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Withania somnifera and COVID-19: Current evidence and future prospective

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Review Article

Abstract:

The most recent pandemic of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has challenged the health systems around the world. Currently, there is no definite treatment for COVID-19 and researchers are exploring herbal plant species. *Withania Somnifera* (WS) and its active ingredients may have potential benefits against COVID-19 activity and related cytokine storm. COVID-19 manifestations are not limited to the respiratory system and extend to vital body organs, a syndrome called *multiple organ failure*. WS also showed protective effects in different organs such as the lung, heart, liver, and kidneys. In this review, we aimed to summarize the pharmacological effects and underlying mechanisms of WS against COVID-19 and related complications. WS showed anti-inflammatory, antioxidant, hepatoprotective, cardioprotective, antifibrotic, anticancer, and immunomodulatory effects, mainly by downregulating NF-κB and related pathways. The

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suggested clinical benefits of WS for COVID-19 were investigated by clarifying their underlying mechanisms in this review.

Keywords: Coronavirus, Ashwagandha, *Withania Somnifera*, Herbal medicine, pharmacology

INTRODUCTION

The severe acute respiratory coronavirus 2 (SARS-CoV2) pandemic is the most recent outbreak which has caused a potential threat to human life. In symptomatic cases, the disease develops with flu-like symptoms and then lung injury (1). However, recent studies have revealed that the disease symptoms will progress into endotheliitis, cardiovascular diseases, cardiac injury, renin-angiotensin system disorders, renal involvement and kidney failure, liver damage with the portal and enzymatic changes, and gastrointestinal involvement. Other potential late complications related to coronavirus disease (COVID) are nervous system manifestations and rhabdomyolysis (2). The innate and adaptive immune system function is associated with viral replication and host response control. The activation of T cell and its subsets ($CD4^+$ and $CD8^+$) is essential for immune response against invasions. Exaggerated immune response caused by SARS- CoV2, is responsible for hyperproduction of inflammatory cytokines, i.e., *cytokine storm* (3). Interleukin-6 (IL-6) acts as a key mediator in hyperinflammation and cytokine storm. Hypercytokinaemia may then lead to acute respiratory distress syndrome and other clinical outcomes such as multiorgan failure (4, 5).

The breakout of the disease and also no scientific evidence that any alternative remedies can prevent or cure COVID-19, made researchers seek out novel approaches using natural products and alternative medicine for the prevention and treatment of COVID-19. Currently, researchers are trying to find remedies to improve clinical outcomes (6, 7). *Withania Somnifera* (WS) also known as *Ashwagandha* or *Indian ginseng* is a widely used herbal medicine that has been suggested as a complementary therapy for COVID-19 (8, 9). Previous studies have identified a wide range of chemical components in WS, including steroidal lactones (withanolides, Withaferin A) and alkaloids (withanine, withananine, tropanol, somniferiene, pseudotropine, cuscohygrine), that produce anti-inflammatory, antiviral, antimicrobial, antitumor, immunomodulatory, and antistress effects (10-14).

The main suggested mechanism by which SARS-CoV-2 exerts its influences on beginning and amplifying systemic inflammation, is activating transcription of pro-inflammatory cytokines by mediating nuclear factor κB (NFκB) (15, 16). Besides this, the active ingredients of different parts of WS also showed potent regulatory effects against the production of inflammatory mediators, probably by inhibiting NFκB and related pathways (17, 18).

In this narrative review, we aimed to summarize the potential benefits of WS on inflammation and organ protection in patients with SARS-CoV-2.

MATERIALS AND METHODS

This narrative review is aimed to investigate the potential benefits of WS in COVID-19 patients. The search strategy for this review was entirely Internet-based. PubMed, Web of Science, Scopus, and Google Scholar databases were searched to retrieve eligible publications. A list of terms and phrases, including *Withania somnifera*, Ashwagandha, Indian ginseng, 2019 novel coronavirus, coronavirus, SARS-CoV-2, COVID-19, and 2019-nCoV infection were used to narrow down the search. There was no restriction on the date, place, and type of study to select articles to be reviewed. Studies published in non-English languages were excluded.

RESULTS and Discussion

Phytochemical properties of Ashwagandha: Withanolide A and withaferin A at a glance

Preliminary phytochemical analyses have been conducted to identify the bioactive components of Ashwagandha. Different parts of the plant have been investigated, and the extracts from leaves and roots showed potential immunomodulatory and anti-inflammatory properties (19). Malik et al. observed that Ashwagandha root extract could exert an up-regulating effect on humoral and cell-mediated immune response in mice model. The amplification of subdividing CD4+ T cells into T helper 1 cells, was attributed to the main component of Ashwagandha, Withanolide A. They also observed an increase in macrophage functions in mouse splenocytes following treatment with

Ashwagandha root extract (20). In another study, treatment with isolated withanolide A in stress-induced rats enhanced the expression of interferon-gamma and interleukine-2. They also found elevated levels of glutathione in plasma (21).

Withanolide A also induced antioxidant activity in microglial BV-2 cells. In a study carried out by Sun et al., pretreatment of the cells with withanolide A attenuated oxidative stress induced by lipopolysaccharide (LPS); hence, withanolide A resulted in reduction in reactive oxygen species (ROS) production and increase in nuclear factor erythroid 2–related factor 2 and heme-oxygenase 1 expression (22). Besides this, there is evidence suggesting withanolide A as a promising therapeutic agent for neuritic and synaptic dysfunction (23).

