan has been shown to have immunomodulating properties through stimulation of NK cells, T-cells, and B-cells. It could activate macrophages through TLR6 signaling, NFkappaB translocation, and cytokine production.[39,40] The immunomodulatory effect of *T. cordifolia* can be attributed to a collaborative activity of the components such as 11-hydroxymustakone, N-methyl-2-pyrrolidone, N-formylannonain, Cordifolioside A, magnoflorine, tinocordiside, and syringin.[41] *In silico* analysis makes use of bioinformatics to analyze the molecular docking effectiveness

Table 2: Reported bioactive components

Plant part	Reported bioactive components
Whole plant	Diterpenes[8-14] Furanolactone diterpenes, Clerodane diterpene and derivatives, Columbin, Tinosporon, Tinosporides
	Aliphatic compounds[15-18] Octacosanol, Heptacosanol
	Others[10,11,19-23] Nonacosan-15-one3,(α,4-dihydroxy-3-methoxy-benzyl)-4-(4-hydroxy-3-methoxy-benzyl)-tetrahydrofuran, Giloin, Jatrorrhizine, Tinosporidine, Cordifolone, Tinosporon, Tinosporine, Tinosporol Tinosporic acid, 20p-hydroxyecdysone
STEM	Alkaloids[10,24] Berberine, Palmatine, Tinosponone and Tinocordioside Glycosides[5,19] 18-norclerodane glucoside, Furanoid diterpene glucoside, tinocordiside, Tinocordifolioside Cordioside, Cordifolioside a Cordifolioside b, Syringin, syringin apiosylglycoside Palmatosides, Cordifolisides A, B, C, D, E Steroids[17,18,23,26] Hydroxyecdysterone, Makisterone A, Giloinsterol, Beta Sitosterol Sesquiterpenoids[27,28] Tinocordifolins, Furano diterpene glucosides (Amritoside A, B, C, D)
ROOT	Alkaloids[25,29] Tembetarine, Magnoflorine Choline, Tinosporine, Isocolumbin, Palmatine, Tetrahydropalmatine

of plant-specific phytochemicals and target proteins on the virus. Innumerable research findings have been published on *in silico* experiments involving the activity of *T. cordifolia* against severe acute respiratory syndrome corona virus-2 (SARS-COV-2). The present review is an attempt to appraise the efficacy of *T. cordifolia* as an anti-viral agent and its usefulness in combating viral infections.

BIOACTIVE COMPONENTS OF *T. CORDIFOLIA* WITH ANTIVIRAL ACTIVITY

Among the many diverse classes of bioactive components that have been so far isolated from *T. cordifolia*, some have shown promising antiviral efficacy. These components have been studied through *in silico*, *in vitro,* and *in vivo* models. Some important bioactive components reported to have *in silico* antiviral efficacy are shown in Table 3. *T. cordifolia* extract has been extensively explored and reported for its use in combating the following viruses and viral infections.

