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Medicinal and therapeutic potential of withanolides from *Withania somnifera* against COVID-19

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ABSTRACT

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the etiological agent of the potentially fatal coronavirus disease 2019 (COVID-19), has currently affected over 87 million people with worldwide deaths nearing 1.9 million. Amidst the developing vaccines and effective therapies, there is a need to develop alternative and supportive strategies for ameliorating the effects of SARS-CoV-2 infections in humans and treat COVID-19 patients. Several medicinal plants and herbs contain useful phytochemicals, which are being explored to develop medicines and drugs to counter the COVID-19 pandemic. *Withania somnifera* is a medicinal herb of growing importance that is extensively utilized in Ayurveda. The medicinal attributes of *W. somnifera* are owing to a broad range of bioactive secondary metabolites including steroidal lactones [withanone, withanolide D, withanolide A, and withaferin A (WFA)]. Among these, WFA is one of the most interesting naturally occurring bioactive compounds that possess potent anti-tumorigenic, anti-inflammatory, pro-apoptotic, anti-angiogenic, and anti-invasive activities. It might bind to SARS-CoV-2 S protein and alter the S protein, thereby hindering its access into the host cells. Withanone and Withanoside V can impede the functional activities of SARS-CoV-2 main protease (Mpro). Withanolides have been found to control cytokine secretions during infection and could alleviate the cytokine storm in the lungs. The combined use of withanolides are several other drugs or therapeutic modalities, such as hydroxychloroquine and dexamethasone, has been demonstrated as an efficient strategy to improve the effectiveness of standard chemotherapy or design a robust therapeutic regime for COVID-19 treatment. Nevertheless, exhaustive research efforts are required to explore the anti-inflammatory and immunomodulatory potentialities of withanolides for alleviating the severity of the disease during SARS-CoV-2 infections. This review highlights the medicinal and therapeutic potential of withanolides against COVID-19.

INTRODUCTION

The coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has presently postured a high worldwide health threat and challenges to limit the spread of the pandemic situation posed (Boopathi *et al*., 2020; Dhama *et al*., 2020a, 2020b). Millions of people have been infected by this virus, while it has killed hundreds of thousands of people across the world (WHO, 2020a). The rapid spread and continuous rising numbers of SARS-CoV-2 cases warrant devising early therapeutic and preventive measures to tackle COVID-19 (Chen *et al*., 2020; Dhama *et al*., 2020b; Dhawan *et al*., 2020; Rabaan *et al*., 2020; Yatoo *et al*., 2020). As of today, no effective therapeutic drugs or vaccine candidates are at hand for the COVID-19 treatment, although very high efforts are underway in this direction, and few of these have reached the final stages of clinical investigations (Khan *et al*., 2020; Rabaan

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et al., 2020; Yatoo *et al*., 2020). Implementing adequate prevention and control measures, including prompt diagnosis of COVID-19, contact tracing, immediate quarantine, and biosafety measures; and discovering effective vaccines, drugs and therapies could altogether prevent the devastating consequences of this pandemic (Dhama *et al*., 2020a; Lythgoe and Middleton, 2020). Developing a vaccine against COVID-19 could take insufficient time to be made available that could safeguard the health of millions of people worldwide (WHO, 2020b; Yatoo *et al*., 2020). Hence, currently available antiviral drugs are being explored against COVID-19 via drug repurposing for identifying new therapeutic use for old and existing drugs that appears to be a prospective approach to cure COVID-19 (Harrison *et al*., 2020). A mixture of anti-viral drugs, including favipiravir, ritonavir, lopinavir (Khan *et al*., 2020), and antimalarial drugs (hydroxychloroquine and chloroquine) (Muralidharan *et al*., 2020), are presently employed as promising therapeutic agents against COVID-19. Apart from these drugs, corticosteroids, like dexamethasone, have proven to be among the most effective drugs in treating COVID-19 (Sharun *et al*., 2020).