Withaferin A is another main component of Ashwagandha, which mainly accumulates in the leaves of the plant. This steroidal lactone component exhibits antioxidant and anti-inflammatory properties probably by prevention of the NF-κB and related pathways. In a study conducted by Sorelle et al., inflammatory responses were measured in human pancreatic islets after treatment with a cytokine cocktail including TNF-α, IFN-γ, and IL-1β. After adding withaferin A to the culture, they observed reduction in the levels of tissue factor, induced nitric oxide synthase and monocytic chemotactic protein-1, and IFNγ-induced protein 10 (24). Withaferin A shows a protective role against endothelial dysfunction induced by palmitic acid in rat aortic tissue. Inhibition of ROS production, restoration of nitric oxide (NO) production, and vasorelaxation have also been observed following withaferin A treatment (25). Some studies have also shown withaferin A as an inhibitor of NF-κB activity (26, 27), probably through modulation of NEMO/IKKβ complex, which is responsible for the augmented expression of inflammatory cytokines (28).

Table 1. Summary of bioactive components and their potential activitie

Component (34-37)	**Activity (34-37)**	**Plant part (34-37)**
Withanolide A	Immunomodulatory, neuritic rejuvenation	Leaves and roots
Withanolide D	Immunomodulatory, inhibition of tumor growth	Leaves and roots
Withanolide E	Immunomodulatory, anti-leukemia	Leaves and roots
Withanolide F	Anticancer	Leaves
Withaferin A	Anticancer, antiarthritic, anti-inflammatory, antiangiogenic, antibacterial and antifungal	Leaves and roots
Withanone	Anti-inflammatory, antiarthritic	Leaves and roots
Sominone	Neural growth promoter	Whole plant
Withasomniferol A	Immunomodulatory	Roots
Viscosalactone B	Antiproliferative	Whole plant

Table 2. Potential benefits of Ashwagandha in COVID-19 patients

Organ/ System	**Plant part/ Extract**	**Findings**	**Potential mechanism**	**Study**	
Cardiovascular	Root extract	Vasorelaxation in the aortic rings	Enhancing nitric oxide generation	Animal study	(48)
	Root extract	Decreasing systolic blood pressure (on workload exercise)	Adaptogenic activity on sympathetic nervous system	Clinical trial	(46)
	Root powder	Decreasing systolic and diastolic blood pressure	Reducing the sensitivity of the heart to adrenergic stimulation	Animal study	(47)

	Root and leaf extract	Protecting against cardiotoxicity	Attenuating oxidative stress (MDA, P. carbonyl, MPO levels, bcl-2 expression), and calcium content in heart tissue	Animal study	(44)
	Leaf extract	Reducing serum cardiac troponin I and LDH, improving cardiac fibers histology, elevating SOD, GPx, GR, and GST, and decreasing TBARS levels	Reducing inflammation, activation of Nrf2 pathway, improving contractile apparatus	Animal study	(45)
	Root powder	Attenuating blood lipids (TC, LDL, TG, and VLDL)	Improving lipid mechanisms in the liver	Animal study	(64)
	Plant extract	Improving blood lipids (TC, TC, LDL, and HDL), SBP, and DBP	Attenuating inflammation and oxidative stress	Clinical trial	(72)
Pulmonary system	Withaferin A	Inhibiting lung injury and fibrosis progression	Downregulating TGF-β1, collagen I, III, and α-SMA expression	Animal study	(73)
	Withaferin A	Reducing pulmonary fibrosis progression	Suppressing expression of NFκB p65, IL-1β, TNF-α, and pro-fibrotic proteins	*In vivo* and *in vitro*	(74)
	Root powder	Improving pulmonary endothelial dysfunction, reversing right ventricular hypertrophy, reducing apoptosis changes	Attenuating eNOS expression, reducing HIF-1α and NFκB expression	Animal study	(52)

	Withaferin A	Reducing the expression of adhesion molecules (ICAM-1, VCAM-1)	Inactivating Akt and NFκB translocation	*In vitro*	(31)
	Different types of supplementations	Increasing VO_{2max}	Improving mitochondrial function	Human study (meta-analysis)	(75)
Renal system	Root extract	Improving renal toxicity and histopathology	Increasing protein content in renal tissue, increasing antioxidant enzymes (GSH, CAT, SOD), decreasing MDA levels	Animal study	(56)
	Root extract	Retrieving serum protein concentrations	Improving renal corpuscles, tubules and epithelial cells	Animal study (fish)	(76)
	Plant extract	Protection against nephrotoxicity and improving renal function	Inhibiting the increase of BUN, creatinine, and uric acid	Animal study	(60)
	Root extract	Improving histopathology and renal function, increasing total protein, decreasing urea and creatinine levels	Inducing antioxidant and anti-inflammatory effects, inhibiting TNF-α and IL-1β	Animal study	(58)
	Root extract	Protecting against nephrotoxicity, decreasing serum urea and creatinine levels	Reversing oxidative stress in renal tissue	Animal study	(59)
	Root extract	Improving histopathological and enzymatic changes	Increasing the activities of GSH and SOD in renal	Animal study	(57)

