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**Rahmati M, Moghtaderi H, Mohammadi S, Al-Harrasi A.** Aryl hydrocarbon receptor dynamics in esophageal squamous cell carcinoma: From immune modulation to therapeutic opportunities. *World J Exp Med* 2024; 14(3): 96269 [DOI: [10.5493/wjem.v14.i3.96269](https://doi.org/10.5493/wjem.v14.i3.96269)]

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

Prateek Rai, Tanya Garain, Deepshikha Gupta

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## Abstract

Various important medicines make use of secondary metabolites that 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 has folkloric importance in different parts of the world. The aim of this review is to summarize the phytochemical profiles, folkloric importance, and primary pharmacological activity of *W. somnifera* and *T. cordifolia* with emphasis on their action against the novel coronavirus.

**Key Words:** Phytochemical analysis; *Tinospora cordifolia*; *Withania somnifera*; COVID-19; Immunomodulators; Giloy; Ashwagandha

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**Core Tip:** This review provides insights into the phytochemical profiles and therapeutic activities of *Tinospora cordifolia* and *Withania somnifera*, which are medicinally significant plants of great importance in the practice of traditional medicine. Currently, the potential of these plants as antiviral agents against severe acute respiratory syndrome coronavirus (SARS-CoV), particularly SARS-CoV-2, is of interest.

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## INTRODUCTION

Immunomodulators are natural or synthetic chemical substances that are used to treat infectious diseases by modifying and regulating the immune system, which is the first barrier. Immunomodulators are generally grouped into three categories by their activity as immunosuppressants, immunostimulants, and immunoadjuvants[1]. Cytotoxicity and side effects reported to be associated with immunomodulators have led to the increased use of plant products for medicinal purposes in recent years. Plants have long been used for medicinal and therapeutic purposes. Pharmacologically active secondary metabolites produced by medicinal plants include alkaloids, steroids, glycosides, flavonoids, polyphenols and terpenoids[2-6]. In Ayurvedic literature, these medicinal plants are regarded as “Rasayana” and are known as “Amrita,” which indicates they have significant medical properties and uses[7-12]. These plants have been analyzed for the presence of chemical compounds, such as those mentioned above, that can be used in the synthesis of drugs with target activity. Phytochemicals are isolated from dried plant material with various solvents including alcohols, ether, dichloromethane, or chloroform[13-16]. 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 food derived from animals, are essential for both human and animal health and immunity.

*Tinospora cordifolia* is a climbing plant in family *Menispermaceae* and grows throughout the Indian subcontinent and in some African countries *T. cordifolia* is important because of its medicinal properties. In Hindi, it is called giloy, which in Hindu mythology is a potion that helped the Gods stay permanently young[17-23]. *Withania somnifera*, known as winter cherry, or Indian ginseng[24], is a xerophytic plant in family *Solanaceae* and is found in arid areas and at altitudes above 5500 feet in the Himalayas. Strong immunomodulation by extracts of *W. somnifera* have been reported and were associated with activation of macrophages that are involved in the destruction of various pathogens like bacteria, fungi, viruses, etc[6,25-29].

A comprehensive search of PubMed Central, Scopus, and Google Scholar of all important articles published on *T. cordifolia* and *W. somnifera* from 1996 until the writing of this review manuscript was performed. Duplicate articles were merged. The primary outcome of this review was re-establishing the medicinal importance of these two plants, with reference to the important constituents present in their extracts. Their medicinal properties were attributed to the alkaloids, terpenoids, phenolics, flavonoids, and saponins that they contain. The potential of these plants to be used as antiviral agents against severe acute respiratory syndrome coronavirus (SARS-CoV), and SARS-CoV-2 in particular, was the secondary outcome.