Ayurveda, known as "The Science of Life," an ancient traditional medicinal system that originated and is practiced in India, has been utilized for reducing SARS-CoV-2 infection and treating COVID-19-associated patients (Gautam *et al*., 2020; Rastogi *et al*., 2020; Singh *et al*., 2015). It describes many medicinal plants and herbs possessing a broad range of therapeutic usefulness in curing various kinds of ailments, diseases, and disorders, such as *Allium sativum* (Garlic), *Withania somnifera* (*W. somnifera)* (Ashwagandha), *Zingiber officinale Roscoe* (Ginger), *Tinospora cordifolia* (Giloy), *Ocimum sanctum* (Tulsi), *Curcuma longa* (Turmeric, Haldi), *Glycyrrhiza glabra* (Licorice, mulethi), and others (Dhama *et al*., 2018; Singh *et al*., 2015, 2017; Tiwari *et al*., 2018). Hence, researchers are also focusing on exploiting medicines and drugs based on the medicinal, aromatic herbs and plants possessing active phytochemical constituents that could aid in treating COVID-19 patients (Adhikari *et al*., 2020; Ang *et al*., 2020; Chen and Nakamura, 2004; Divya *et al*., 2020; Panyod *et al*., 2020; Shree *et al*., 2020). Herbal bioproducts and their derived purified bioactive substances may exhibit anti-SARS-CoV-2 activities by directly impeding the entry or replication of the virus. Remarkably, some natural products are reportedly involved in the blocking of receptor angiotensin-converting enzyme 2 (ACE2) or the Transmembrane protease serine 2-encoded serine protease enzyme, which is needed by coronavirus to induce infection in host cells. Moreover, plant-based products have also shown the inhibiting effects on the life cycle-associated proteins of SARS-CoV-2, like chymotrypsin or papain-like proteases (PLpros) (Benarba and Pandiella, 2020; Pandey *et al*., 2020).

Withania somnifera L. (Solanaceae), popularly recognized as Ashwagandha or Indian ginseng, is used in Ayurveda for vitality, cardio-protective action, and curing several disorders, like respiratory diseases, skin, and neurological disorders (Tetali *et al*., 2020; Tiwari *et al*., 2014). *Withania somnifera* is recognized for its antiviral, anti-inflammatory, immunomodulatory, antioxidant, antimicrobial, anti-diabetic, neuroprotective, analgesic, anti-tumor, anti-aging, anti-arthritic, anti-stress, and immunomodulatory effects (Fugner *et al*., 1973; Singh *et al*., 2015, 2017; Tiwari *et al*., 2018). It is a potent source of various phytochemicals including Withaferin A (WFA), steroidal alkaloids and lactones, and many other chemical compounds (Tiwari *et al*., 2014; Tong *et al*., 2011) (Fig. 1). *Withania somnifera* helps in maintaining sound mental and physical state, body rejuvenation in deteriorated health status, and improves immunity (Singh *et al*., 2015; Tetali *et al*., 2020; Tiwari *et al*., 2018). Phytochemicals of *W. somnifera* have revealed potent antiviral activities against numerous viral infections, such as chikungunya, human papillomavirus (HPV), hemagglutinin type 1 and neuraminidase type 1, herpes simplex, hepatitis C virus,

