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Phytochemical analysis of *Tinospora cordifolia* & *Withania somnifera* and their therapeutic activities with special reference to COVID-19

Prateek Rai, Tanya Garain, Deepshikha Gupta

Abstract

Various important medicines make use of the secondary metabolites which are produced by plants. Medicinal plants, such as *Withania somnifera* and *Tinospora cordifolia*, are rich sources of chemically active compounds and are reported to have numerous therapeutic applications. The therapeutic use of medicinal plants is widely mentioned in Ayurveda, and they have a lot of folkloric importance in different parts of the world. *Tinospora cordifolia*, also known as *Giloy*, is considered as 'Amrit' in ancient texts. *T. cordifolia* can be utilized in the treatment of several ailments such as diabetes, dyspepsia, fever, urinary problems, cardiac diseases, etc. *Withania somnifera*, which is commonly known as *Ashwagandha*, is a popular Indian medicinal plant. Withaferin A, an important drug, used solely or after combining with other drugs, is obtained from the roots of the *Withania somnifera* plant. This review article aims to summarize the phytochemical profiling, folkloric importance, and prominent pharmacological activities of *Withania somnifera* and *Tinospora cordifolia* with special emphasis on their action against Novel Coronavirus.

INTRODUCTION

Immunomodulators are natural or synthetic chemical substances that are used to provide therapeutic aid by modifying and regulating the immune system, which is the

first barrier against infectious diseases. Based on their pertinent actions, immunomodulators are typically categorized into three groups in clinical settings: Immunosuppressants, immunostimulants, and immunoadjuvants. Immunomodulatory activities have been reported time and again for their cytotoxic nature and several side effects. As a result, the use of plant products for medicinal purposes has become more popular in recent years. Plants have long been utilized for medicinal and therapeutic purposes. Certain pharmacologically active secondary metabolites produced by medicinal plants include alkaloids, steroids, glycosides, flavonoids, polyphenols and terpenoids. In Ayurvedic literature, these medicinal plants are regarded as 'Rasayana' and are known as 'Amrita' which indicates their significant properties for medical use. These plants are analyzed for the above-mentioned chemical compounds which can be further utilized for the synthesis of active drugs targets. The isolation of these phytochemicals is done using various solvents like alcohols, ether, dichloromethane or chloroform from the dried plant material. Plant based nutraceuticals can aid in the prevention of viral invasion. Glutathione and functional amino acids (such as arginine, cysteine, glutamate, glutamine, glycine, taurine, and tryptophan), which are plentiful in diets derived from animals, are essential for both human and animal health and immunity.

Tinospora cordifolia is a climber that belongs to the *Menispermaceae* family prominently found in the Indian subcontinent and some of the African countries. *T. cordifolia* finds a huge amount of importance for its medicinal properties. In Hindi, it is called 'Giloy' which according to Hindu mythology means a potion that has helped the Gods to stay permanently young.

Withania somnifera, or winter cherry, or Indian ginseng, is from the family of *Solanaceae* and is a xerophytic plant found in the arid areas and also at higher altitude areas (ascending 5,500 feet) of the Himalayas. The extracts of *Withania somnifera* have been reported to show outstanding immunomodulation by activation of macrophages which are involved in the destruction of various pathogens like bacteria, fungi, viruses, etc.

A comprehensive literature search was done that covered all important articles published on *T. cordifolia* and *W. somnifera* since 1996 till date of communicating the manuscript using PubMed central, Scopus and Google scholar. The duplicated articles were merged. The primary outcome of this review is re-establishing the medicinal importance of these two plants, with reference to the important constituents present in their extracts. Their medicinal properties may be correlated to the alkaloids, terpenoids, phenolics, flavonoids, and saponins present in them. In the current state of art, the potential of these plants to be used as an antiviral agent against SARS-CoV, and SARS-CoV 2 is the secondary outcome of this literature review.