## DETECTION OF VARIOUS CLASSES OF PHYTOCHEMICALS FROM *T. CORDIFOLIA* AND *W. SOMNIFERA*

*T. cordifolia* and *W. somnifera* contain various classes of phytochemicals that are responsible for their role in Ayurvedic and Unani medicine[6,30]. Table 1 describes the various classes of phytoconstituents reported to be present in both *T. cordifolia* and *W. somnifera* extracts. Both medicinal plants were found to contain alkaloids, phenolics, saponins, glycosides, steroids, phytosterols, flavonoids, carbohydrates, and amino acids as the major classes of natural products. These classes were evaluated by diagnostic testing as mentioned in Table 1[31-54]. Figures 1 and 2 show some of the important phytoconstituents responsible for the broad pharmacological activity of *T. cordifolia* and *W. somnifera*. Xia et al[43] recently attempted to list all the withanolides present in all the *Withania* species.

## PHARMACOLOGICAL ACTIVITY OF *T. CORDIFOLIA* AND *W. SOMNIFERA*

The literature available on the therapeutic uses of *T. cordifolia* indicates that it possesses important medicinal properties, including immunostimulatory, microbial, antioxidant, and hepatoprotective activities. It has been reported that glycosides such as cordifolioside A and B and syringin are the compounds primarily responsible for the immunomodulatory activity of *T. cordifolia*[18,22,35,40,55-60]. Tinocordiside[50], cordioside, and palmatosides were found to have neuroprotective activity in Parkinson’s disease and dementia[44-50], and borapetoside C had antidiabetic activity[61]. The immunomodulatory substances included 11-hydroxymustakone, N-methyl-2-pyrrolidone, N-formylannonain, cordiofolioside A, and syringin. Furanolactone, and tinosporides were reported to have anti-inflammatory action in viral diseases, and tinosporin, isocolumbin, palmatine, and berberine had anticancer activity[49].

It has been reported that withanolides with steroidal cores account for the primary pharmacological activity of *W. somnifera* and are believed to be precursors in the synthesis of hormones. Withaferin A and withanolide D are examples of such compounds[51-54,62-65]. Withanolides were found to be potent anticancer, anti-inflammatory, antibacterial, and

**Table 1** Various classes of phytoconstituents reported to be present in both *Tinospora cordifolia* and *Withania somnifera* extracts and their diagnostic tests