HUMAN IMMUNODEFICIENCY VIRUS

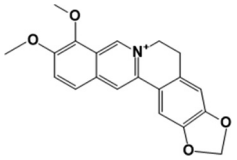
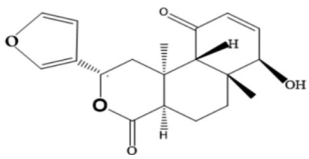
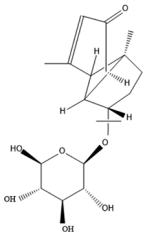
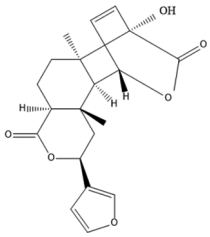
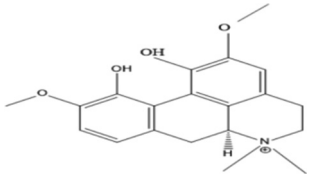
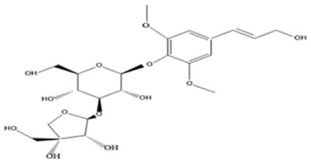
In a controlled trial where HIV-positive patients were administered *T. cordifolia* extract, it was observed that the treatment showed a reduction in eosinophil count, which can be attributed to its reported immunomodulatory effect. There were no significant changes in the average lymphocyte count. However, patients receiving *T. cordifolia* reported a decrease in clinical symptoms (Kalikar *et al*., 2008).[47] In Ayurveda, HIV infection is associated with ojokshaya (loss of vitality) for which Rasayana Chikitsa, which enhances immunity is considered the primary form of therapy. In a study involving HIV-positive patients, one group of subjects was orally administered Shilajatu (Mineral pi *T. cordifolia*) treated with *T. cordifolia*, *Centella asiatica,* and *Emblica officinalis* along with routine antiretroviral therapy (ART). It was found that these patients responded better in terms of clinical symptoms and biochemical profile thus showing an overall decrease in ART resistance.[48] In an *in vitro* experiment, the petroleum ether, ethanol, and aqueous extract of *T. cordifolia* stem powder was subjected to anti-HIV testing *in vitro* by employing reverse transcriptase (RT) inhibition assay and GP120 binding inhibition assay. It was observed that the petroleum ether and ethanol extracts of exhibited significant inhibition of GP120-CD4 binding and RT, respectively.[49] Ethanolic extracts of *T. cordifolia* leaves have been reported to possess considerable inhibitory activity against HIV protease.[50] In another *in vitro* study using peripheral blood mononuclear cells, ethyl acetate extract of dried leaves of *T. cordifolia*, at a concentration of 20 mg/mL, was reported to show a very high degree of 85% inhibition of HIV-1 RT almost at par with the standard drug, while exhibiting medium cell cytotoxicity.[51]

A herbal treatment of AIDS reported that *T. cordifolia* in a synergistic formulation with various other herbs stimulates immunity, enhances CD4 levels, and decreases viral load.[52] Another formulation consisting of chitin and 10% bioactive metabolite tinosporin from *T. cordifolia* claims to work as an immunostimulant along with the HIV-inhibitory action of the latter. The precise mode of action of tinosporin on HIV could not be deduced; however, it was reportedly attributed to inhibition of virus entry into cells or virus inactivation.[53]

H1N1 INFLUENZA

The novel H1N1 influenza A virus, causative agent of the 2009 outbreak, was deemed to originate from a genetically reassorted swine flu virus often causing severe infection with mortality, in immunocompromised patients.[54,55] Traditional medicine recommends an oral intake of a concoction of one foot long of *T. cordifolia* and seven leaves of *Ocimum* sps to prevent swine. The immunomodulatory activities of *T. cordifolia* enhance macrophage activation, induce immunoglobulin G antibodies levels in serum, and stimulate humoral and cell-mediated immunity, thus helping in

Table 3: Bioactive components of *T. cordifola* with reported *in silico* antiviral activity

Name of the compound with pubchem ID	Structure	Mode of activity
Berberine (2353)		*In silico* studies against 3CLpro Protease of SARS-CoV-2[42] Molecular docking studies against Surface glycoprotein and RNA-dependant RNA polymerase of SARS-CoV-2[43]
Tinosponone (15215479)		*In silico* studies against 3CLpro Protease of SARS-CoV-2[44]
Tinocordiside (177384)		*In silico* studies against Mpro Protease of SARS-CoV-2[45] *In silico* studies against receptor biding domain Surface of SARS-CoV-2[43]
Isocolumbin (24721165)		*In silico* studies against SARS-CoV-2 protease, glycoprotein, and RNA polymerase[43]
Magnoflorine (73337)		*In silico* studies against protease of SARS-CoV-2[43]
Cordiofoliside A (101676711)		*In silico* studies against spike 1 receptor binding protein of SARS-CoV-2 And *in vitro* against the SARS-CoV-2 S1-RBD using an enzyme-linked immunosorbent assay[46]