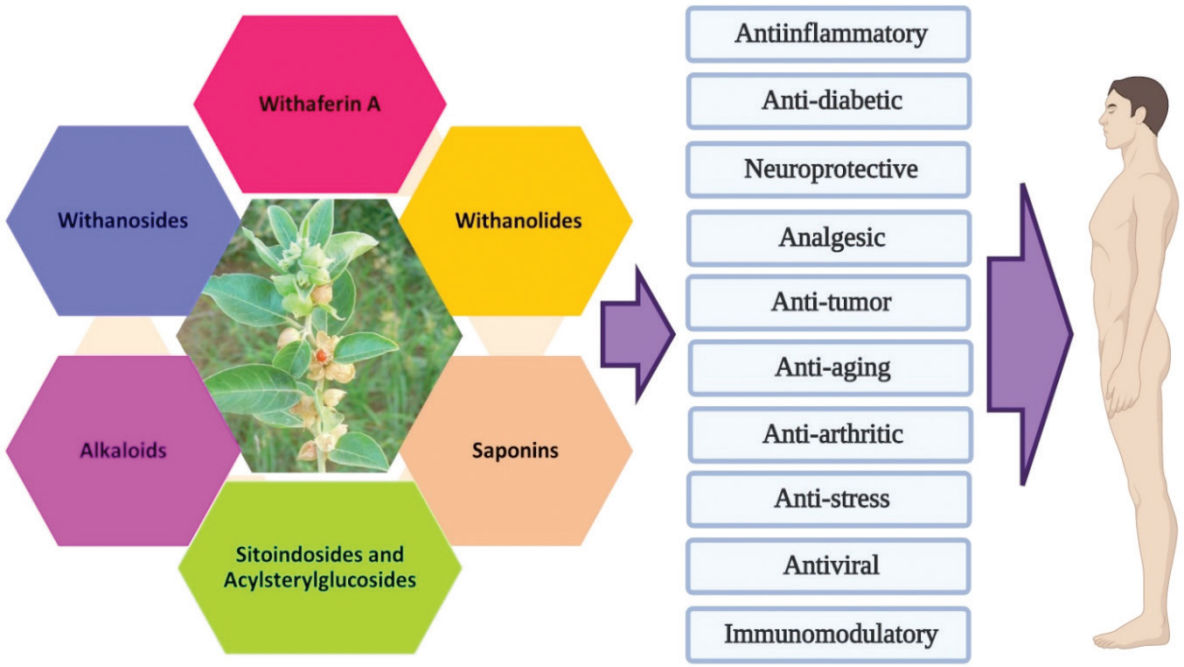

Figure 1. Broad range of phytochemicals and secondary metabolites in *Withania somnifera.*

parainfuenza-3, SARS-CoV, and SARS-CoV-2 (Cai *et al*., 2015; Jain *et al*., 2018; Kashyap *et al*., 2020; Kumar *et al*., 2020a; Leung *et al*., 2020; Mandlik Ingawale *et al*., 2020; Straughn and Kakar, 2020; Tandon and Yadav, 2020; Tripathi *et al*., 2020). Currently, the Indian government, the Indian Medical Research, and the Council of Industrial and Scientific Research have recommended the utilization of *W. somnifera* as a therapy against COVID-19.

Withanolides, the active ingredients of *W. somnifera*, have displayed promising potential to manage COVID-19, and the significant biological action is rendered by Withanolide D, Withaferin-A, Withanoside X, and Withanoside I–VII (Matsuda *et al*., 2001). Several reports have revealed the potential of withanolides such as WFA, Withanoside V and X, and withanone (Wi-N) as therapeutic agents for reducing the severity of SARS-CoV-2 and usefulness in treating COVID-19 patients (Chikhale *et al*., 2020; Kumar *et al*., 2020a; Straughn and Kakar, 2020). The present article focuses on the therapeutic and medicinal potentialities of *W. somnifera* and its phytoconstituents for ameliorating the SARS-CoV-2 severity and usefulness in treating patients with COVID-19.

Methodology for literature review

Research articles were searched and screened from in different databases such as PubMed, Science Direct, and Google Scholar until October 2020 by using the keywords such as "withanolides and COVID-19"; "medicinal properties and *W. Somnifera*"; therapeutic potential and withanolides"; "Antiviral properties and withanolides"; "*W. Somnifera* and COVID-19"; "antiviral Properties and *W. somnifera*". The research articles which were published only in the English language were selected.

Inclusion and exclusion criteria

Research articles were screened and selected independently by authors based on the inclusion and exclusion parameters such as relatedness with the present review. The research findings used in the present review are majorly computational, virtual screenings, and *in silico* evaluations of withanolides from *W. somnifera* for therapeutic potentials against COVID-19. Clinical studies, including *in vivo* and *in vitro* studies, on *W. somnifera* and withanolides against COVID-19 were searched but not available at the time of search to the best of our knowledge. However, the clinical studies including the immunomodulatory effects of *W. somnifera* extracts under other various pathological conditions were considered to illustrate the medicinal and therapeutic potential of *W. somnifera*. The research articles which were selected are published in peer-reviewed, and SCOPUS indexed journals. The related review papers on *W. somnifera*, and withanolides were excluded but selected for any references for supplementary information such as chemical properties, etc. The titles and abstracts of the research articles were screened first, and irrelevant studies were excluded. Furthermore, full research articles were selected based on their relevance with the present review.