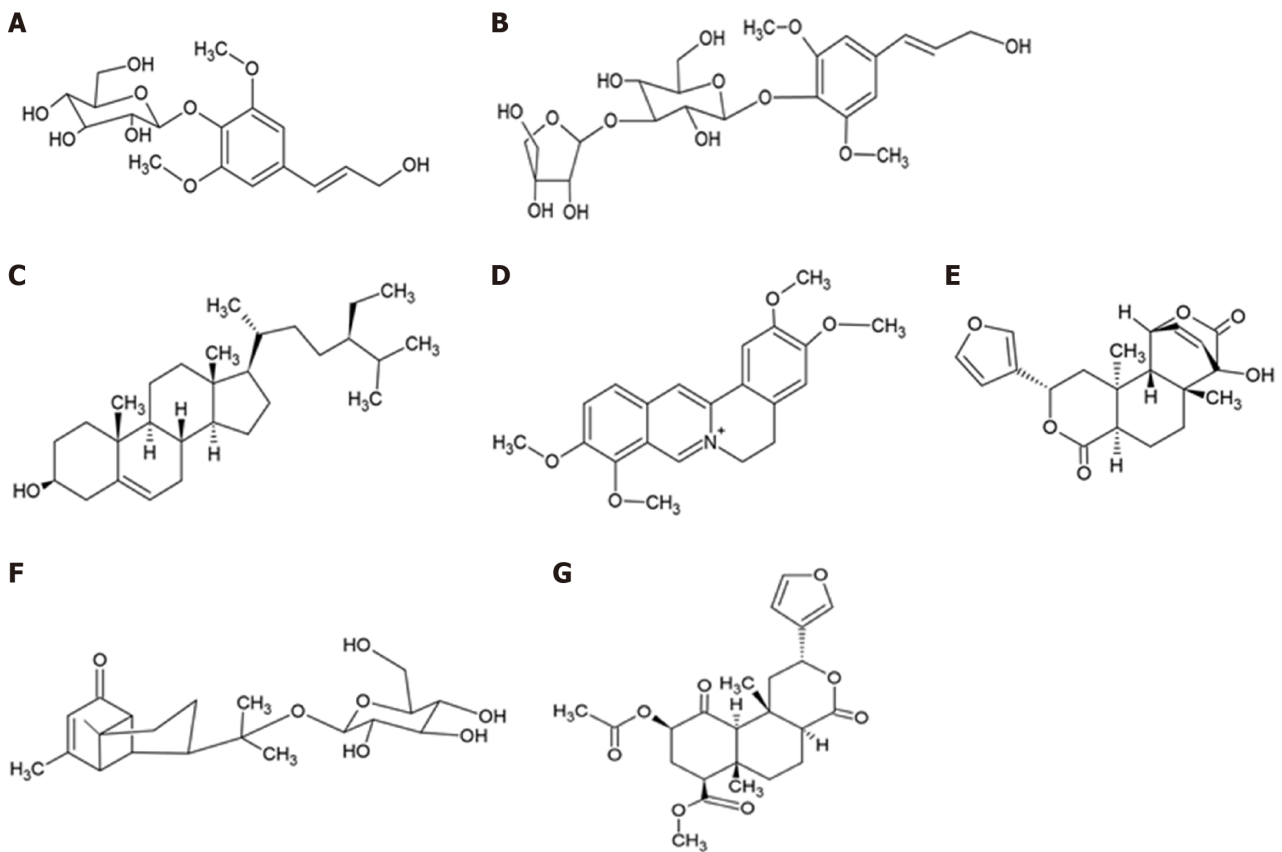
S/No.	Compound class	Tests	<i>Tinospora cordifolia</i>					<i>Withania somnifera</i>				
			Extract types	A	B	C	D	E	A	B	C	D
1	Alkaloids	Mayer's test	√	√	√	√	X	X	X	X	√	X
		Dragendorff's test	√	√	√	√	X	X	X	X	√	X
		Hager's test	√	√	√	√	X	X	X	X	√	X
2	Glycosides	Legal's test	X	X	√	√	X	X	X	√	√	X
3	Phenols	Ferric chloride test	√	√	√	√	X	X	X	√	√	X
4	Saponins	Foam test	X	√	√	√	X	X	X	X	√	X
5	Steroids and Terpenoids	Liebermann-Burchard's test	X	X	X	X	√	√	X	X	√	X
6	Phytosterols	Salkowski's test	X	X	√	X	√	√	X	X	X	X
7	Flavonoids	Alkaline reagent test	√	√	√	√	X	X	X	X	X	√
8	Amino acids and Proteins	Ninhydrin test	√	X	√	√	X	X	X	X	X	√
9	Carbohydrates	Molisch's test	√	X	√	√	X	X	X	√	√	X
		Fehling's test	√	√	√	√	X	X	X	√	√	X

A: Hexane extract; B: Chloroform extract; C: Ethyl acetate extract; D: Alcohol extract; E: Aqueous extract; F: Hydroalcoholic extract. 'X' indicates not detected; '√' indicates detected.