T. cordifolia: *Tinospora cordifolia*, 3CLpro: 3C-like protease, SARS-CoV-2: Severe acute respiratory syndrome corona virus-2, Mpro: Main protease, RBD: Receptor-binding domain

overcoming the flu symptoms and reduction of viral load.[56-58] Tinosporaside, a naturally occurring diterpene, isolated from *T. cordifolia* reportedly has antipyretic activity which can be efficiently used in the treatment of H1N1 patients.[59]

SARS-COV-2

COVID-19 caused by SARS-COV-2 emerged as the most significant pandemic affecting more than eight million people with high morbidity and mortality rates.[60] *T. cordifolia* was one of the plants which were extensively explored for its *in silico* analysis against the virus. Among the many proteins encoded by the SARS-CoV-2 genome, the primary drug targets include its main protease (Mpro), spike protein, RNA-dependent RNA polymerase, papain-like protease, and 3C-like protease (3CLpro). Two most important host proteins which aid in the SARS-COV-2 entry into host cells are angiotensin-converting enzyme-2 (ACE-2) and transmembrane protease, serine-2 (TMPRSS-2). The binding of viral spike (S)-protein to ACE-2 and its cleavage by TMPRSS-2 results in the viral entry into the host cells. Thus mode of action in the inhibition of the virus could include binding of the drug molecules to the host's ACE-2 and TMPRSS-2 receptors besides induction of immune stimulation of inflammatory mediators and TLRs.[61] Berberine, columbamin, columbine, magnoflorine,

menisperine, syringin, tinocordiside, and tinosporide, identified in the water and alcoholic extracts of *T. cordifiolia*, were docked against SARS-CoV-2 spike, Mpro, and RNA-dependent RNA polymerase. Columbin, tinocordiside, and tinosporaside had better docking scores of around -8 kcaL/moL for Mpro.[62] Tinocordiside, a phytochemical isolated from *T. cordifolia,* showed the highest binding affinity to the protease of SARS-COV-2, one of the prominent drug targets.[45] *T. cordifolia* bioactive compounds were investigated by molecular docking studies to analyze if they can interfere with ACE-2-virus spike protein receptor complex. Tinocordiside exhibits docking capacity, binding to the middle of ACE-2 receptor-binding domain (RBD) complex. Further, molecular dynamic studies revealed that this phytocompound could interfere with the electrostatic forces of the complex, thereby reducing its stability, in turn reducing its capacity to facilitate viral entry into cells.[63]

Tinocordiside, berberine, isocolumbin, and magnoflorine of *T. cordifolia* showed high binding efficacy against surface glycoprotein (6VSB) and Mpro (6Y84) which are the crucial targets for SARS-COV-2 alongside RBD (6M0J) and RNA-dependent RNA polymerase (6M71).[43] A study suggested that berberine, β-sitosterol, octacosanol, tetrahydropalmatine, and choline, isolated from this plant were found to be very active against targets such as 3CLpro I and II of the Mpro enzyme from SARS-COV-2.[42]

Apart from the above-mentioned phytocompounds, tinosponone also showed increased binding potential against the 3CLpro Mpro, a primary target of coronavirus.[44] 7-desacetoxy-6,7dehydrogedunin and columbin of *T. cordifolia* incurred great stability against 7NEG and Mpro (7MGS and 6LU7) and selected spike target (7NEG and 7NX7), respectively.[64]

The manufacturers of a commercial herbal formulation, Giloy Ghanavati, have reported its the effect of on influencing the measurable characteristics of SARS-CoV-2 spike-protein-induced disease in humanized zebrafish. The spike-protein induced elevated inflammatory response, fever, and kidney damage. The extract countermanded all the characteristics on par with the reference compound, Dexamethasone.[65]

HEPATITIS A VIRUS (HAV)