		(BUN, creatinine, total protein [decreased], ALB [decreased])	tissue, reducing MDA levels		
	Root powder	Improving renal histological and functional markers (urea, creatinine, and uric acid)	Decreasing renal lipid peroxidation, lysosomal enzymes and glycoproteins	Animal study	(61)
Liver tissue	Root extract	Improving histopathology and hepatic function, Decreasing the levels of AST, ALT, and ALP	Producing antioxidant and anti-inflammatory effects, inhibiting TNF-α and IL-1β, hepatoprotection via the Nrf2 pathway	Animal study	(58)
	Root extract	Improving hepatic enzymes (ALP, ALT, and AST)	Removing urea-related peptides, increasing the antioxidant activity and free radical scavenging	Animal study	(57)
	Root powder	Improving hepatic enzymes (AST and ALT) and total bilirubin level	Removing urea-related peptides, increasing total antioxidant status and SOD levels, decreasing MDA levels	Animal study	(64)
	Plant extract	Improving histopathology and liver markers (ALT, AST, ALP, and total bilirubin), increasing serum total protein	Reducing the production of ROS, increasing antioxidant markers (SOD, CAT, GST, and active GSH)	Animal study	(65)
	Root extract	Decreasing liver markers (AST, ALT, and LDH) and TBARS	Reducing oxidative stress (lipid peroxidation)	Animal study	(66)

	Root extract	Decreasing liver damage markers (AST, ALT, ALP, GGT, and MDA), improving antioxidant markers (SOD, GPx, and GSH)	Inhibiting NFκB activation, protecting against oxidative stress	Animal study	(63)
Immune system	Root extract	Elevating RBCs, CD4 and CD8 counts	Improving anti-inflammatory effects and immune responsivity	Clinical study	(68)
	Root extract	Increasing the number of $CD4^+$ and $CD3^+$ T cells	Stimulating responsiveness in certain immune effector cells	Animal study	(70)
	Root extract	Increasing $CD4^+$ and $CD8^+$ T cells	Adaptogenic properties, decreasing cortisol	Animal study	(69)
	Plant extract	Attenuating $CD4^+$ and $CD8^+$ T cells, decreasing viral load	Improving selective cell-mediated immune response Th1 by increasing IFN-γ and IL-2 cytokine production	Animal study (chicks)	(71)
	Root extract	Enhancing total WBC count and bone marrow cells, increasing circulating antibody titer and antibody forming cells	Anti-inflammatory and immunomodulatory properties, enhancing the differentiation of stem cells	Animal study	(77)

The preventive impact of withaferin A against myocardial ischemia/reperfusion injury was studied in a study, in which low doses of withaferin A improved cardiac function, reduced infarct size, and inhibited cardiomyocyte apoptosis after administration of withaferin A in an animal model (29). The administration of withaferin A has also been reported to reduce myocardial fibrosis following isoproterenol treatment in mice (30).

In the case of pulmonary cells, withaferin A suppressed nuclear translocation of NF-κB and phosphorylation of Akt. Inflammation-induced expression of adhesion molecule-1 and vascular cell adhesion molecule-1 is also inhibited by withaferin A in A549 cell line (31). Gao et al. investigated the effectiveness of withaferin A on acute lung injury in neonatal rats. Withaferin A attenuated pulmonary neutrophil infiltration (measured by myeloperoxidase), pathological changes, and pulmonary edema. Moreover, Pretreatment with withaferin A decreased inflammatory cytokines including TNF-α, interleukine-6, IL-1β, and macrophage inflammatory protein-2 (32).

There are some evidence that indicates that the bioactive components of WS can act as potent anti-inflammatory, anti-apoptosis, antioxidant, anti-arthritic, and humoral and cellular immune-modulating agents (33). Table 1 summarizes the bioactive components of the plant and their activities observed in previous studies.

Probable benefits of Ashwagandha for COVID-19 patients

As mentioned earlier, not only COVID-19 patients are afflicted by pulmonary complications but also the virus can spread beyond the lungs and damage other organs including the liver, kidneys, lymphocytes, heart, and nervous system (38). In addition to antiapoptotic and anti-inflammatory benefits, WS extracts have shown immunomodulatory and multiple organ-protective properties, suggesting that the plant can be used as an adjuvant therapy for COVID-19 (38, 39).

Cardiovascular system

Several studies have reported cardiovascular complications such as

cardiomyopathy, myocarditis, endothelial dysfunction, and arrhythmias in SARS-CoV2 cases (40). In a systematic review of cardiac autopsies from COVID-19 patients, cardiac hypertrophy, cardiac dilation, myocardial fibrosis, myocardial edema, myocardial infarction, myocarditis, and microscopic ischemia were seen in postmortem examination (41). Elevated levels of Troponin 1 and Lactate dehydrogenase were also observed in patients (42, 43).

Protective effects of WS have been studied in doxorubicin-induced cardiac toxicity in rats. following WS supplementation, attenuated oxidative damage through reducing cardiac Malondialdehyde (MDA), protein carbonyl, and increasing expression of anti-apoptotic protein Bcl-2 (44). WS leaf extract also induced an improving effect on cardiac troponin I and lactate dehydrogenase (LDH) levels, and histopathological alterations in contractile apparatus (45). Improving effects on systolic (46) and diastolic blood pressure (47), and vasorelaxation of the aortic rings (48) have been observed in human and animal trials; therefore, WS may protect the cardiovascular system against hyperinflammation induced by SARS-CoV-2.