Potential of withanolides in treating COVID-19

The S-protein of SARS-CoV-2 binds to the ACE2 receptors present on the surface of diverse types of human cells, particularly in the lung cells, and gains entry into the host cells (Lan *et al*., 2020). Coronavirus mostly targets the airway, alveolar and vascular endothelium, and lung macrophages expressing the ACE2 receptor. ACE2 is demonstrated to express at a higher rate in the respiratory alveolar cells, giving the principal entry site for SARS-CoV-2 into the human host (Ge *et al*., 2013; Gheblawi *et al*., 2020). Two subunits have been identified in the SARS-CoV-2, of which the S1 subunit exhibits a receptor-binding domain (RBD) that binds with receptor ACE2 of the host cell, whereas the S2 subunit coordinates fusion between the host cell and viral membrane (Du *et al*., 2009). It is unveiled that SARS-CoV-2 possesses a 10-times greater ACE2 receptors affinity in comparison to SARS-CoV that is correlated with high severity of COVID-19 (Shang *et al*., 2020). Clinical and experimental trials are being conducted to assess the utmost effective therapeutic regime for COVID-19; blocking the entry of viral particles into the host cell by interrupting the interactions of S-protein with the host ACE2 receptor is an efficient strategy to cure COVID-19.

Natural compounds, such as withanone, WFA, caffeic acid phenethyl ester, and various other biological active compounds, are able to interact with the host cell receptor (ACE2) of SARS-CoV-2 and its main protease (Mpro) (Aanouz *et al*., 2020; Bhardwaj *et al*., 2020; Kumar *et al*., 2020a). WFA is a steroidal lactone obtained from *W. somnifera*, possessing high anti-inflammatory and anti-tumorigenic potentials. WFA has been found useful in reducing the release of several cytokines, like tumor necrosis factor-α (TNFα), IL-6, IL-8, and IL-18, in ovarian cancer (Straughn and Kakar, 2019). Several reports have suggested that the treatment with WFA can modulate the gravity of cytokine syndrome/storm owing to its anti-inflammatory actions (Kakar *et al*., 2017). Recent reports suggested that phytochemicals present in *Withania somnifera* can be utilized to develop effective therapeutic agents against COVID-19 (Kumar *et al*., 2020b). Molecular docking analysis suggests the possible interactions of WFA with S-protein RBD, thus inhibiting the interactions with host cell receptors (ACE2) (Balkrishna *et al*., 2020). Virtual screening and *in silico* molecular docking analysis of *W. somnifera* revealed that its phytoconstituents firmly bind to SARS-CoV-2 S glycoproteins, two main viral proteases, and host ACE2 receptor to put forth significant antiviral activity; the number of oxygen atoms in the withanolide backbone and structural rearrangements play a critical role for effectual binding (Srivastava *et al*., 2020) (Table 1). WFA also exerts inhibition activities against influenza and HPV viruses (Cai *et al*., 2015; Latheef *et al*., 2017). The blocking of the SARS-CoV-2 binding site to ACE2 is a valuable approach to combat COVID-19 (Fig. 2).

Withanone, a well-known steroidal Withanolide, protects the cells from increased pro-inflammatory cytokines levels, like TNFα, IL-6, and IL-1 beta (Pandey *et al*., 2018), which might aid in treating COVID-19. In a recent study, Balkrishna *et al*. (2020) reported that Withanone significantly decreased the interfaces between ACE2 and RBD on the SARS-CoV-2 S-protein. Recognition of two salt bridges at the interface was found to be destabilized by the incorporation of Withanone in the ACE2-RBD complex. The interruption of electrostatic forces between the ACE2 and RBD blocks virus from entering into the host cells and its subsequent infectivity.

Withanone (Wi-N) is also predicted to interact with the Mpro and shows an inhibitory potential for SARS-CoV-2 protease (Fig. 2). The inhibition or interference of SARS-CoV-2 protease is

Table 1. Antiviral activities of most active Withanolides as phytochemicals present in *Withania somnifera* according to computational studies, specifically against SARS-CoV-2.

