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THE ABILITY OF WITHANIA SOMNIFERA (L.) DUNAL TO MODULATE IMMUNE RESPONSES IN INFLAMMATORY DISORDERS

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Abstract

Withania somnifera (L.) Dunal (also known as ashwagandha), a drug-producing plant, has been used for many years to treat a variety of chronic illnesses, including high blood pressure, arthritis, diabetes, Alzheimer's disease, and depression. *W. Somnifera* appears to possess anti-inflammatory, antioxidant, anticarinogenic, anti-diabetic, and anti-asthmatic effects similar to other medical plants. *Somnifera* is frequently linked to the ginseng plant because of its ability to lower stress, improve cognitive functions (including memory), and maintain a healthy immune system. *Somnifera* is frequently linked to the ginseng plant because of its ability to lower stress, improve cognitive functions (including memory), and maintain a healthy immune system. It encourages immune modulatory effects that help the adaptive immune systems humoral and cellular responses balance one another. Some of the active ingredients in *w. Somnifera* is believed to have medicinal benefits, including alkaloids, steroidal saponins, and steroidal lactones (including withanolides and withaferins). B. *Somnifera* is a safe and extremely effective treatment for a number of ailments, but its exact mechanism of action is still partially understood. One of the put-up theories states that *W. Somnifera* promotes cellular-mediated immunity or initiates chemical processes that aid in the production of therapeutic effects. *Withania* has been demonstrated to have a significant impact in immunological diseases by modifying a variety of cytokines, increasing T-cell proliferation, and enhancing macrophage activity. The current review is based on the most recent therapeutic effects of *W. somnifera* on a number of illnesses by affecting immunological markers and the active components of *W. somnifera* that cause these therapeutic actions. Additionally, there has been discussion of the chemical makeup of *W. somnifera* and its immunomodulatory function in type 2 allergic disorders.

Keywords: Immunomodulation, immunostimulatory effects, *Withania somnifera*, innate immunity, immune receptors, adaptive immunity

1. Introduction

The immune system responds effectively to self-antigens from host tissues while dealing with a variety of external antigens derived from microorganisms (such as bacteria and viruses). Immune system infections are typically cleared by the innate immune organs and cells; however, when innate immunity is restored, adaptive immunity is triggered. The innate immune system is comprised of the skin; tears, low stomach pH, and body temperature, whereas the majority of the adaptive immune system is made up of T and B cells. When the innate immune system fails to eradicate infections, the adaptive immune response can function in one of two ways (cell-mediated or humoral), depending on the kind of organism. Cell-mediated immunity is required

for defence against intracellular bacteria and viruses. When viruses cause microbiological infection, the innate natural killer cells (NK cells), the adaptive T helper 1 (Th1), and the cytotoxic CD8+ cells can reduce virally infected cells. [1] Although considering that NK cells and CD8 cells differ from one another in a number of areas, including antigen recognition, specificity, and memory, both cell types work towards the same objective. On the other hand, fighting parasite and extracellular infections calls for humoral immunity, which consists of T helper 2 (Th2), B cells, and antibodies. When infections are introduced, neutrophils are the body's early innate immune reaction. [2] After then, phagocytosis ensues as dendritic cells and other antigen-presenting cells (APCs) carry the microbe (i.e., bacteria) to secondary lymphoid organs like lymph nodes where they form an antigenic peptide for adaptive Th2 cells. [3] Such B cells (which likely encountered the same antigen in a different organ) will get the activation signal once Th2 is triggered by the antigen peptide. It will create B lymphocytes, which develop into plasma cells, which are known to make antibodies [4]. Immunoglobulins, often known as antibodies, come in five different subtypes: IgM, IgA, IgG, IgE, and IgD [6]. As viral infections result in the formation of IgG antibodies, parasite disorders cause the creation of IgG and IgE antibodies, which are crucial in allergic diseases [8]. Antibiotics are frequently used to treat microbial infections, which releases a small number of memory CD4 and CD8 cells to prevent infections from the same organism.