Detection of various classes of phytochemicals from *T. cordifolia* and *W. somnifera*

Both *T. cordifolia* and *W. somnifera* contain varied class of phytochemicals which are responsible for their role in Aryurvedic, and Unani system of medicine (6,30). Table 1 describes the various classes of phytoconstituents reported to be present in both *T. cordifolia* and *W. somnifera* extracts and their diagnostic tests.

Figure 1 and figure 2 depict some of the important phytoconstituents responsible for immense pharmacological activity of *T. cordifolia* and *W. somnifera*. Xia *et al* have recently attempted to list all the naturally occurring withanolides in all the *Withania* sp. (43)

Pharmacological action of *Tinospora cordifolia* and *Withania somnifera*

Based on the literature available subjecting to the therapeutic uses of *T. cordifolia*, it can be said that it possesses various important medicinal properties such as immunostimulatory, anti-microbial, antioxidant and hepatoprotective. It has been reported that glycosides such as Cordifolioside A, B, and Syringin are the main active compounds that are responsible for the immunomodulatory action of *T. cordifolia* (18,22,40,55–60) Tinocordiside (50), cordioside, palmatosides were found to show neuroprotective character and treat parkinson and dementia. Borapetoside C was an active antidiabetic agent (61). Main immunomodulatory substances were 11-

hydroxymustakone, N-methyl-2-pyrrolidone, N-formylannonain, Cordiofolioside A, Syringin. Furanolactone, and tinosporides were reported to have anti-inflammatory action in viral diseases whereas tinosporin, isocolumbin, palmatine, and berberine showed anticancer effects (49).

It has been reported that the main pharmacological activities of *Withania somnifera* are accounted to withanolides having steroidal nucleus which are believed to serve as prominent precursors for the synthesis of hormones. Withaferin A and withanolide D are examples of such compounds (51,52,54,62–65). Withanolides are found to be potent anti-cancer, anti-inflammatory, antibacterial, and anti-leishmaniasis agents (65). 3- β -hydroxy-2,3-dihydro-withanolide was reported to be neuroprotective in nature (66). Withanamide (A-H) help neutralize the toxicity of β -amyloid protein and protect the cells from cell death, effective in treating Alzheimer's disease, and has ability to inhibit lipid peroxidation (67) 4 β , 20-dihydroxy-i-oxo-5 β ,6 β , epoxy-witha-2,24-dienolide was found to have antitumour activity. Withanolide-E showed antifeedant activity (43). Sitoindoside IX, X were responsible for immunomodulatory activity of *Withania* species.

Immunomodulatory action against Novel Coronavirus

The importance of medicinally important natural products has increased due to the present calamitous situation of (68–71). The lack of an effective medicine or vaccine has led the researchers to search for such natural products that are easily available and can help to fight this disease by either being viricidal or by strengthening the immunity system. Proper understanding of the interaction between coronavirus and the cell-surface receptors forms the basis of developing curative medications to combat Novel Coronavirus. Several medicinal plants have been reported to produce pharmacologically active compounds. These compounds show effective antiviral properties (1,72). This study is formulated by studying the natural compounds that reduce the risk of coronavirus infection by inhibiting the viral entry into the host cell. *Withania somnifera* and *Tinospora cordifolia* have proven to be one of the most important plants in combating novel coronavirus. Computational studies have been carried out to

understand the efficacy of active compounds obtained from both these plants against coronavirus (30).