Withanolides	Molecular formula	Antiviral action against SARS-CoV-2	References
WFA	$C_{28}H_{38}O_6$	Blocks the binding site of SARS-CoV-2 to the host receptor (ACE2), and Inhibition of SARS-CoV-2 protease (Mpro)	Balkrishna *et al.* (2020), Kumar *et al.* (2020a), Pandit and Latha (2020)
Withanone	$C_{28}H_{38}O_6$	Inhibition of 3-chymotrypsinlike protease (3CLpro), i.e., main viral protease, and Blocking the ACE2 receptors	Kumar *et al.* (2020b), Balkrishna *et al.* (2020)
QGRG	$C_{33}H_{40}O_{21}$	Inhibition of NSP15 endoribonuclease	Chikhale *et al.* (2020)
Withanoside V	$C_{40}H_{62}O_{14}$	Blocks entry of virus by binding with spike (S) glycoprotein.	Shree *et al.* (2020)
		Inhibition of SARS-CoV-2 protease (Mpro)	Chikhale *et al.* (2020)
Withanoside X	$C_{40}H_{62}O_{15}$	Blocks the viral entry by binding with spike (S) protein	Chikhale *et al.* (2020)
Withanolide A	$C_{28}H_{38}O_6$	Inhibition of SARS-CoV-2 protease (Mpro)	Pandit and Latha (2020)
Withanolide D	$C_{28}H_{38}O_6$	Inhibition of PLpro	Khanal *et al.* (2020)
Withanolide G	$C_{28}H_{38}O_5$	Inhibition of PLpro	Khanal *et al.* (2020)
Withanolide M	$C_{28}H_{38}O_6$	Inhibition of 3CLpro, and binding to spike (S) protein	Khanal *et al.* (2020)
Withanolide Q	$C_{28}H_{38}O_6$	Modulation of various essential SARS-COV-2 proteins	Khanal *et al.* (2020)