Pulmonary system

The pulmonary system, particularly the lungs, are the most affected organ by SARS-CoV2. Acute lung injury, pulmonary edema, pulmonary hypertension, and pulmonary vasculature are main symptoms among COVID-19 patients. Interstitial inflammation and alveolar injury (40), followed by pulmonary fibrosis (49), have also been reported in patients with SARS-CoV2.

In an animal study, withaferin A exhibited protective properties against lung injury and fibrosis progression via downregulating expression of transforming growth factor-β1 (TGF-β1), collagen type I and III, and also α-smooth muscle actin (α-SMA) [24]. These types of collagens are upregulated in the lung tissues of patients with idiopathic pulmonary fibrosis (50). α-SMA is a well-known protein used for the assessment of activated fibroblasts in different tissues

including the lungs (51). The improvement of endothelial dysfunction and apoptotic changes were observed after WS root powder supplementation. The probable underlying mechanism is reduction of NFκB expression and hypoxia-induced factor 1 (HIF-1), whose functions are reversed by WS extract (52). Inactivation of AKT and NFκB translocation, followed by reduced expression of adhesion molecules such as intercellular adhesion molecule (ICAM) and vascular cell adhesion molecule-1 (VCAM-1), were observed in an *in vitro* study (31). ICAM-1 seems to have high expression in the lung tissues of COVID-19 patients, while it could induce endotheliitis and hyper-inflammation by attracting leukocytes (51). It has been widely acknowledged that cytokine storm and the related inflammation resulting from SARS-CoV2, are detrimental to the lung tissue by the same token in other tissues (40). WS may play a beneficial role in reversing the hyperinflammation with respect to the proposed mechanisms.

Renal system

In addition to other endothelial disorders, acute kidney injury (AKI) is another common underlying disorder in patients with COVID-19. Development of AKI is associated with higher mortality among hospitalized patients. Abnormal urinary analysis was observed along with impaired antioxidant defense (40, 53). Patients with SARS-CoV2 showed decreased levels of total protein, whole blood cell, and superoxide dismutase (SOD) in COVID-19 patients compared to the control group (54). Bastug et al. reported elevated urea and creatinine concentrations, and reduced levels of glomerular filtration rate (GFR), total protein, and albumin levels in COVID-19 patients in ICU (55).

Several studies have demonstrated curative and protective properties of WS extract for nephrotoxicity and renal markers. In the study of Chand et al., increased antioxidant enzymes and protein content in renal tissue were observed after WS supplementation in mice model (56). Another study demonstrated histopathological improvement (57, 58) and renal

function (decreased urea creatinine levels) (58, 59). The underlying mechanism due to which renal dysfunction and altered GFR may be associated with oxidative stress is the impacts of ROS and free radicals on mesangial cells. Free radicals may lead to a contraction of mesangial cells and eventually decrease in GFR (60). By increasing the levels of antioxidants such as glutathione (GSH), SOD, and reducing MDA, WS can improve oxidative stress and inflammation in renal tissue (57). And renal histopathology alterations and dysfunction may be reversed by WS probably through decreasing lipid peroxidation products (61) and inhibiting TNF-α and IL-1β expression (58).

Liver tissue

Liver dysfunction is another complication of SARS-Cov2. Acute liver failure (ALF) occurs due to direct invasion of SARS-CoV2 but the exact mechanism remains unknown (40). Histopathological examinations have shown a number of manifestations such as sinusoidal dilatation and occasional necrosis in COVID-19 liver tissues; however, there are no clear cytopathic changes. Serum analyses have demonstrated increased AST, ALT, and GGT levels and decreased albumin levels (hypoalbuminemia). Increased serum bilirubin levels also reflect liver dysfunction (62).

WS root extract attenuates liver damage markers (AST, ALT, ALP, GGT, and MDA) in animal models (63). Similarly, studies have shown the improvement of total bilirubin levels, MDA (64), serum total protein, and antioxidant markers (SOD, CAT, and GSH) (65). Decrease in LDH and TBARS have also been reported after treatment with WS root powder or extracts (66).

Vasavan et al. observed a protective effect of WS root extract in nandrolone decanoate - induced hepatorenal toxicity in rats. The alteration of histology and biochemical parameters of hepatic damage such as AST, ALT, and ALP were attenuated after treatment with WS root extract. They also attributed this hepatoprotective effect to WS's role in activating Nrf2 signaling, by which TNF-α and IL-1β and related pathways are inhibited (58). Govindappa et al.

claimed that the reverse of hepatic dysfunction and damage might be related to the capability of WS bioactive components for removal of urea-related peptides and scavenging free radicals (57).

Immune system

Hematological changes including lymphopenia, decreased CD4 and CD8 counts, thrombocytopenia, and occasionally leukopenia are common among COVID-19 patients. $CD4^+$ and $CD8^+$ T lymphocytes are important subtypes of lymphocytes that play an important role in eliminating virus-infected cells, and both cell counts are useful in predicting clinical outcomes. $CD3^+$, $CD4^+$, and $CD8^+$ T lymphocytes are inversely associated with COVID-19 severity and decrease in critical cases of the disease (67).

