10-1-2020

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Vivek K. Kashyap
The University of Texas Rio Grande Valley

Anupam Dhasmana
The University of Texas Rio Grande Valley

Murali M. Yallapu
The University of Texas Rio Grande Valley

Subhash C. Chauhan
The University of Texas Rio Grande Valley

Meena Jaggi
The University of Texas Rio Grande Valley

Recommended Citation

Kashyap, V. K., Dhasmana, A., Yallapu, M. M., Chauhan, S. C., & Jaggi, M. (2020). Withania somnifera as a potential future drug molecule for COVID-19. Future Drug Discovery. https://doi.org/10.4155/fdd-2020-0024

Future Drug Discovery

Commentary

Withania somnifera as a potential future drug molecule for COVID-19

Vivek K Kashyap[1,2], Anupam Dhasmana[1,2], Murali M Yallapu[1,2], Subhash C Chauhan[1,2] & Meena Jaggi*[,1,2]

[1]Department of Immunology & Microbiology, School of Medicine, The University of Texas Rio Grande Valley, McAllen, TX 78504, USA

[2]South Texas Center of Excellence in Cancer Research, School of Medicine, University of Texas Rio Grande Valley, McAllen, TX 78504, USA

*Author for correspondence: Tel.: +1 956 296 2008; meena.jaggi@utrgv.edu

"*W. somnifera* can bind to the key targets (Spike protein, ACE-2, RdRp, 3CLpro and PLpro) of SARS-CoV-2, indicating it may be a good potential therapeutic candidate for COVID-19 treatment."

First draft submitted: 4 September 2020; Accepted for publication: 14 September 2020; Published online: 1 October 2020

Keywords: acute respiratory distress syndrome • angiotensin-converting enzyme 2 • intranasal delivery • SARS-CoV-2 • *Withania somnifera*

COVID-19 is an infection disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). COVID-19 is a mild to severe respiratory illness which has caused significant disruption to normal life over the past few months, nearly bringing parts of the world to a halt. As of 26 August 2020, more than 24 million COVID-19 infections have been reported and 821,000 deaths are associated with this disease [1]. According to the WHO (Geneva, Switzerland) and the US CDC (MD, USA), the clinical manifestation of COVID-19 is the presence of fever or chills, sore throat, dry cough, fatigue, muscle/body aches, headache, loss of taste/smell, congestion/runny nose, nausea/vomiting or diarrhea, in addition to respiratory symptoms [2]. Unfortunately, SARS-CoV-2 infection in patients with pre-existing disease conditions (e.g., hypertension and diabetes) can cause severe complications and, as a result, mortality [2]. Until today, no drugs or vaccine(s) have been approved to combat this disease. About 3115 clinical trials are registered to develop efficient vaccines or treatments for COVID-19 [3]. Several antivirals, such as lopinavir, ritonavir and nelfinavir, as well as the antimalarials chloroquine and hydroxychloroquine have been screened as potential therapeutic agents to combat SARS-CoV-2 [4]. However, none of them proved clinically beneficial. Considering the emergence of COVID-19, the development of antiviral agents that can block the virus' entry into cells or target various elements of viral replication is highly sought.

Withania somnifera as a future drug candidate for COVID-19

When compared with conventional pharmaceuticals, bioactive natural compounds tend to have good biocompatibility, bioavailability, less toxicity and are rich in various phytoconstituents like phenols, steroids and flavonoid molecules. Several natural compounds have been screened for their possible therapeutic effects against various viral diseases including SARS-CoV-2 [5,6]. Ashwagandha (*Withania somnifera*) has been used in traditional medicine systems like Ayurveda, Unani, and Siddha, and has been known for its therapeutic benefits for more than 5000 years [7]. It is considered an important herbal restorative in Ayurvedic medicine and is also known as 'Sattvic Kapha Rasayana', which can be used for various pharmacologic properties and could be a potential candidate for the management of COVID-19 as a safer alternative to currently available disease-modifying drugs such as hydroxychloroquine [4,8,9]. More than 40 withanolides, 12 alkaloids and rare sitoindosides have been discovered in *W. somnifera* [10–13]. A total of 69 (39 preclinical and 30 clinical) studies documented the safety and clinical efficacy of *W. somnifera* [9]. Components of this plant are considered to influence multiple signaling pathways and have been found to possess anticancer, anti-inflammatory, antidiabetic, antimicrobial, anti-arthritic, antistress/adaptogenic, neuroprotective, cardioprotective, hepatoprotective, chemo-/radiation sensitizing and immunomodulatory properties [4,7–10].