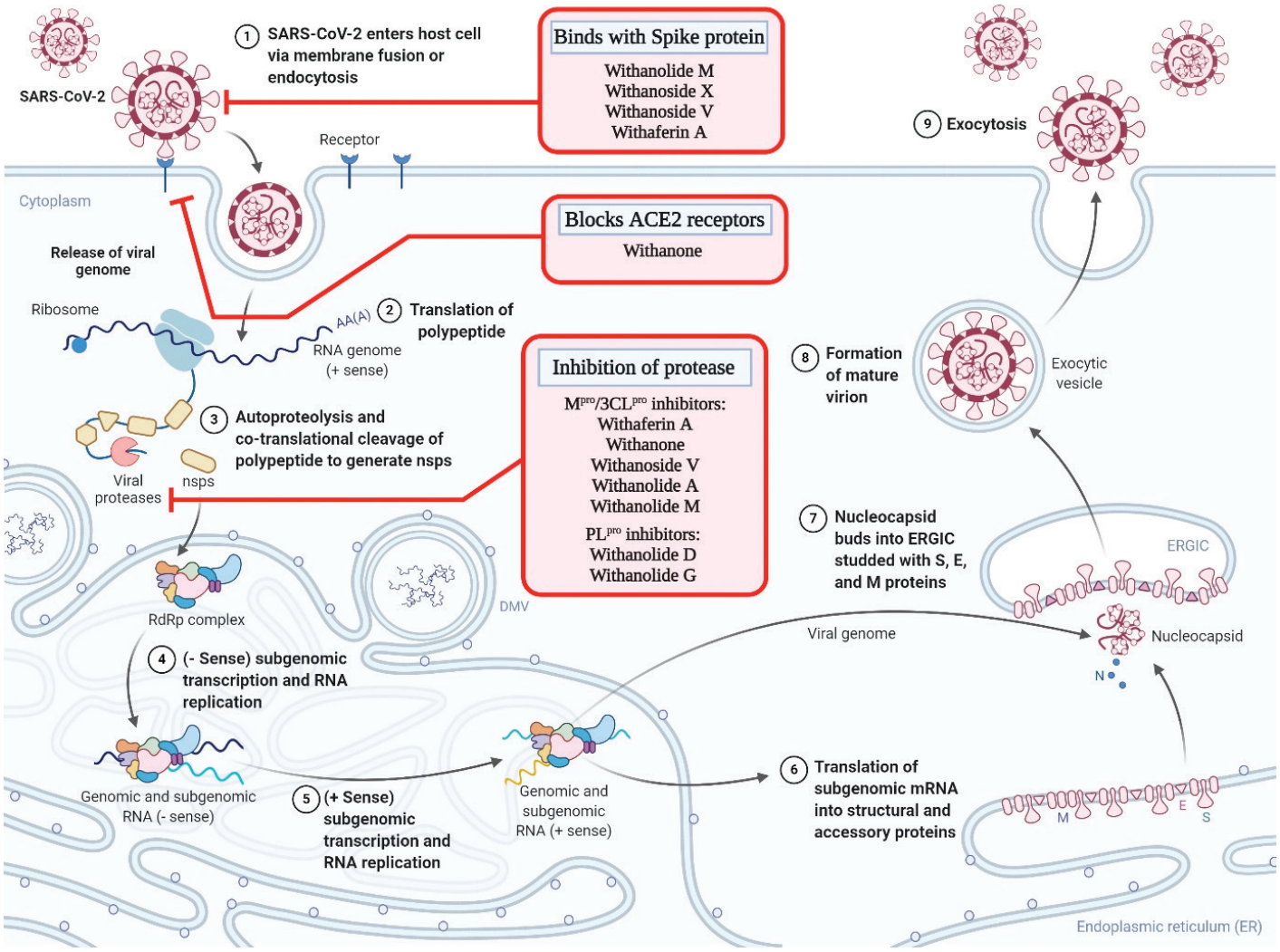

Figure 2. Proposed mechanism of action of *Withanolides*. *Withanolides* such as WFA and Withanone (Wi-N) block the process of viral entry by binding with SARS-CoV-2 Spike protein; Withanone (Wi-N) and Withanoside V inhibiting the activity of Viral protease and interrupting the cleavage of poly proteins. The image was created with BioRender.com.

an efficient therapeutic approach for treating COVID-19 (Kumar *et al*., 2020a, 2020b). A recent docking investigation proposed that four constituents of *W. somnifera*, such as Sitoindoside IX, Withanoside II, Withanoside V, and Withanoside IV, exhibit strong binding affinities with the Mpro, which is also named as 3-chymotrypsin-like protease (3CLpro) of the SARS-CoV-2. Among the four phytoconstituents, Withanoside V has the highest hydrogen-bonding interactions and binding affinity with the active site of the protein, indicating its active site stability. Hence, Withanoside V can be exploited as a potent inhibitor of Mpro and might provide an effective cure for COVID-19 (Tripathi *et al*., 2020). In different molecular dynamics simulation and molecular docking studies, among all the selected *W. Somnifera* phytochemicals, Withanoside V and Somniferine revealed significantly strong interactions with the main viral protease (Mpro). The binding of bioactive phytocompounds with the viral Mpro constrains the process of viral genome replication and transcription by downregulating the cleavage of polyproteins that release non-structural proteins (Shree *et al*., 2020) (Table 1). The inhibition of the activity of Mpro hinders the replication of the viral genome in the host cell (Zhang *et al*., 2020).

Chikhale *et al*. (2020) also reported that Quercetin-3-O-galactosyl-rhamnosyl-glucoside (QGRG) found in *W. somnifera* could be a potential Withanolide, as it showed the highest binding affinity with NSP15 endoribonuclease, a crucial and essential protein of the viral machinery. They also reported that Withanoside X, Ashwagandanolide, and Dihydrowithaferin A exhibit strong binding affinities with various essential viral proteins (S-protein). Hence, these phytochemicals can interrupt the essential SARS-CoV-2 viral proteins under disease conditions.

A recent computational study revealed that WFA exhibits stronger binding with Mpro compared to the hydroxychloroquine and a plethora of other widely used repurposed drugs for treating COVID-19. Withanolide A also showed significant interactions with Mpro; thus, there is proven evidence of the effectiveness of *W. somnifera* as a potential medicinal plant for the COVID-19 treatment (Pandit and Latha, 2020) (Table 1). Sudeep *et al*. (2020) studied the interactive patterns of curcumin, artemisinin, andrographolide, and WFA with the cell receptor "GRP78" exhibiting lower binding energies using molecular docking tools. They also investigated the interaction attributes of these plant-originated biologically active molecules with Mpro of SARS-CoV-2 for gaining deeper understanding and insights. The docking analyses unveiled the highest affinity of WFA with GRP78-SBD target receptor, among the tested compounds. Therefore, it was speculated that WFA inhibits the viral entrance by blocking the receptor. Likewise, among all the other biomolecules, WFA presented superior affinity with the binding site of the protein. This study further corroborated the antiviral properties of medicinal herb-derived WFA against SARS-CoV-2 either by obstructing the host cell's receptor or interfering with the activities of the main viral protease necessary for replication (Grover *et al*., 2010).