Immunological reactions brought on by immunogenic microbe components, which are utilised therapeutically, resemble those brought on by parasitic and viral illnesses. For instance, double-stranded RNA (dsRNA) architecture and immunogenic Cytosine-phosphate-Guanine (CpG) motifs are shared by both bacteria and viruses (Hartmann, 2017). DsRNA and CpG DNA are regarded as adjuvants because they trigger the immune system's production of type I interferon (IFN) and CD4+ and CD8+ cells by activating innate receptors such toll-like receptors (TLRs) 3 and 9 [9]. Since there have been less side effects connected with their usage and the bulk of these botanical compounds have been used by humans for thousands of years, using them as immunomodulators is substantially safer than using conventional adjuvants.

For thousands of years, people have utilised the plant medicine withania somnifera (L.) Dunal (Solanaceae) for a range of purposes, including as dietary supplements as a remedy for a number of diseases. Excellent outcomes have been seen when withania has been used therapeutically in mice and people as an adjuvant or immunomodulator (e.g., anticancerogenic, arthritis therapy) (10. Adjuvants or immunomodulators typically exploit the immunological receptors on innate cells like dendritic cells to initiate signalling cascades. TLRs are crucial innate immune receptors that react to a range of agonists, both natural and artificial [12]. It has been determined that w. Somnifera affects TLRs similarly to microbial components by preventing influenza A virus-induced activation of TLR2/4 and TLR2 and TLR4 mRNA expression. In 2020, Kashyap et al.Additionally, when type 2 inflammation predominates in allergy problems, w. Somnifera has been used to treat such diseases [10].

1.1 W. Somnifera function in type 2 inflammation

The immune system has a varied response to foreign particles while having tolerance for self- or harmless particles. The majority of the time, innocuous particles does not induce immunological responses. On the other hand, some substances (referred to as allergens) might lead to unfavorable immunological reactions, such as skin rashes, increased mucus production, constriction of the respiratory smooth muscles, diarrhea, and other symptoms [13]. IgE antibody is the primary immunoglobulin in charge of the majority of allergy symptoms [13]. Mast cells and basophils are equipped with IgE antibody receptors to prepare them for future allergen exposure [14]. After a second interaction, the IgE receptor on these cells reacts to allergens, increasing type 2 allergic inflammation [13]. Type 2 allergic inflammation is marked by the activation of Th2 and B cells, which leads to the production of IgE antibodies, an increase in eosinophils, a large concentration of group 2 innate lymphoid cells (ILC2), and elevated Th2 cytokines (IL-4, IL-5, IL-13) [13].

It is now apparent that allergic reactions experienced by patients result from both innate and adaptive immunological responses (Maeda et al., 2019). It was previously believed that the adaptive T helper (Th2) cell is the main cause of type 2 inflammation, but recent studies have shown that innate immune cells such ILC2 cells are crucial for the development of allergic diseases [17]. Inflammatory mouse models have shown that activating innate cells to immunomodulators or adjuvants at active concentrations of 1.0 mg/kg or as low as 0.001 mg/kg intratracheally can skew the Th2 immune response to the Th1 immune response, which also results in attenuated allergic immunity, decreased levels of histamine and eosinophils, and attenuated allergic immunity [18]. Use of the plant W. Somnifera is one of the methods suggested to lessen the type 2 inflammation found in asthma [21]. According to a recent research, w. Somnifera lowers the levels of type 2 cytokines (such IL-4 and IL-13) and type 2 inflammation markers like TNF- and IgE generated by OVA, indicating that it possesses immunomodulatory qualities that might be used to diminish type 2 inflammation [22]. One of the current immunotherapy approaches to reduce type 2 inflammation using adjuvants skews Th2 immune response towards Th1 immune response. It would be helpful to know how effectively W. Somnifera cures allergy diseases like atopic dermatitis and hay fever.

1.2 *w. Somnifera* with other immunomodulators

Inhibiting, activating, or modulating the elements of the innate and adaptive immune systems, immunomodulators have an impact on immunological reactions. Adjuvants have immunomodulatory effects when combined with vaccines by fostering stronger immunological responses mediated by T and B cells. By priming CD4+ and CD8+ cells and activating Th2 immune responses through dendritic cells, adjuvants like alum, which has been used since 1930, boost immunity. (McKee et al., 2009). Adjuvant usage has been expanded to include shifting immune responses from Th2 to Th1, as is the case in allergy disorders [23]. TLR3, TLR4, and TLR9 ligands have been employed as adjuvants to slant type 2 immune responses towards Th1 responses or Regulatory T cells (Tregs) responses (19, 24). As part of the development of immunotherapy for conditions like cancer, clinical trials for the use of different

immunomodulators, including adjuvants such Poly (I: C) and synthetic dsRNA, are now being conducted [25]. More study is being done on the use of natural plant immunomodulators as an alternative to synthetic adjuvants as a result.