In a clinical study, WS root extract, as an adjuvant therapy, in patients with tuberculosis resulted in the elevation of CD4 and CD8 cell counts. Health-related quality of life also improved in the WS group compared to the placebo group (68). WS can exert adaptogenic properties and improve Th1 lymphocyte subset distribution in stress-induced mice. The augmentation of CD3+, CD4+, and $CD8^+$ T cells occurs alongside a decrease in cortisol levels (69). Mikolai et al. found an elevation of $CD3^+$ and $CD4^+$ T cells after supplementation with WS root extract, and the suggested underlying mechanism was stimulation of responsiveness in certain immune effector cells, which are crucial for immunomodulation (70). In a study on the effectiveness of WS extract on infected chicks (via chicken infectious anemia virus), $CD4^+$ cell count decreased in the positive control group while in the WS group, $CD4^+$ cell count increased. The flow cytometry results demonstrated a significant decrease in $CD8^+$ T cells but a slight reduction in the cell count was observed in the WS group. They concluded that WS might induce an effective resistance in infected chicks probably by improving cell-mediated immune response Th1 and increasing IFN-γ and IL-2 cytokine production (71).

Abbreviations: MDA: malondialdehyde, MPO: myeloperoxidase, bcl-2: B-cell

lymphoma 2, LDH: lactate dehydrogenase, SOD: super-oxide dismutase, GPx: glutathione peroxidase, GR: glutathione reductase, GST: glutathione-S-transferase, TBARS: Thiobarbituric acid reactive substances, Nrf2: nuclear factor erythroid 2-related factor 2, TC: total cholesterol, LDL, low-density lipoprotein, HDL: high-density lipoprotein, SBP: systolic blood pressure, DBP: diastolic blood pressure, WBC: white blood cell, PT: prothrombin time, COX: cyclooxygenase, TGF: transforming growth factor, SMA: smooth muscle actin, NF-κB: Nuclear factor kappa B, eNOS: endothelial nitric oxide synthase, ICAM: Intercellular Adhesion Molecule, VCAM: vascular cell adhesion molecule, CAT: catalase, BUN: blood urea nitrogen, TNF: tumor necrosis factor, GSH: [reduced] glutathione, ALB: albumin, ALP: alkaline phosphatase, ALT: alanine trans-aminase, AST: aspartate trans-aminase, GGT: gamma-glutamyl transferase, Th1: T-helper 1, IFN: interferon, IL: interleukin

CONCLUSION

This narrative review addressed the possible inhibitory effects of WS on SARS-CoV-2 based on research findings. Current evidence demonstrates that WS can produce a wide range of anti-inflammatory and antioxidant effects against SARS-CoV-2 and the resulting multiple organ failure. This review suggested the efficacy of WS in combating COVID-19-induced cytokine storm that is mainly attributed to its bioactive components. However, there are limited clinical trial studies examining the benefits of WS in human COVID-19 cases. Therefore, WS can be considered as a medicinal herb if further preclinical and clinical investigations on the treatment of COVID-19 confirm the argument; high-quality human trials using WS and its compounds for COVID-19 should be conducted. Studies on the coagulation system cited in this study suffered from some limitations.

CONFLICT OF INTERESTS

None.

References

1. Acter T, Uddin N, Das J, Akhter A, Choudhury TR, Kim S. Evolution of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) as coronavirus disease 2019 (COVID-19) pandemic: A global health emergency. Science of the Total Environment. 2020;730:138996.
2. Zaim S, Chong JH, Sankaranarayanan V, Harky A. COVID-19 and multiorgan response. Current problems in cardiology. 2020;45(8):100618.
3. Tufan A, Güler AA, Matucci-Cerinic M. COVID-19, immune system response, hyperinflammation and repurposing antirheumatic drugs. Turkish journal of medical sciences. 2020;50(SI-1):620-32.
4. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. The lancet. 2020;395(10229):1033-4.
5. Sinha P, Matthay MA, Calfee CS. Is a "cytokine storm" relevant to COVID-19? JAMA internal medicine. 2020;180(9):1152-4.
6. Kadhom M, Al-Doori AN, Ahmed DS, Yousif E. Herbal medicine as an alternative method to treat and prevent COVID-19. Baghdad Journal of Biochemistry and Applied Biological Sciences. 2021;2(01):1-20.
7. Nugraha RV, Ridwansyah H, Ghozali M, Khairani AF, Atik N. Traditional herbal medicine candidates as complementary treatments for COVID-19: a review of their mechanisms, pros and cons. Evidence-Based Complementary and Alternative Medicine. 2020;2020.
8. Chopra A, Gautam PC, Tillu G, Saluja M, Borse S, Sarmukaddam S, et al. Randomized, double blind, placebo controlled, clinical trial to study co-administration of Ashwagandha on safety, immunogenicity, and protection with COVID-19 vaccine: A Study Protocol. medRxiv. 2021.
9. Yadav B, Rai A, Mundada PS, Singhal R, Rao B, Rana R, et al. Safety and efficacy of Ayurvedic interventions and Yoga on long term effects of COVID-19: A structured summary of a study protocol for a randomized controlled trial. Trials. 2021;22(1):1-3.
10. Dhawan M, Parmar M, Sharun K, Tiwari R, Bilal M, Dhama K. Medicinal and therapeutic potential of withanolides from Withania somnifera

against COVID-19. J Appl Pharm Sci. 2021;11:6-13.

11. John J. Therapeutic potential of Withania somnifera: a report on phyto-pharmacological properties. International Journal of Pharmaceutical sciences and research. 2014;5(6):2131-48.