HAV is the etiological agent of the communicable water and food-borne hepatitis A infection. The whole plant of *T. cordifolia* was subject to ethanolic extraction and investigated for its anti-HAV efficacy in Huh-7 cell lines. The extract showed promising anti-HAV activity on par with that of the standard drug camptothecin.[66] Molecular docking studies have revealed that menispermacide, tinosporaside, and tinosporinone exhibited robust binding affinities with HAV and can be considered as potent anti-HAV drugs.[67]

HERPES SIMPLEX VIRUS

In an *in vitro* analysis, the crude extract *T. cordifolia* revealed significant activity against herpes simplex virus which causes oral sores or lesions. The antiviral assay was carried out in vero cell lines, wherein the crude extract of the plant showed considerable inhibition of 61.43%.[68]

CHIKUNGUNYA VIRUS

An experimental *in vitro* analysis of the antiviral activity of *T. cordifolia* silver nanoparticles (AgNPs) against chikungunya virus revealed promising results. The assay was based on the inhibition or reduction of cytopathic effects (CPE) of the virus in vero cells, measured by 3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide assay. The AgNps of *T. cordifolia* inhibited the CPE by 25–49%.[69]

AVIAN VIRUSES

T. cordifolia being an effective immunomodulator, which is recommended for use in poultry feed. In one research, the methanolic extract of *T. cordifolia* led to enhanced production of avian T- and B-cell.[70] Fortifying broiler feed with *T. cordifolia* significantly increased the humoral and cell-mediated immunity against Newcastle disease.[71] In a similar kind of study, an *in vivo* experiment to analyze the effect of *T. cordifolia* against the immunosuppressive chicken infectious anemia virus revealed promising results. In this investigation, the chickens in the treatment groups, which were fed with with 1% pure extract of *T. cordifolia* containing tinosporin, demonstrated better cellular immune responses with increased CD41 T-cell counts, in comparison to the chickens in the untreated virus infected control. The treated birds also presented a decreased viral load when compared to the untreated virus control group.[72,73]

Infectious bursal disease (IBD) leads to extreme immunosuppression in the young chicken population. The disease is caused by IBD virus (IBDV). In an *in vivo* study aimed to determine the immunomodulatory effects of *T. cordifolia* stem aqueous extract, chicks were infected with very virulent IBDV. Aqueous extract of the plant was given to the test group. The test group showed a considerable rise in the levels of IFN-γ, interleukin (IL-2), IL-4, and IL-1 post-IBD infection, and a decrease in mortality was observed. In addition, *T. cordifolia* extract alone and in combination with another immunostimulants showed improved vaccine response in terms of better antibody titer after vaccination.[74]

CONCLUSION

The battle against viral diseases and its devastating effects on mankind is an ongoing process, with an inevitable need

to develop better systems of disease management and novel anti-viral therapeutics. With the immense bioresources available in India, medicinal plants are promising explorable resources. *T. cordifolia* is an herb of potent medicinal value. In the present review, an attempt has been made to appraise the various facets of *T. cordifolia* as an antiviral agent and its role in combating viral infections. As detailed in the review, all parts of the plant show considerable activity against various viruses and are effective in therapeutic management of viral diseases. The presence of an interesting array of phytochemicals including alkaloids, terpenoids, flavonoids, phenols, and polysaccharides make *T. cordifolia* a potent anti-viral source. The plant also possesses significant immunostimulatory activity as evident from various studies. Amalgamating, in-depth, evidence-based investigations with innovative technology can lead to the development of potent antiviral drugs from *T. cordifolia.*