Based on other computational studies, Khanal *et al*. (2020) found that withanolide-D, G, M, and -Q from *W. somnifera* boost the immune system and inhibit the extent of COVID-19. Withanolide Q modulated the highest numbers of SARS-CoV-2 proteins and revealed the highest drug-likeness score. Moreover, Withanolide D and G had a superior binding energy with PLpro (Table 1). Based on the number of hydrogen-bonding interactions and binding energy, it has been analyzed that among a wide range of withanolides, Withanolide M has higher levels of interaction with 3CLpro, and S-protein of SARS-CoV-2 (Khanal *et al*., 2020). Parida *et al*. (2020) carried out molecular dynamics simulations for exploring the potential inhibitory activities of phytocompounds against SARS-CoV-2. Among the therapeutic phytochemicals screened from various Indian herbs and plants, 2,3-dihydro WFA and Withanolide R showed the minimum binding energy for S-protein and Mpro, respectively. The newly explored bioactive chemicals displayed multitherapeutic effectiveness by modulating several biological and cancer pathways.

SARS-CoV-2 infection is associated with cytokine release syndrome and storm, deadly immune reactions, in which the body rapidly releases a vast number of cytokines into the blood. Infection with SARS-CoV-2 caused the build-up of monocytes and macrophages, releasing various cytokines, such as IL-6, IL-1β, TNF-α, and IFN-γ, which trigger adaptive T and B cell immunity for clearing the infection (Huang *et al*., 2020; Ye *et al*., 2020). Dysfunctional and violent immune responses resulting in a cytokine release disorder or storm can cause a severe form of pulmonary and lung pathology, leading to excessive inflammation (Tay *et al*., 2020). Furthermore, the unregulated and excessive cytokine secretions cause myocardial injury and multiorgan dysfunction (Ruan *et al*., 2020). A current *in vitro* study on the potential of medicine named "Coronil" containing various withanolides suggested its effectiveness in regulating the cytokine secretions. Coronil attenuated the release of TNF-α and IL-6 cytokines, and reduced TNF-α triggered nuclear factor-kappaB (NF-κB)/ activator protein-1 (AP-1) transcriptional activities (Balkrishna *et al*., 2020). The decrease in cytokine (IL-6, IL-10, and TNF-α) secretions by withanolides can aid in controlling the cytokine blast during the SARS-CoV-2 infection. Moreover, NF-κB and AP-1 are involved in cytokine secretion and orchestrating lung inflammation (Zhao *et al*., 2020). Inhibitory action of the withanolides and additional phytoconstituents present in a herbal medicine named Coronil on the NF-κB/AP-1 pathway indicates a probable contribution of withanolides in interfering with the secretion of cytokines observed during the COVID-19 (Balkrishna *et al*., 2020).

Hence, withanolides present in *W. somnifera* can be explored as potential biomolecules that interact with SARS-CoV-2 and needs additional investigation as drug candidates to treat COVID-19. Until now, withanolides have been studied solely using *in silico* approaches such as molecular dynamics simulation and docking, which provide a basic understanding of the binding energy as well as the ligands stabilization with viral proteins. The SARS-CoV-2 Mpro is crucial as it plays an important role in stimulating the viral RNA maturation processing into the functional form of proteins, i.e., exoribonuclease, endoribonuclease, and RNA polymerase, which also impair the intrinsic host immunity. Thus, the Mpro might be considered a vital target in designing effective drugs to fight against COVID-19 (Fig. 2) (Shree *et al*., 2020). In the future, there is an urgent need to evaluate the potential of several phytochemicals present in *W. somnifera* against SARS-CoV-2 in amalgamation with other available drug candidates for aiding to formulate a promising cure against COVID-19.