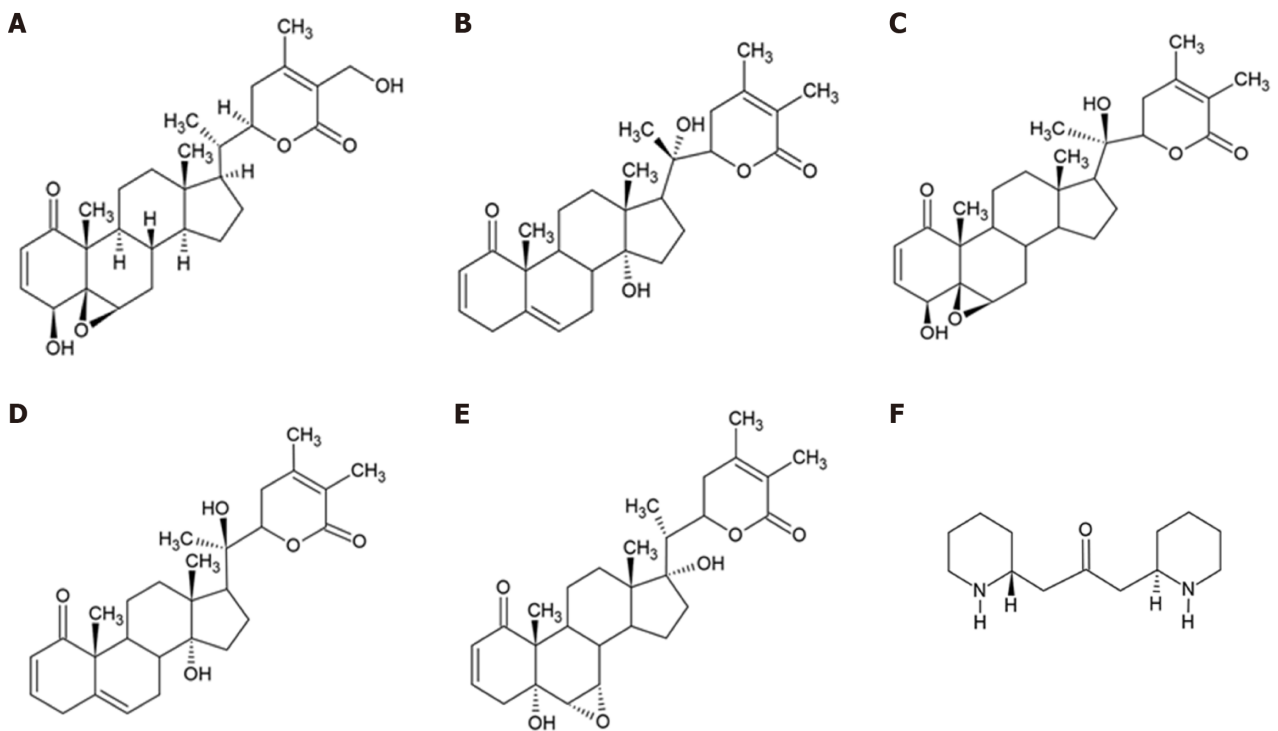
antileishmaniasis agents[65], and 3- $\beta$ -hydroxy-2,3-dihydro-withanolide was reported to be neuroprotective[66]. Withanamide (A-H) was shown to help neutralize the toxicity of  $\beta$ -amyloid protein and protect against cell death in Alzheimer's disease. It also inhibited lipid peroxidation[67]. The compound 4 $\beta$ , 20-dihydroxy-i-oxo-5 $\beta$ ,6 $\beta$ , epoxy-witha-2,24-dienolide was found to have antitumor activity. Withanolide-E had antifeedant activity[43]. Sitoindosides IX and X were responsible for the immunomodulatory activity of the *Withania* species. Bioactive constituents present in *Withania* such as withanosides, sitoindosides, steroidal lactones, and alkaloids were found to have a broad spectrum of therapeutic potential[35].

## IMMUNOMODULATORY ACTION AGAINST NOVEL CORONAVIRUS

The importance of medicinally important natural products has increased because of the coronavirus disease 2019 (COVID-19) pandemic and its aftermath[68-71]. The lack of an effective medicine or vaccines led investigators to search for natural products that are easily available and can help fight this disease either by being viricidal or by strengthening the immune system. Proper understanding of the interaction between the coronavirus and cell-surface receptors forms the basis of developing curative medications to combat novel coronavirus. Several medicinal plants have been reported to



**Figure 1** Important compounds isolated from *Tinospora cordifolia*. A: Syringin; B: Cordiofolioside A; C:  $\beta$ -sitosterol; D: Palmatine; E: Columbin; F: Tinocordiside; G: Furanolactone.



**Figure 2** Important compounds isolated from *Withania somnifera*. A: Withaferin A; B: Withanolide A; C: Withanolide D; D: Withanolide G; E: Withanone; F: Anaferrine.



produce pharmacologically active compounds that have effective antiviral properties[1,72]. This study included natural compounds that reduce the risk of coronavirus infection by inhibiting viral entry into the host cell. *W. somnifera* and *T. cordifolia* have proven to be among the most important plants in combating novel coronavirus. Computational studies have been carried out to determine the efficacy of active compounds obtained from both plants against coronavirus[30].