REFERENCES

1. World Health Organization. Progress Report by Director General Document No: A44/20. Geneva: World Health Organization; 1991.
2. Subhose V, Srinivas P, Narayana A. Basic principles of pharmaceutical science in Ayurvĕda. Bull Indian Inst Hist Med Hyderabad 2005;35:83-92.
3. Thornber CW. Alkaloids of the Menispermaceae. Phytochemistry 1970;9:157-87.
4. Kirtikar KR, Basu BD, editors. Indian Medicinal Plants. 2nd ed., Vol. 1. New Connaught Place, Dehradun: M/S Bishen Singh, Mahendra Pal Singh; 1975.
5. Saha S, Ghosh S. *Tinospora cordifolia*: One plant, many roles. Anc Sci Life 2012;31:151-9.
6. Ministry of Health and Family Welfare. The Ayurvedic Pharmacopoeia of India. Vol. 1. Part I. New Delhi: Ministry of Health and Family Welfare, Government of India; 1986.
7. Singh J, Sinha K, Sharma A, Mishra NP, Khanuja SP. Traditional uses of *Tinospora cordifolia* (Guduchi). J Med Aromat Plant Sci 2003;25:748-51.
8. Akhila A, Rani K, Thakur RS. Biosynthesis of the clerodane furano-diterpene lactone skeleton in *Tinospora cordifolia*. Phytochemistry 1991;30:2573-6.
9. Maurya R, Wazir V, Tyagi A, Kapil RS. Clerodane diterpene from *Tinospora cordifolia*. Phytochemistry 1995;38:659-61.
10. Hanuman JB, Bhatt RK, Sabata BK. A diterpenoid furanolactone from *Tinospora cordifolia.* Phytochemistry 1986;25:1677-80.
11. Hanuman JB, Bhatt RK, Sabata BK. A clerodane furano-diterpene from *Tinospora cordifolia.* J Nat Prod 1988;51:197-201.
12. Bhatt RK, Hanuman JB, Sabata BK. A new clerodane derivative from *Tinospora cordifolia*. Phytochemistry 1988;27:1212-6.
13. Khuda MQ, Khaleque A, Ray N. *Tinospora cordifolia* constituents of plants fresh from the field. Sci Res 1964;1:177-83.
14. Swaminathan K, Sinha UC, Bhatt RK, Sabata BK, Tavale SS. Structure of tinosporide, a diterpenoid furanolactone from *Tinospora cordifolia* Miers. Acta Crystallogr C 1989;45:134-6.
15. Thippeswamy G, Sheela ML, Salimath BP. Octacosanol isolated from *Tinospora cordifolia* downregulates VEGF gene expression by inhibiting nuclear translocation of NF-<kappa>B and its DNA binding activity. Eur J Pharmacol 2008;588:141-50.
16. Dixit SN, Khosla RL. Chemical investigations on *Tinospora cordifolia* (Willd.) Miers. Chem Abstr 1974;80:24816y.
17. Khaleque A, Miah MA, Huq MS, Basar KA. *Tinospora cordifolia* III. Isolation of tinosporine, heptacosanol, β sitosterol, Pakistan. J Sci Ind Res 1971;14:481.
18. Khaleque A, Miah MA, Huq MS, Basar KA. *Tinospora cordifolia* III. Isolation of tinosporine, heptacosanol, β sitosterol. Chem Abstr 1972;77:137377n.
19. Singh SS, Pandey SC, Srivastava S, Gupta VS, Patro B, Ghosh AC. Chemistry and medicinal properties of *Tinospora cordifolia* (Guduchi). Indian J Pharmacol 2003;35:83-91.
20. Kidwai AR, Salooja KC, Sharma VN, Siddiqui S. Chemical examination of *Tinospora cordifolia*. J Sci Indian Res 1949;8:115-8.
21. Bisset NG, Nwaiwu J. Quaternary alkaloids of *Tinospora* species. Planta Med 1983;48:275-9.
22. Qudrat-I-Khuda M, Khaleque A, Bashir A, Roufk MD, Ray N. Studies on Tinospora cordifolia-Isolation of tinosporon, tinosoric acid and tinosporol from fresh creeper. Sci Res 1966;3:9-12.
23. Pathak AK, Agarwal AK, Jain DC, Sharma RP, Howarth OW. NMR studies of a 20β-hydroxyecdysone, a steroid, isolated from *Tinospora cordifolia*. Indian J Chem 1995a;34B:674.
24. Pachey P, Schneidir J. Alkaloids from *Tinospora cordifolia* Miers. Arch Pharm 1981;314:251-6.
25. Maurya R, Wazir V, Kapil A, Kapil RS. Cordifolioside A and B, two new phenylpropene disaccharides from *Tinospora cordifolia* possessing immunostimulant activity. Nat Prod Lett 1996;8:7-10.
26. Gangan VD, Pradhan P, Sipahimalani AT. Phytoecdysones from *Tinospora cordifolia*: Structural elucidation of ecdysterone and makisterone A by 2D NMR spectroscopy. Indian J Chem 1997;36:787-92.
27. Maurya R, Handa SS. Tinocordifolin, a sesquiterpene from *Tinospora cordifolia*. Phytochemistry 1998;49:1343-5.
28. Maurya R, Manhas LR, Gupta P, Mishra PK, Singh G, Yadav PP. Amritosides A, B, C and D: Clerodane furano diterpene glucosides from *Tinospora cordifolia*. Phytochemistry 2004;65:2051-5.
29. Pathak AK, Jain DC, Sharma RP. Chemistry and biological activities of the genus *Tinospora*. Int J Pharmacogn 1995b;33:277-87.