Studies conducted on the phytochemicals of *Withania somnifera* have shown that they have great potential to act as antiviral agents against many viral diseases like HPV, H1N1, Herpes simplex, SARS-CoV, and SARS-CoV 2. The Indian Government, the Indian Council of Medical Research (ICMR), and the Council of Scientific and Industrial Research (CSIR) have issued advisories, emphasizing the consumption of *Withania somnifera* as a therapeutic agent against COVID-19 (64,73–76). The main active constituent of *Withania somnifera* is withanolide, as mentioned previously. Significant and effective biological actions have been seen by Withanolide D, Withaferin-A, and Withanoside I-VII in managing COVID-19. Molecular docking techniques have suggested that natural ingredients of *Withania somnifera* namely, Withanone, Caffeic acid phenyl ester and some other biologically active substances interact with receptor cells of novel coronavirus and impedes its interaction with the host cell (77,78). In a docking study carried out by Borse *et al*, Ashwagandhanolide has shown highest docking score (-9.9 Kcal/mol) for all 3 SARS-CoV-2 protein targets its drug-likeness (70). Molecular docking results by Prajapati showed that flavone glycoside, sugar alcohol, and flavonoid present in *W. somnifera* showed - 11.69, - 11.61, - 10.1, - 7.71 kcal/mole binding potential against S-protein, CD26, RdRp, and TMPRSS2 proteins (79).

There are 28 important phytochemicals present in *Tinospora cordifolia* and out of these, one of the active ingredients known as Tinocordiside shows great binding affinity to the novel coronavirus. This phytochemical has proven to be an effective immunomodulator and has been found to inhibit the infection of the host cell from coronavirus (50,80–85). Docking analysis and ADMET properties revealed that 6 of 31 potential constituents (alkaloids. Steroids and terpenoids) from the extract of *T. cordifolia* found to have strong interactions with human receptor for SARS-CoV-2 could prevent the entry of the virus and thus could act as a prophylactic for COVID-19 (86). A ketone, tinosponone from *T. cordifolia* is a strong inhibitor of 3CL major protease of SARS-CoV-2, as demonstrated by

the computer-aided drug design technique. Furthermore, confirmation of its inhibitory action on SARS-CoV-2 will need to be done by *in vitro* and *in vivo* research (87). Silico studies revealed ¹Saponarin, a phytochemical present in *T. cordifolia* showed a very promising result with the binding affinity of -8.75 kcal/mol and a potential inhibitor for main protease of the COVID-19 (86-89). In another study conducted by Thakkar *et al.*, ³Columbin, Tinosporide, N-trans-feruloyl-tyramine-diacetate, Amritoside C, Amritoside B, Amritoside A, Tinocordifolin, Palmatoside G, Palmatoside F, and Maslinic acids are the key molecules based on their docking score (range between -5.02 to -5.72 Kcal/mol) (88,90).

Giloy, however, has been linked in certain studies to autoimmune-featured acute hepatitis and can reveal autoimmune hepatitis in patients. In the interest of public health, further research on the safety (and effectiveness) of unproven but highly marketed herbal remedies in alternative medical systems is lacking, and it is particularly crucial in light of the current worldwide health crisis (91,92).

CONCLUSION

This review has laid necessary evidence that both the plants, *i.e.*, *Tinospora cordifolia* and *Withania somnifera*, hold a special place in the ancient texts and they have proved to be equally important in modern medicines. Their extraction and phytochemical analysis have revealed that they are rich sources of numerous biologically active compounds. Since, the COVID-19 pandemic outbreak, a huge amount of attention has been directed towards increasing the immunity of the human body against various pathogens such as bacteria, viruses, *etc.* The immunomodulatory activities of *Tinospora cordifolia* and *Withania somnifera* have been a part of Ayurvedic medication for a long time. In recent times, clinical studies on the products obtained from these plants have confirmed their therapeutic action in benefiting the body's immune system.

While the preliminary findings are promising, further clinical trials and research are essential to establish standardized dosages, safety, and efficacy of these phytochemicals in the context of COVID-19. Integration of these herbal remedies with conventional

treatments could offer a holistic approach to managing the disease, improving patient outcomes, and enhancing overall health resilience. In conclusion, *Tinospora cordifolia* and *Withania somnifera* hold significant therapeutic potential, particularly as supportive treatments in the fight against COVID-19. Their rich phytochemical composition and multifaceted health benefits underscore the importance of further research and validation in clinical settings.

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