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Several studies have shown that derivatives of *W. somnifera* can efficiently inhibit various viral infections, including HPV, herpes simplex, parainfuenza-3, HCV, H1N1, bursal disease viruses and coronaviruses – including SARS-CoV and SARS-CoV-2 [7,9,11–17]. As *W. somnifera* is considered an important Ayurvedic medicine and as it has demonstrated notable antiviral, immunomodulatory, anti-inflammatory, prophylactic and therapeutic activities, the Indian Government (Ministry of Ayurveda, Yoga & Naturopathy, Unani, Siddha and Homoeopathy) along with the Council of Scientific and Industrial Research and the Indian Council of Medical Research (New Delhi, India) have recently approved its use for clinical trials against SARS-CoV-2 [18].

The biological & pharmacological role of *W. somnifera*

SARS-CoV-2 is a single-stranded, positive RNA virus (~34 kb) with a diameter of 80–160 nm and a nucleocapsid of helical symmetry [19]. The SARS-CoV-2 genome has high homology to SARS-CoV; a recent study has shown a 79.6% genetic correlation between these viruses and 96% to the BatCoV RaTG13 [19]. Mechanistically, the integrity of the SARS-CoV virion is maintained by several proteins: The S protein (Spike glycoprotein), the abundant M protein (membrane), the E protein (envelope) and the N protein (nucleocapsid). The SARS-CoV-2 virus binds to ACE2 receptors on the host cell surface to facilitate its cellular entry through the actions of TMPRSS2. Viral particles are eventually internalized into endosomes, where the acidic environment leads to a release of viral genome for protein synthesis. This in turn leads to the generation of new infectious particles which are assembled and released following viral RNA and protein synthesis [4,11]. Various recent *in silico* studies have reported several plausible antiviral actions of the derivatives from *W. somnifera* by inhibiting Viral protease (3CLpro and PLpro), host cell produced protease (TMPRSS2), RNA polymerase (RdRp) and the interaction site of viral S protein with host receptor ACE-2 [11–15,20,21]. Moreover, Kumar *et al.* demonstrated that withanone and caffeic acid phenethyl ester act as a potential inhibitor of the SARS-CoV-2 main protease through molecular docking studies [12]. The withanone, a derivative from *W. somnifera* can significantly downregulate the expression of TMPRSS2 in MCF7 cells at mRNA level [20]. In addition, the various derivatives of *W. somnifera* effectively modulate the expression of the Alpha7 nicotinic acetylcholine receptor, which is associated with greater patient vulnerability to COVID-19 with pre-existing chronic obstructive pulmonary disease [9,16,17]. In addition, *W. somnifera* inhibits other potential targets, including downstream transduction pathways, IRF3, NF-κB and the JAK/STAT signaling pathway. Furthermore, this molecule has also been shown to activate sphingosine-1-phosphate receptor 1 signaling pathways, including noncoding RNAs (microRNAs and long noncoding RNAs) which are essential to the antiviral response [9,22].

SARS-CoV-2 viral entry into cells has been shown to cause a 'cytokine storm' involving excess production of pro-inflammatory cytokines/chemokines which can lead to pulmonary edema, atelectasis and acute lung injury, which may result in shock, tissue damage in the heart, liver and kidney, as well as respiratory or multiple organ failure which can lead to death in patients with severe COVID-19-related complications [4,11,23]. Of particular note, *W. somnifera* has been reported to inhibit the release of and suppress numerous pro-inflammatory cytokines/chemokines including IL-6, IL-2, IL-7, TNF-α, IFN-γ, IFN-γ-induced protein10, MCP3 and GM-CSF; this was correlated with clinical improvement in conditions associated with cytokine storm [7,9]. Furthermore, *W. somnifera* has anti-inflammatory and antifibrotic effects by reducing the expression of crucial chemokines and cytokines involved in lung infection such as IFN-γ, MCP-1, IL-6 and IL-10 [9].