12. Mir BA, Khazir J, Mir NA, Hasan T-u, Koul S. Botanical, chemical and pharmacological review of Withania somnifera (Indian ginseng): an ayurvedic medicinal plant. Indian J Drugs Dis. 2012;1(6):147-60.

13. Namdeo AG, Ingawale DK. Ashwagandha: Advances in plant biotechnological approaches for propagation and production of bioactive compounds. Journal of Ethnopharmacology. 2020:113709.

14. Gajbhiye NA, Makasana J, Kumar S. Accumulation of three important bioactive compounds in different plant parts of Withania somnifera and its determination by the LC–ESI-MS-MS (MRM) method. Journal of chromatographic science. 2015;53(10):1749-56.

15. Bhaskar S, Sinha A, Banach M, Mittoo S, Weissert R, Kass JS, et al. Cytokine storm in COVID-19—immunopathological mechanisms, clinical considerations, and therapeutic approaches: the REPROGRAM consortium position paper. Frontiers in immunology. 2020;11:1648.

16. Fara A, Mitrev Z, Rosalia RA, Assas BM. Cytokine storm and COVID-19: a chronicle of pro-inflammatory cytokines. Open biology. 2020;10(9):200160.

17. Sikandan A, Shinomiya T, Nagahara Y. Ashwagandha root extract exerts anti‐inflammatory effects in HaCaT cells by inhibiting the MAPK/NF‐κB pathways and by regulating cytokines. International journal of molecular medicine. 2018;42(1):425-34.

18. Grunz-Borgmann E, Mossine V, Fritsche K, Parrish AR. Ashwagandha attenuates TNF-α-and LPS-induced NF-κB activation and CCL2 and CCL5 gene expression in NRK-52E cells. BMC complementary and alternative medicine. 2015;15(1):1-8.

19. Bhasin S, Singh M, Singh D. Review on bioactive metabolites of Withania somnifera.(L.) Dunal and its pharmacological significance. Journal of Pharmacognosy and Phytochemistry. 2019;8(3):3906-9.

20. Malik F, Singh J, Khajuria A, Suri KA, Satti NK, Singh S, et al. A standardized root extract of Withania somnifera and its major constituent withanolide-A elicit humoral and cell-mediated immune responses by up regulation of Th1-dominant polarization in BALB/c mice. Life Sciences. 2007;80(16):1525-38.

21. Kour K, Pandey A, Suri K, Satti N, Gupta K, Bani S. Restoration of stress-induced altered T cell function and corresponding cytokines patterns by Withanolide A. International immunopharmacology. 2009;9(10):1137-44.

22. Sun GY, Li R, Cui J, Hannink M, Gu Z, Fritsche KL, et al. Withania somnifera and its withanolides attenuate oxidative and inflammatory responses and up-regulate antioxidant responses in BV-2 microglial cells. Neuromolecular medicine. 2016;18(3):241-52.

23. Kuboyama T, Tohda C, Komatsu K. Neuritic regeneration and synaptic reconstruction induced by withanolide A. British journal of pharmacology. 2005;144(7):961-71.

24. SoRelle J, Itoh T, Peng H, Kanak M, Sugimoto K, Matsumoto S, et al. Withaferin A inhibits pro-inflammatory cytokine-induced damage to islets in culture and following transplantation. Diabetologia. 2013;56(4):814-24.

25. Batumalaie K, Amin MA, Murugan DD, Sattar MZA, Abdullah NA. Withaferin A protects against palmitic acid-induced endothelial insulin resistance and dysfunction through suppression of oxidative stress and inflammation. Scientific reports. 2016;6(1):1-11.

26. Maitra R, Porter MA, Huang S, Gilmour BP. Inhibition of NFκB by the natural product Withaferin A in cellular models of Cystic Fibrosis inflammation. Journal of Inflammation. 2009;6(1):1-5.

27. Martorana F, Guidotti G, Brambilla L, Rossi D. Withaferin A inhibits nuclear factor-κB-dependent pro-inflammatory and stress response pathways in the astrocytes. Neural plasticity. 2015;2015.

28. Fang R, Wang C, Jiang Q, Lv M, Gao P, Yu X, et al. NEMO–IKKβ are essential for IRF3 and NF-κB activation in the cGAS–STING pathway. The Journal of Immunology. 2017;199(9):3222-33.

29. Guo R, Gan L, Lau WB, Yan Z, Xie D, Gao E, et al. Withaferin A prevents myocardial

ischemia/reperfusion injury by upregulating AMP-activated protein kinase-dependent B-cell lymphoma2 signaling. Circulation Journal. 2019;83(8):1726-36.

30. Challa AA, Vukmirovic M, Blackmon J, Stefanovic B. Withaferin-A reduces type I collagen expression in vitro and inhibits development of myocardial fibrosis in vivo. 2012.

31. Oh JH, Kwon TK. Withaferin A inhibits tumor necrosis factor-α-induced expression of cell adhesion molecules by inactivation of Akt and NF-κB in human pulmonary epithelial cells. International immunopharmacology. 2009;9(5):614-9.

32. Gao S, Li H, Zhou X, You J, Tu D, Xia G, et al. Withaferin A attenuates lipopolysaccharide-induced acute lung injury in neonatal rats. Cellular and Molecular Biology. 2015;61(3):102-6.

33. Gupta A, Singh S. Evaluation of anti-inflammatory effect of Withania somnifera root on collagen-induced arthritis in rats. Pharmaceutical biology. 2014;52(3):308-20.