Similar to those synthetic adjuvants, there are various fungi- or plant-based medications that have an immune-modulating effect. The immune cell activation of T cells, macrophages, and natural killer cells is encouraged by Ganoderma lucidum, for example [20]. Similar to this, Curcuma longa L. produces a range of immunomodulatory traits, most notably antiallergic properties via reducing histamine production. These traits include those that are anti-inflammatory, antiseptic, anti-cancer, and antioxidant [27].

Additionally, it has been demonstrated that Lentinula edodes (Shiitake) mushrooms improve immune system performance by increasing -T and NKT cells, raising IL-4, IL-10, TNF-, and IL-1 levels, and decreasing macrophage inflammatory protein-1/chemokine C-C ligand 3 (MIP-1/CCL3) and inflammatory protein C-reactive protein levels (CRP) [28].

In various investigations, the *w. Somnifera* immunomodulatory properties have been investigated(Figure 1).It has been demonstrated that *Withania somnifera* root powder inhibits the production of T cells, excessive complement activation, and humoral antibody responses, among other inflammatory mediators [22]. The effectiveness of w. Somnifera in reducing arthritis has also been investigated [29], an autoimmune disorder characterised by increased levels of inflammatory markers such IL-6, IL-10, and TNF-. Withanolides, flavonoids, and lactones, among other compounds, provide w. Somnifera its immunomodulatory effects [22].

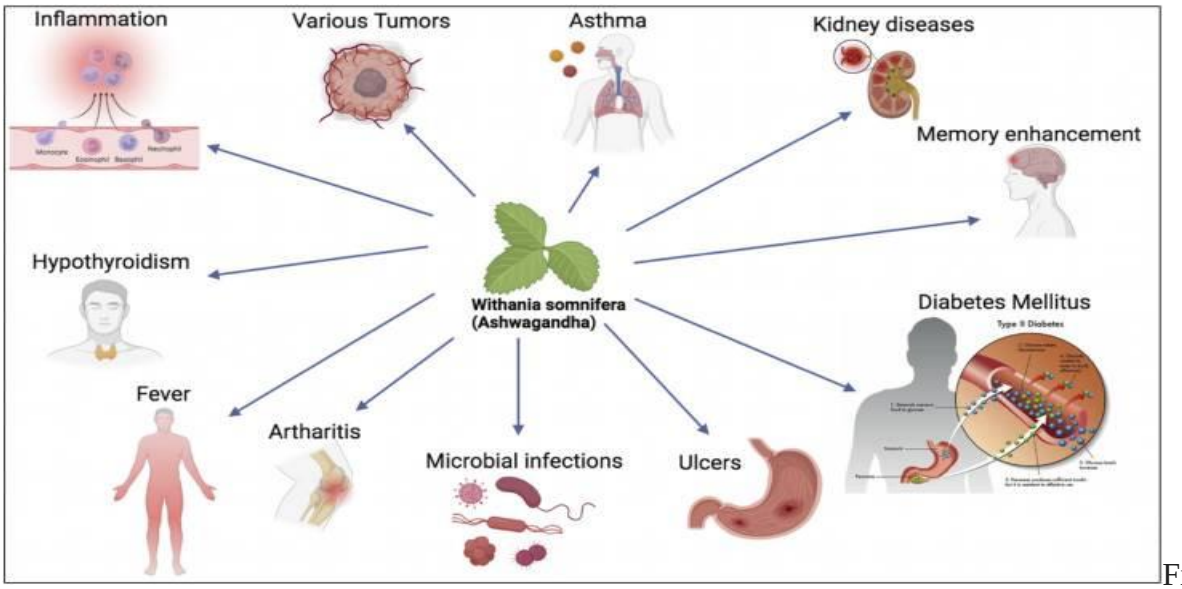

Figure 1: As an herbal medicine, *w. Somnifera* is used to treat a number of chronic illnesses, including diabetes mellitus, renal disease, and asthma.