30. Hackett CJ. Innate immune activation as a broad-spectrum biodefense strategy: Prospects and research challenges. J Allergy Clin Immunol 2003;112:686-94.
31. Mueller SN, Rouse BT. Immune responses to viruses. In: Rich RR, Fleisher TA, Shearer WT, Schroeder HW, Frew AJ, Weyand CM, editors. Clinical Immunology. 3rd ed. United States: Mosby; 2008. p. 421-31.
32. García-Sastre A, Biron CA. Type 1 interferons and the virus-host relationship: A lesson in detente. Science 2006;312:879-82.
33. Malik YS, Kuldeep S, Jeena LM, Naveen K, Sircar S, Rajak KK, *et al*. Tollâ€ receptors: The innate immune receptors with ingenious antiâ€ viral paradigm. South Asian J Exp Biol 2013;3:207-13.
34. Rege N, Bapat RD, Koti R, Desai NK, Dahanukar S. Immunotherapy with *Tinospora cordifolia*: A new lead in the management of obstructive jaundice. Indian J Gastroenterol 1993;12:5-8.
35. Nagarkatti DS, Rege NN, Desai NK, Dahanukar SA. Modulation of kupffer cell activity by *Tinospora cordifolia* in liver damage. J Postgrad Med 1994;40:65-7.
36. Thatte UM, Chhabria S, Karandikar SM, Dahanukar SA. Immunotherapeutic modification of *Escherichia coli* induced abdominal sepsis and mortality in mice by Indian medicinal plants. Indian Drugs 1987;25:95-7.
37. Thatte UM, Dahanukar SA. Immunotherapeutic modification of experimental infections by Indian medicinal plants. Phytother Res 1989;3:43-9.
38. Kapil A, Sharma S. Immunopotentiating compounds from *Tinospora cordifolia*. J Ethnopharmacol 1997;58:89-95.
39. Nair PK, Rodriguez S, Ramachandran R, Alamo A, Melnick SJ, Escalon E, *et al*. Immune stimulating properties of a novel polysaccharide from the medicinal plant *Tinospora cordifolia*. Int Immunopharmacol 2004;4:1645-59.
40. Nair PK, Melnick SJ, Ramachandran R, Escalon E, Ramachandran C. Mechanism of macrophage activation by (1,4)-alpha-D-glucan isolated from *Tinospora cordifolia*. Int Immunopharmacol 2006;6:1815-24.
41. Sharma U, Bala M, Kumar N, Singh B, Munshi RK, Bhalerao S. Immunomodulatory active compounds from *Tinospora cordifolia*. J Ethnopharmacol 2012;141:918-26.
42. Chowdhury P. *In silico* investigation of phytoconstituents from Indian medicinal herb '*Tinospora cordifolia* (giloy)' against SARS-CoV-2 (COVID-19) by molecular dynamics approach. J Biomol Struct Dyn 2021;39:6792-809.
43. Sagar V, Kumar HS. Efficacy of natural compounds from *Tinospora cordifolia* against SARS-CoV-2 protease, surface glycoprotein and RNA polymerase. Biol Eng Med Sci Rep 2020;6:6-8.
44. Krupanidhi S, Peele KA, Venkateswarulu TC, Ayyagari VS, Bobby MN, Babu DJ, *et al.* Screening of phytochemical compounds of *Tinospora cordifolia* for their inhibitory activity on SARS-CoV-2: An *in silico* study. *J Biomol Struct Dyn* 2020;39:5799-803.