34. Saleem S, Muhammad G, Hussain MA, Altaf M, Bukhari SNA. Withania somnifera L.: Insights into the phytochemical profile, therapeutic potential, clinical trials, and future prospective. Iranian Journal of Basic Medical Sciences. 2020;23(12):1501.

35. Krutika J, Tavhare S, Panara K, Kumar P, Karra N. Studies of ashwagandha (Withania somnifera dunal). Int J Pharm Biol Arch. 2016;7(1):1-11.

36. Berghe WV, Sabbe L, Kaileh M, Haegeman G, Heyninck K. Molecular insight in the multifunctional activities of Withaferin A. Biochemical pharmacology. 2012;84(10):1282-91.

37. Kumar V, Dey A, Hadimani MB, Marcovic T, Emerald M. Chemistry and pharmacology of Withania somnifera: An update. CELLMED. 2015;5(1):1.-.13.

38. Tillu G, Chaturvedi S, Chopra A, Patwardhan B. Public health approach of ayurveda and yoga for COVID-19 prophylaxis. The Journal of Alternative and Complementary Medicine. 2020;26(5):360-4.

39. McCord JM, Hybertson BM, Cota-Gomez A, Geraci KP, Gao B. Nrf2 activator PB125® as a potential therapeutic agent against COVID-19. Antioxidants. 2020;9(6):518.

40. Mokhtari T, Hassani F, Ghaffari N, Ebrahimi B, Yarahmadi A,

Hassanzadeh G. COVID-19 and multiorgan failure: A narrative review on potential mechanisms. Journal of molecular histology. 2020:1-16.

41. Roshdy A, Zaher S, Fayed H, Coghlan JG. COVID-19 and the heart: a systematic review of cardiac autopsies. Frontiers in cardiovascular medicine. 2020;7.

42. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. The lancet. 2020;395(10223):497-506.

43. Salvatici M, Barbieri B, Cioffi SMG, Morenghi E, Leone FP, Maura F, et al. Association between cardiac troponin I and mortality in patients with COVID-19. Biomarkers. 2020;25(8):634-40.

44. Hamza A, Amin A, Daoud S. The protective effect of a purified extract of Withania somnifera against doxorubicin-induced cardiac toxicity in rats. Cell biology and toxicology. 2008;24(1):63-73.

45. Khalil M, Ahmmed I, Ahmed R, Tanvir E, Afroz R, Paul S, et al. Amelioration of isoproterenol-induced oxidative damage in rat myocardium by Withania somnifera leaf extract. BioMed research international. 2015;2015.

46. Tripathi R, Salve B, Petare A, Raut A, Rege N. Effect of Withania somnifera on physical and cardiovascular performance induced by physical stress in healthy human volunteers. Int J Basic Clin Pharmacol. 2016;5:2510-6.

47. Kushwaha S, Betsy A, Chawla P. Effect of Ashwagandha (Withania somnifera) root powder supplementation in treatment of hypertension. Studies on Ethno-Medicine. 2012;6(2):111-5.

48. Pathak P, Shukla P, Kanshana JS, Jagavelu K, Sangwan NS, Dwivedi AK, et al. Standardized root extract of Withania somnifera and Withanolide A exert moderate vasorelaxant effect in the rat aortic rings by enhancing nitric oxide generation. Journal of Ethnopharmacology. 2021:114296.

49. Spagnolo P, Balestro E, Aliberti S, Cocconcelli E, Biondini D, Della Casa G, et al. Pulmonary fibrosis secondary to COVID-19: a call to arms? The Lancet Respiratory Medicine. 2020;8(8):750-2.

50. Nielsen SH, Willumsen N, Leeming DJ, Daniels SJ, Brix S,

Karsdal MA, et al. Serological assessment of activated fibroblasts by alpha-smooth muscle actin (α-SMA): a noninvasive biomarker of activated fibroblasts in lung disorders. Translational oncology. 2019;12(2):368-74.

51. Nagashima S, Mendes MC, Camargo Martins AP, Borges NH, Godoy TM, Miggiolaro AFRdS, et al. Endothelial dysfunction and thrombosis in patients with COVID-19—brief report. Arteriosclerosis, thrombosis, and vascular biology. 2020;40(10):2404-7.

52. Kaur G, Singh N, Samuel SS, Bora HK, Sharma S, Pachauri SD, et al. Withania somnifera shows a protective effect in monocrotaline-induced pulmonary hypertension. Pharmaceutical biology. 2015;53(1):147-57.

53. Sardu C, Gambardella J, Morelli MB, Wang X, Marfella R, Santulli G. Hypertension, thrombosis, kidney failure, and diabetes: is COVID-19 an endothelial disease? A comprehensive evaluation of clinical and basic evidence. Journal of clinical medicine. 2020;9(5):1417.

54. Zhao G, Su Y, Sun X, Cui X, Dang L, Zhao L, et al. A comparative study of the laboratory features of COVID-19 and other viral pneumonias in the recovery stage. Journal of Clinical Laboratory Analysis. 2020;34(10):e23483.

55. Bastug A, Bodur H, Erdogan S, Gokcinar D, Kazancioglu S, Kosovali BD, et al. Clinical and laboratory features of COVID-19: Predictors of severe prognosis. International immunopharmacology. 2020;88:106950.