Clinical studies suggesting the therapeutic potential of *W. somnifera*

Malik *et al*. (2007) reported a significant increase in the immune response of Bagg Albino/c mice which were administrated with root extracts of *W. somnifera*. The screening of lymphocyte's (T and B cells) markers showed the prominent enhancement in proliferation and differentiation of a pool of various lymphocytes and their cytokines. They found a significant increase in the expression of T helper (Th1) cells-related cytokines, whereas they found a steep decline in Th2 cells related cytokine IL-4. However, they also reported withanolide-A as a major phytoconstituent in the alcoholic root extract of *W. somnifera* which is responsible for the enhanced response of the Th1 cells.

Teixeira *et al*. (2006) reported the use of *W. somnifera* extracts as a prophylactic measure to treat *Listeria monocytogenes* infection. They reported enhanced proliferation of immunologically important cells such as lymphocytes as a result of *W. somnifera*. Furthermore, the enhanced production of interferon-gamma due to *W. somnifera* modulates the immune response which provides protection against intracellular bacterial infection.

In another study, leaf and root extracts of *W. somnifera* have been found to possess anticancerous properties and the potential to enhance the Th1-mediated immune response. They found an enhanced proliferation of T lymphocytes (CD4+/CD8+) and Natural Killer cells along with an increased proliferation of a pool of various other immunologically important cells. The studies suggested the usefulness of *W. somnifera* to modulate the immune response during intracellular infections such as viral infections (Malik *et al*., 2009).

A recent randomized and double-blind placebo control study on 60 pulmonary TB patients proposed *W. somnifera* root extract's usefulness as an adjuvant in the administration of antibiotics in TB patients. The root extract of *W. somnifera* was reported as an effective adjuvant for antibiotics delivery and recorded a significant increase in T lymphocytes (CD4 and CD8) count compared to control groups. *Withania somnifera* extracts as an adjuvant combined with anti-TB drugs used in pulmonary TB patients exhibited a positive impact on symptoms and immunological parameters in patients with pulmonary TB conditions and can be used as effective adjuvants with antiviral drugs (Kumar *et al*., 2018).

In contrast to this, a current immunological study on HIV patients treated with root extracts of *W. somnifera* showed a significant reduction of CD38 expressing cytotoxic T lymphocytes (CD8+ T cells). They further suggested that the immune response may differ significantly during different clinical conditions of HIV patients. The reason behind the reduction in immune response was difficult to predict, which varied among the populations. Therefore, there is an urgent need for extensive study covering the impact of withanolides on the immunologically important cellular response (i.e., CD4+ and CD8+ cells) in a large group of patients with viral infections (Maurya *et al*., 2019).

CONCLUSION AND FUTURE PROSPECTS

SARS-CoV-2 has constituted high global health emergencies as a devastating pandemic. There is an urgent need to develop promising and successful targeting strategies to counter COVID-19. Apart from chemical and allopathic drugs, naturally available phytoconstituents provide a valuable and rich source of chemical moieties possessing potent antiviral properties. *Withania somnifera* is well known for the potential of its phytochemicals such as withanolides in treating several ailments and diseases, including viral infections. Withanolides, such as WFA, inhibit the ACE2 receptor-mediated entry of SARS-CoV-2 into the host cells, and Withanone, Withanolide A, and Withanosides inhibit the Mpro of SARS-CoV-2. Targeting the ACE2 entry receptor and the Mpro is an efficient strategy to inhibit virus replication and spread in the body. Anti-inflammatory and immunomodulatory properties of withanolides are needed to explore to their utmost potential to alleviate the pathology of the disease during SARS-CoV-2 infections. Withanolides can be combined with drugs, such as hydroxychloroquine and dexamethasone, which could aid in designing a robust therapeutic strategy for COVID-19 treatment. Phytoconstituents of *W. somnifera* are considered safe, and no harmful effects of their long-term use have been reported. Further explorative research is required for *in vivo* and *in vitro* assessment of each Withanolide individually as well as in groups/combination to scrutinize the therapeutic levels of these phytoconstituents against COVID-19.

AUTHOR CONTRIBUTIONS

All the authors substantially contributed to the conception, compilation of data, checking, and approving the final version of the manuscript, and agreed to be accountable for its contents.

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CONFLICT OF INTEREST

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