1.3 Chemical properties of *w. Somnifera* in comparison to other immunomodulators

The steroidal lactones of group C28 known as withanolides are compounds that can be found in nature. Its structure consists of three cyclohexane rings, one cyclopentane ring, and four distinct cycloalkane ring configurations [30]. Withaferin A is very reactive because of its unsaturated

lactone ring, epoxide in the B ring, and ketone-containing unsaturated A ring. The main cytotoxic components of ring an area its double bond and epoxide ring. The ergostane skeleton undergoes oxidation under the influence of withaferin A and similar steroidal metabolites, resulting in the formation of a six-membered delta lactone unit on the 22nd and 26th carbons. The potential to treat neurological, autoimmune, neoplastic, inflammatory, and inflammatory disorders using these analogues is being researched. According to Saleem et al. (2020), withaferin A's anti-inflammatory activities are explained by its capacity to inhibit NF-B, AP1, and alpha-2 macroglobulin. Withaferin A's anti-tumor properties were originally studied in PC-3 human prostate cancer cell line xenografts in naked mice. The androgen receptor (AR) was demonstrated to mediate cytotoxicity. By ATP-independently inhibiting the heat shock protein 90 (HSP90) in an in vivo pancreatic model, it prevents the growth of tumours [32]. In experiments using cancer cell cultures, it inhibits proliferation, demonstrating its cytotoxic and apoptotic effects. Mcl-1 expression has increased in in vitro breast cancer apoptosis models. The majority-conserved alpha-helical coiled 2B domain of withaferin A can bind to the intermediate filament protein and vimentin by covalently switching the cysteine residue [33]. Withaferin A has two actions that might cause apoptosis: vimentin accumulation and aggregation. Both in vitro and in vivo investigations used WA to treat the solid and ascites tumour cells of the mouse sarcoma 180 (S-180). In the cells, the chemical changed the spindle microtubules, as seen under an electron microscope [34].

Withaferin A affects the immune system, which could assist to explain why it's utilised as a general tonic to boost energy and ward off sickness. The immunomodulatory and central nervous system (antistress, memory, and learning) effects of glycowithanolides and a combination of sitoindosides IX and X isolated from withaferin A were investigated in Swiss mice (15-25 g, 5-6 months old) and Wistar breeds albino rats (120-150 g and 250-300 g) [35]. Both drugs markedly boosted peritoneal macrophage recruitment and activation in addition to phagocytosis and elevated lysosomal enzyme activity. Both medications significantly reduced stress in albino mice and rats and significantly improved learning and memory retention in both young and old animals (50-200 mg/kg orally). Using different animal myelosuppression models that included cyclophosphamide, azathioprine, or prednisolone, the root extract of withaferin A was examined for immunomodulatory action [36]. Withaferin A caused statistically significant increases (p 0.05) in hemoglobin concentration, red blood cell count, white blood cell count, platelet count, and body weight when compared to untreated control mice.

In early Ayurvedic literature, the natural remedies mentioned above are typically referred to as revitalizing "Rasayana" with a variety of health advantages. The potential for the inclusion of phytocomponents with immunostimulatory, immunomodulatory, cytoprotective, anti-cancer, anti-inflammatory, and adjuvant properties affected the decision to use those particular plant parts. There are several recipes that use the allegedly common botanical medication. The therapeutic and pharmacognostic effects of herbal medications, including ashwagandha, have been demonstrated in both in vitro and in vivo research. In-depth combinatorial studies are still needed to increase the availability of chemical components and strengthen the body's

immunological defences, despite the fact that there is a wealth of research and publications on the health benefits of traditional botanical antioxidants.

1.4 Possibility of using W. Somnifera as a pharmaceutical agent

Withanolides (steroidal lactones with an ergostane structure), which make up the majority of w. Somnifera's bioactive components, are a class of drugs. Withanolides are six-membered lactone rings with a C9 side chain attached to their steroidal C28 nucleus. Withanolides are highly oxygenated phytochemicals, and oxidation at different skeleton locations is what gives the withanolide classes their particular structural characteristics (Logie and VandenBerghe, 2020).The pharmacological activity of ashwagandha is believed to be largely attributed to two of the plant's main components, withaferin-A and withanolide-D [38]. Significant toxicological study has been conducted on w. somnifera, and findings from several clinical research initiatives have demonstrated that the plant is safe at a range of realistic dosages. The levels at which its formulations are advised for use in humans are probably also quite safe. Studies on the interactions between herbal remedies and other herbal remedies or with other herbal remedies and Somnifera have not yet been reported. We don't yet know the hazards associated with w. Somnifera or how secure it is over time. The somnifera drug may cause nausea, vomiting, or diarrhoea. A small body of research on humans suggests that w. Somnifera might cause sleepiness, possibly fatal respiratory depression, low blood pressure, and irregular heartbeat [39]. The chemistry and pharmacology of numerous w. Somnifera extracts made from the plant's many sections have been studied, and the results strongly suggest that these extracts, when combined with those from other plants, might be used to treat and prevent a variety of illnesses and chronic disorders. The major subject of this chapter is recent and historical advancements in the chemistry and pharmacology of w. Somnifera.