56. Sharma V, Sharma S, Pracheta PR, Sharma S. Therapeutic efficacy of Withania somnifera root extract in the regulation of lead nitrate induced nephrotoxicity in Swiss albino mice. J Pharm Res. 2011;4(3):755-75.

57. Govindappa PK, Gautam V, Tripathi SM, Sahni YP, Raghavendra HLS. Effect of Withania somnifera on gentamicin induced renal lesions in rats. Revista Brasileira de Farmacognosia. 2019;29:234-40.

58. Vasavan SS, Jagadesan V, Sivanesan S, Rajagopalan V. Protective effect of Withania somnifera on nandrolone decanoate-induced biochemical alterations and hepatorenal toxicity in wistar rats. Pharmacognosy Magazine. 2020;16(68):218.

59. Rasheed A, Younus N, Waseem N, Badshsah M, editors. Protective Effect of Withania Somnifera Root Extract Against Cisplatin Induced Nephrotoxicity Through Renal Function Analysis in Albino Wistar Rats. Med Forum; 2020.
60. Akhtar F, Azhar M, Aslam M, Javed K. Nephroprotective Effect of Asgand Powder (Withania somnifera Dunal) on Cisplatin Induced Renal Injury in Rats. Journal of Drug Delivery and Therapeutics. 2020;10(6-s):22-5.
61. Vedi M, Rasool M, Sabina EP. Protective effect of administration of Withania somifera against bromobenzene induced nephrotoxicity and mitochondrial oxidative stress in rats. Renal failure. 2014;36(7):1095-103.
62. Kumar-M P, Mishra S, Jha DK, Shukla J, Choudhury A, Mohindra R, et al. Coronavirus disease (COVID-19) and the liver: a comprehensive systematic review and meta-analysis. Hepatology international. 2020;14(5):711-22.
63. Mansour HH, Hafez HF. Protective effect of Withania somnifera against radiation-induced hepatotoxicity in rats. Ecotoxicology and environmental safety. 2012;80:14-9.
64. Elsemelawy SAE, Tag Al Deen R. Effect of Feeding Cake Fortified with Different Concentrations of Ashwagandha Root against Sodium Arsenite Toxicity in Male Rats. Bulletin of the National Nutrition Institute of the Arab Republic of Egypt. 2016;47(2):1-22.
65. Sabina EP, Rasool M, Vedi M, Navaneethan D, Ravichander M, Parthasarthy P, et al. Hepatoprotective and antioxidant potential of Withania somnifera against paracetamol-induced liver damage in rats. Int J Pharm Pharm Sci. 2013;5(2):648-51.
66. Bhattacharya A, Ramanathan M, Ghosal S, Bhattacharya S. Effect of Withania somnifera glycowithanolides on iron-induced hepatotoxicity in rats. Phytotherapy Research: An International Journal Devoted to Pharmacological and Toxicological Evaluation of Natural Product Derivatives. 2000;14(7):568-70.
67. Liu R, Wang Y, Li J, Han H, Xia Z, Liu F, et al. Decreased T cell populations contribute to the increased severity of COVID-19. Clinica Chimica Acta. 2020;508:110-4.

68. Kumar R, Rai J, Kajal N, Devi P. Comparative study of effect of Withania somnifera as an adjuvant to DOTS in patients of newly diagnosed sputum smear positive pulmonary tuberculosis. Indian Journal of Tuberculosis. 2018;65(3):246-51.

69. Khan B, Ahmad SF, Bani S, Kaul A, Suri K, Satti N, et al. Augmentation and proliferation of T lymphocytes and Th-1 cytokines by Withania somnifera in stressed mice. International immunopharmacology. 2006;6(9):1394-403.

70. Mikolai J, Erlandsen A, Murison A, Brown KA, Gregory WL, Raman-Caplan P, et al. In vivo effects of Ashwagandha (Withania somnifera) extract on the activation of lymphocytes. The Journal of Alternative and Complementary Medicine. 2009;15(4):423-30.

71. 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(1):115-20.

72. Adi BSABS, Rami SRRES, Reddy E. An open clinical study on the efficacy of Withania somnifera mother tincture in the management of hyperlipidemia. International Journal of Indigenous Herbs and Drugs. 2019:1-6.

73. Zhao H, Gao Z, Xie S, Han X, Sun Q. Withaferin A attenuates ovalbumin induced airway inflammation. injury. 2019;5:6.

74. Bale S, Venkatesh P, Sunkoju M, Godugu C. An adaptogen: withaferin A ameliorates in vitro and in vivo pulmonary fibrosis by modulating the interplay of fibrotic, matricelluar proteins, and cytokines. Frontiers in pharmacology. 2018;9:248.

75. Pérez-Gómez J, Villafaina S, Adsuar JC, Merellano-Navarro E, Collado-Mateo D. Effects of Ashwagandha (Withania somnifera) on VO2max: a systematic review and meta-analysis. Nutrients. 2020;12(4):1119.

76. Chand G, Singh P. POSSIBLE RETRIEVAL OF ORGANOCHLORINE INDUCED RENAL TOXICITY IN FISH BY AQUEOUS ROOT EXTRACT OF WITHANIA SOMNIFERA: IN VIVO STUDY. International Journal of

Pharmaceutical Sciences and Research. 2016;7(6).
77. Davis L, Kuttan G. Immunomodulatory activity of Withania somnifera. Journal of ethnopharmacology. 2000;71(1-2):193-200.