45. Shree P, Mishra P, Selvaraj C, Singh SK, Chaube R, Garg N, *et al*. Targeting COVID-19 (SARS-CoV-2) main protease through active phytochemicals of ayurvedic medicinal plants - *Withania somnifera* (Ashwagandha), *Tinospora cordifolia* (Giloy) and *Ocimum sanctum* (Tulsi) - a molecular docking study. J Biomol Struct Dyn 2020;40:190-203.
46. Basnet S, Marahatha R, Shrestha A, Bhattarai S, Katuwal S, Sharma KR, *et al*. *In vitro* and *in silico* studies for the identification of potent metabolites of some high-altitude medicinal plants from Nepal inhibiting SARS-CoV-2 spike protein. Molecules 2022;27:8957.
47. Kalikar MV, Thawani VR, Varadpande UK, Sontakke SD, Singh RP, Khiyani RK. Immunomodulatory effect of *Tinospora cordifolia* extract in human immuno-deficiency virus positive patients. Indian J Pharmacol 2008;40:107-10.
48. Gupta GD, Sujatha N, Dhanik A, Rai NP. Clinical evaluation of Shilajatu Rasayana in patients with HIV infection. Ayu 2010;31:28-32.
49. Rege AA, Ambaye RY, Deshmukh RA. *In vitro* testing of anti-HIV activity of some medicinal plants. Indian J Nat Prod Resour 2010;1:193-9.
50. Rege A, Chowdhary AS. Evaluation of *Ocimum sanctum* and *Tinospora cordifolia* as probable HIV-protease inhibitors. Int J Pharm Sci Rev Res 2014;25:315-8.
51. Estari M, Venkanna L, Reddy AS. *In vitro* anti-HIV activity of crude extracts from *Tinospora cordifolia*. BMC Infect Dis 2012;12:P10.
52. Ayare S. Herbal Compositions for Effective Treatment of Aids, Preparation Thereof and Method for Treatment of Aids Patients. Publication Number. WO2005030232;2005.
53. Balar C, Nakum A. Composition Comprising Chitin and Tinosporin for Use in the Treatment of Viral Diseases. Publication Number. WO2011135578A1; 2011.
54. Michaelis M, Doerr HW, Cinatl J Jr. An influenza A H1N1 virus revival-pandemic H1N1/09 virus. Infection 2009;37:381-9.
55. Harish M, Ruhatiya RS. Influenza H1N1 infection in immunocompromised host: A concise review. Lung India 2019;36:330-6.
56. Shah A, Krishnamurthy R. Swine flu and its herbal remedies. Int J Eng Sci 2013;2:68-78.
57. Fortunatov MN. Experimental use of phytoncides for therapeutic and prophylactic purpose. Vopr Pediatrii Okhr Materin 1952;20:55-8.
58. Winston D, Maimes S. Adaptogens: Herbs for Strength, Stamina, and Stress Relief. Rochester: Healing Arts Press; 2007.
59. Baghel AS, Tiwari A, Gupta N, Gour M, Pinge K. A review on Swine Flu treatment by tribal medicines using *Tinospora cordifolia*. Int J Pharm Life Sci 2017;8:33.
60. Singh RS, Singh A, Kaur H, Batra G, Sarma P, Kaur H, *et al*. Promising traditional Indian medicinal plants for the management of novel coronavirus disease:

A systematic review. Phytother Res 2021;35:4456-84.
61. Malekmohammad K, Rafieian-Kopaei M. Mechanistic aspects of medicinal plants and secondary metabolites against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Curr Pharm Des 2021;27:3996-4007.
62. Borse S, Joshi M, Saggam A, Bhat V, Walia S, Marathe A, *et al*. Ayurveda botanicals in COVID-19 management: An *in silico* multi-target approach. PLoS One 2021;16:e0248479.
63. Balkrishna A, Pokhrel S, Varshney A. Tinocordiside from *Tinospora cordifolia* (Giloy) may curb SARS-CoV-2 contagion by disrupting the electrostatic interactions between host ACE2 and viral S-protein receptor binding domain. Comb Chem High Throughput Screen 2021;24:1795-802.
64. Choudhary P, Singh T, Amod A, Singh S. Evaluation of phytoconstituents of *Tinospora cordifolia* against K417N and N501Y mutant spike glycoprotein and main protease of SARS-CoV-2-an *in silico* study. J Biomol Struct Dyn 2022;25:4106-23.
65. Balkrishna A, Khandrika L, Varshney A. Giloy ghanvati (*Tinospora cordifolia* (Willd.) Hook. f. and Thomson) reversed SARS-CoV-2 viral spike-protein induced disease phenotype in the xenotransplant model of humanized zebrafish. Front Pharmacol 2021;12:635510.
66. Maddi R, Kandula VL, Vallepu B, Navuluri H, Kollu H. Preliminary phytochemical analysis and *in vitro* antiviral activity of ethanolic extract of whole plant of *Tinospora cordifolia* (Thunb.) miers against hepatitis-A virus. *Int J Sci Res Biol Sci* 2018;5:51-5.
67. Moharana M, Maharana PC, Pattanayak SK, Khan F. Effect of temperature on hepatitis a virus and exploration of binding mode mechanism of phytochemicals from *Tinospora cordifolia*: An insight into molecular docking, MM/GBSA, and molecular dynamics simulation study. J Biomol Struct Dyn 2023;42:598-614.
68. Pruthvish R, Gopinatha SM. Antiviral prospective of *Tinospora cordifolia* on HSV-1. Int J Curr Microbiol Appl Sci 2018;7:3617-24.
69. Sharma V, Kaushik S, Pandit P, Dhull D, Yadav JP, Kaushik S. Green synthesis of silver nanoparticles from medicinal plants and evaluation of their antiviral potential against chikungunya virus. Appl Microbiol Biotechnol 2019;103:881-91.
70. Sonu A, Sonam S, Jyoti V, Osman MS, Uma M. *In vitro* immunopotentiating effects of *Tinospora cordifolia* in chicken lymphocytes culture system. J Immunol Immunopathol 2013;15:113-4.
71. Rajkumar RS, Yadav AS, Kirupasankar M, Saxena VK, Sangeeta S. Effect of *Tinospora cordifolia* supplementation on immunity of broiler chicks. Indian Vet J 2009;86:1244-5.
72. Latheef SK, Dhama K, Wani MY, Samad HA, Barathidasan R, Tiwari R, *et al*. Ameliorative effects of four herbs (*Withania somnifera*, *Tinospora cordifolia, Azadirachta indica* and E Care Se Herbal) on the pathogenesis of chicken infectious anaemia virus. Int J Curr Res 2013;5:2327-31.
73. Latheef SK, Dhama K, Samad HA, Wani MY, Kumar MA, Palanivelu M, *et al*. Immunomodulatory and prophylactic efficacy of herbal extracts against experimentally induced chicken infectious anaemia in chicks: Assessing the viral load and cell mediated immunity. Virusdisease 2017;28:115-20.
74. Sachan S, Dhama K, Latheef SK, Abdul Samad H, Mariappan AK, Munuswamy P, *et al*. Immunomodulatory potential of *Tinospora cordifolia* and CpG ODN (TLR21 agonist) against the very virulent, infectious bursal disease virus in SPF chicks. Vaccines (Basel) 2019;7:106.

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