1.5 Infection with COVID-19 and the involvement of W. Somnifera

The positive and negative effects of w. Somnifera have been examined using infection of COVID-19. w. Somnifera [40] established that the interaction between the SARS-COV-2 spike protein domain and the angiotensin-converting enzyme 2 (ACE2) receptor is broken. The primary receptor for SARS-COV-2 entrance into cells is considered to be the ACE2 receptor, which is present in several organs including the heart, kidneys, and lung tissues [41]. Additionally, it's believed that certain elements of w. Somnifera block the main SARS-CoV-2 protease, a necessary component for viral replication. (42; Chakraborty et al., 2022; Shree et al., 2022). Additionally, results from several independent studies showed that w. Somnifera is quite effective at treating COVID-19 infection. Its ability to stimulate Th1 immune responses and inhibit NF-B is probably what makes it so effective in reducing inflammatory responses. Numerous other phytoconstituents present in w. Somnifera, such as withanolide A and B, withaferin A, withanone, and withanolides, reduce COVID-19 viral transcription and replication [43]. Since it has few side effects and yet has therapeutic efficacy, w. Somnifera is one of the most promising natural treatments for COVID-19 infection.

2 Discussion

Its effectiveness in treating many disorders has been established. The plant withania somnifera is a potent immunity booster. Withania somnifera possesses anti-tumor, anti-stress, anti-inflammatory, and immunomodulatory characteristics that cause favourable and less harmful immunological responses [Figures 2, 3]. For instance, w. Somnifera has very promising therapeutic effects on airway inflammation and high Th2 immune responses. By upregulating Th1 immune responses and increasing CD4 and CD8 T cells, w. Somnifera balances the Th2-Th1 immunological responses in mice [44]. By lowering the generation of pro-inflammatory cytokines in the lungs, withaferin A (derived from w. Somnifera) proved effective in decreasing airway inflammation in asthma mice models. Withaferin A pre-administration at a dose of 20–80 mg/kg was likewise successful. [45]. The fact that w. Somnifera lowers the airway hyperresponsiveness shown in mice models of asthma clearly shows that it has immunomodulatory properties, demonstrating that herbal remedies, like well-known adjuvants, may also positively change diseases [45]. Even if a variety of other botanical medicines (other than w. somnifera) regulate pathophysiological problems through immunological responses, the use of natural w. somnifera as an adjuvant is highly advised. It is possible that w. Somnifera communicates with immune systems by signalling through immunological receptors (such TLR3, 9) found on innate cells like dendritic cells. Finally, the required immunological responses are induced by these receptors.