TGF-β and its signaling pathways are involved in lung fibrosis and TGF-β overexpression is correlated with a poorer prognosis in acute respiratory distress syndrome [11,24]. Withaferin A, a therapeutic component derived from the *W. somnifera* plant, was shown to reduce the expression of various inflammatory cytokines (NF-κB p65, IL-1β and TNF-α) and profibrotic proteins (connective tissue growth factor, collagen 1A2, collagen 3A1 and fibronectin) *in vitro* and *in vivo* [9]. This compound also led to a significant inhibition of angiogenic factors, such as vascular endothelial growth factor, focal adhesion kinase, p38 mitogen-activated protein kinase and PLCγ1. The phosphorylation of SMAD2/3 as induced by TGF-β1 and Bleomycin were also significantly inhibited by Withaferin A [25]. *W. somnifera* potentially reduces renal fibrosis at the priming and activation stages by attenuating TNF-α- and LPS-induced NF-κB activation, CCL2, and *CCL5* gene expression in NRK-52E cells [9,26].

Oxidative stress exists in all severe lung injuries, including acute respiratory distress syndrome induced by SARS-CoV and influenza infections leading to the initiation and maintenance of chronic low-grade inflammation [7,9,27]. SARS-CoV papain-like protease (PLpro) induces significant reactive oxygen species production and stimulates TGF-β1 mediated profibrotic response. *W. somnifera* also inhibits the virally-induced expression of glutathione, reactive oxygen species generation, and indirectly inhibits influenza A virus-induced activation of TLR2/4, MAPK,

and NF-κB pathways [7,9]. Therefore, *W. somnifera* is potentially beneficial antioxidant agent in the treatment of SARS-COV-2 mediated oxidative stress in the lungs.

Efficient delivery of *W. somnifera*

W. somnifera is documented to be most efficacious in high doses, at around 800 mg/kg per day, which is well tolerated orally [7,9,28]. To further enhance the therapeutic efficacy and targeted delivery of *W. somnifera*, newer delivery technologies such as nanoparticles, liposomes, micelles and phospholipid complexes are under evaluation [9,29–31]. Intranasal delivery is considered to be a useful and reliable route for vaccinations and multiple therapeutic modalities against infectious diseases view it as an alternative to oral and parenteral routes [11]. This is mainly due to the highly vascular, permeable, and minimally enzymatic environment of the nasal cavity, which allows for an avoidance of hepatic first pass metabolism leading to a more rapid onset of action and rapid mucociliary clearance [32]. There are several intranasal therapeutic and prophylactic agents, such as AT-301 (Atossa Therapeutics, WA, USA), AdCOVID™ (Altimmune Inc., MD, USA), KONS-COVID-19 (Kerecis Ltd, VA, USA), T-COVIDTM (Altimmune Inc.), and Vazegepant (Biohaven, CT, USA) are under development to deal with SARS-CoV-2 and potentially upcoming infections. The intranasal administration of *W. somnifera* and its formulation may have preventative effects against SARS-CoV-2 infections in humans, as the viral entry site at the ACE2 receptor is predominantly distributed on nasal cells, the mucosal surface of the respiratory tract and surrounding the eyes [32]. Intranasal administration of Withanolide A (derived from *W. somnifera*) delivered an effective amount to the olfactory mucosa to exert a neuroprotective effect in the global cerebral ischemia model [33].

Conclusion

Together, the literature strongly suggests that derivatives of *W. somnifera* can bind to the key targets (Spike protein, ACE-2, RdRp, 3CLpro and PLpro) of SARS-CoV-2, indicating it may be a good potential therapeutic candidate for COVID-19 treatment. Further, the activity of *W. somnifera* or its derivatives may be capable of suppressing multiple cytokines and cytokine activity and may be able to regulate the cytokine storm conditions in experimental models of viral diseases. However, efficient nanoformulations and intranasal delivery may allow therapeutic blood levels of *W. somnifera* or its derivatives to achieve meaningful therapeutic benefits.

Author contributions

VK Kashyap, SS Chauhan, and M Jaggi conceived the idea and written the major portion of manuscript. The manuscript was also written and edited by A Dhasmana and MM Yallapu. The final manuscript has been read and approved by all authors.

Financial & competing interests disclosure

This work was supported by NIH/NC1 grants (R01 CA210192, R01 CA206069 and R01 CA204552) to SC Chauhan, UT star fellow award to SC Chauhan and UTRGV startup funds to SC Chauhan, M Jaggi and MM Yallapu. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

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