Studies of the phytochemicals of *W. somnifera* have shown them to have great potential as antiviral agents for treating viral diseases, including human papillomavirus, H1N1 influenza, *Herpes simplex*, SARS-CoV, and SARS-CoV-2. The Indian Government, the Indian Council of Medical Research, and the Council of Scientific and Industrial Research have issued advisories emphasizing the use of *W. somnifera* as a therapeutic agent against COVID-19[64,73-76]. As mentioned previously, withanolide is the main active constituent of *W. somnifera*. Withanolide D, withaferin A, and withanoside I-VII were reported to have significant and effective biological activity in managing COVID-19. Molecular docking studies have shown that natural ingredients of *W. somnifera* namely, withanone, caffeic acid phenyl ester, and some other biologically active substances interact with novel coronavirus receptors and impede interaction of the virus with host cells [77,78]. In a docking study by Borse et al[70], ashwagandhanolide had the highest docking score (-9.9 Kcal/mol) for all three SARS-CoV-2 protein targets having its drug-likeness. Molecular docking results reported by Prajapati et al[79] showed that flavone glycoside, sugar alcohol, and flavonoid present in *W. somnifera* had binding potentials of -11.69, -11.61, -10.1, and -7.71 kcal/mol, respectively, for the spike-protein on the surface of coronavirus, CD26, RdRp, and TMPRSS2 proteins.

Twenty-eight important phytochemicals are present in *T. cordifolia*, including tinocordiside, an active ingredient with a strong binding affinity for the novel coronavirus. This phytochemical has proven to be an effective immunomodulator and has been found to inhibit the infection of host cells by coronavirus[50,80-85]. Docking analysis and its absorption, distribution, metabolism, excretion, and toxicity revealed that six of thirty-one potential constituents (alkaloids, steroids, and terpenoids) of a *T. cordifolia* extract had strong interactions with human SARS-CoV-2 receptors, prevented the entry of the virus, and thus have potential for COVID-19 prophylaxis[86]. A ketone, tinosponone from *T. cordifolia* is a strong inhibitor of the 3CL major protease of SARS-CoV-2, as shown by computer-aided drug design. Confirmation of its inhibitory activity on SARS-CoV-2 needs to be shown in *in vitro* and *in vivo* studies[87]. *In silico* studies revealed that saponarin, a phytochemical present in *T. cordifolia*, had a binding affinity of -8.75 kcal/mol and was a potential inhibitor of the main protease of COVID-19[86-89]. Thakkar et al[90] reported that columbin, tinosporide, N-transferuloyl-tyramine-diacetate, amritoside C, amritoside B, amritoside A, tinocordifolin, palmatoside G, palmatoside F, and maslinic acids were key molecules for further study based on their docking scores, which ranged from -5.02 to -5.72 Kcal/mol[88,90]. *T. cordifolia* has been linked to autoimmune acute hepatitis and a study found that its use can reveal autoimmune hepatitis in patients[91]. In the interest of public health, further research is needed on the safety and effectiveness of unproven but widely marketed herbal remedies in alternative medical systems, and it is particularly important in light of the current worldwide health crisis[91,92].

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## CONCLUSION

This review has discussed evidence that both *T. cordifolia* and *W. somnifera* hold a special place in the ancient texts and they have proven to be equally important in modern medicine. Extraction and phytochemical analysis have revealed that these plants are rich sources of numerous biologically active compounds. Since the COVID-19 pandemic outbreak, a lot of attention has been directed toward increasing the immunity of the human body against various pathogens such as bacteria, viruses, etc. The immunomodulatory activities of *T. cordifolia* and *W. somnifera* have been a part of Ayurvedic medication for a long time. Recent clinical studies of the products obtained from these plants have confirmed their therapeutic action in benefiting the immune system.

While the preliminary findings are promising, further clinical trials and research are needed to establish standard dosages and the safety and efficacy of these phytochemicals in the context of COVID-19. Integration of these herbal remedies with conventional treatment would offer a holistic approach to managing the disease, improving patient outcomes, and enhancing overall health resilience. In conclusion, *T. cordifolia* and *W. somnifera* have significant therapeutic potential, particularly as supportive treatment of 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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