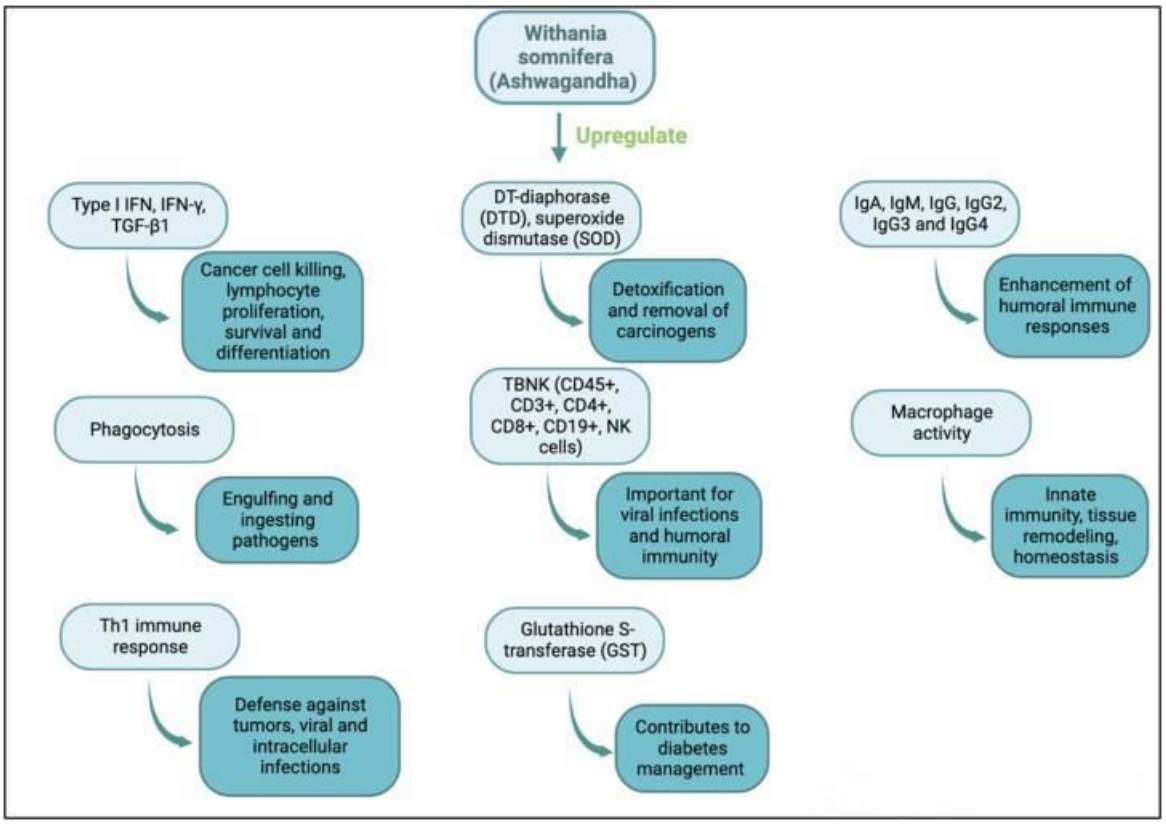

Figure 2: W. somniferacc immunomodulatory properties involve upregulating immune mediators, cytokines, cells, and enzymes. (Alanazi, et al., 2023) [10]

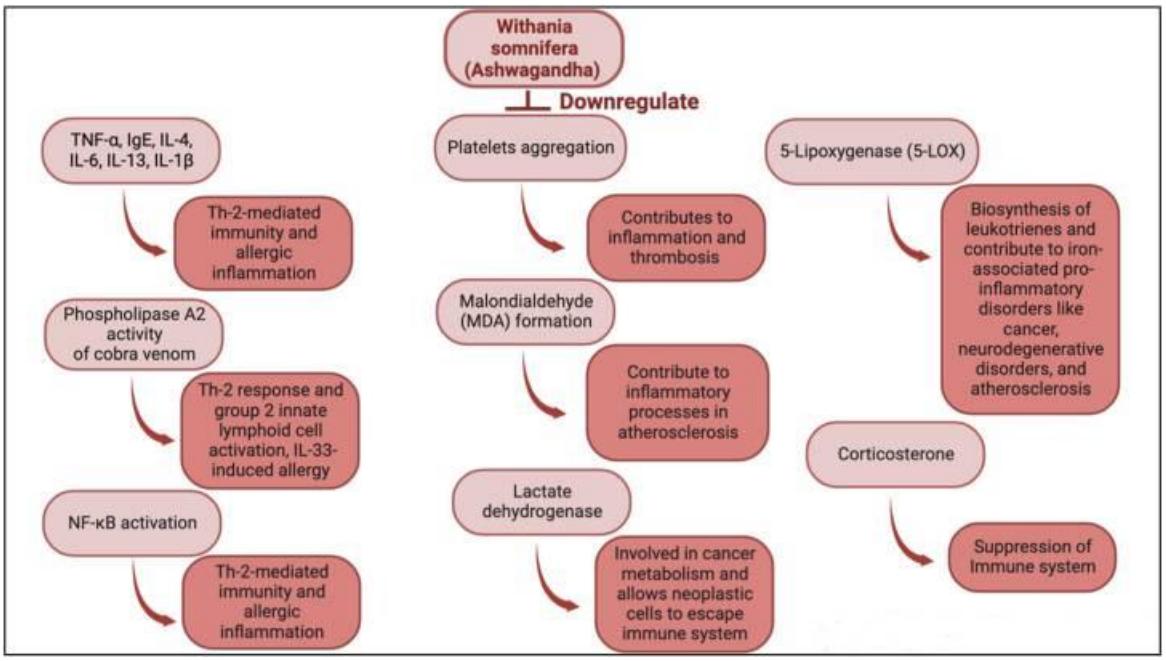

Figure 3: W. Somnifera's immunomodulatory properties include its ability to inhibit immunological mediators, cytokines, cells, and enzymes. (Niraj andVarsha, (2020) [14]

3 Conclusion, future directions and restrictions for employing W. somnifera as an immunomodulator

In earlier studies, w. Somnifera was successfully used to treat a variety of illnesses, including bacterial and viral illnesses, as well as asthma and other allergic conditions [46]. It would be intriguing to investigate the specific mechanisms employed by w. Somnifera to reduce the severity of diseases and allergic inflammation. (Table 1) The vast majority of studies investigating the therapeutic potential of W. somnifera do not fully characterise the whole signalling pathways from the moment cells are first activated until a particular immune component effector function is carried out. Through the activation of immunological receptors on innate cells (such dendritic cells and macrophages), it is thought that the active components in w. Somnifera (like withaferin A) treat chronic disorders. These cells are stimulated, which activates downstream adaptor proteins like TRIFF or MAVS, which in turn activates transcription factors like IRF3 and upregulates defense mechanisms including the Th1 immune response. Current research focuses more on the medicinal benefits of *w. Somnifera* in treating many disorders, especially those that affect the immune system. In this study, we discussed a few signaling systems that *w. Somnifera* induces to lessen allergy disorders and situations. For example, w. Somnifera increases the production of type I IFN, which lowers type 2 immune reactions in allergic reactions (where type 2 immune response is strong). Using a therapeutic plant medicine like *w. Somnifera* offers a safer and more potent alternative to employing existing synthetic adjuvants, which can occasionally induce cytotoxicity to the host and unintended immunological responses. Somnifera's usage in several clinical studies looking for treatments for cancer, inflammatory, and metabolic illnesses would be empowered and encouraged by defining

the entire tactics used by it when used as a therapeutic agent. More research is highly recommended to determine w. Somnifera's potential as an immunomodulator in the future.

Table 1: W. Somnifera immunomodulatory impact on multiple diseases.

From of WS	**Immunomodulatory effects of WS**	**Involved diseases**	**References**
w. Somnifera leaf and root extracts	Maintain normal levels of serum enzymes like aspartate transaminase (AST), alanine transaminase (ALT), acid phosphatase (ACP), and alkaline phosphatase (ALP), as well as blood sugar, hemoglobin (Hb), glycosylated hemoglobin (HbA1C), liver glycogen, and proteins in serum and tissues.	Activity in Diabetes Mellitus (DM) with hypoglycaemic and hypolipidemic conditions	(Ray, 2023)
w. Somnifera root	Redue serum urea, creatinine	Kidney dysfunction	(Prabhu,2022)
w. Somnifera root, leaf extract	Increased levels of immunoglobulins, IFN-gamma, CD3+ and CD4+ T cells, T-helper 1 (TH1) cytokines, and CD8+ T cells	Viral Diseases	(Verma et al., 2022)
w. Somnifera root powder	Natural cell (NK) cell activity has increased	Ovarian cancer	(Padhy, 2020)
Withaferin A	TNF, COX-2, and iNOS are examples of mediators involved in the stress response and inflammation that are inhibited.	Inflammatory diseases	(Alanazi, et al., 2023)
Withaferin A	inhibits the adhesion, migration, and respiratory burst of neutrophils	Apoptosis, gout, acute pancreatitis, and acute lung damage	(Tewari et al., 2022)
Aqueous root extract of *w. Somnifera*	Significantly reduce the high hepatotoxicity indicators, lower lipid peroxidation, and significantly increase the activities of glutathione, catalase, glutathione reductase, and glutathione peroxidase	chronic inflammation, liver cancer, and liver damage	(Balkrishna et al., 2021)

There have been certain adverse consequences associated with using *w. Somnifera*, just as with any other herbal or pharmaceutical medications (Chauhan et al., 2022).Seven adult men who participated in clinical research said that taking ashwagandha capsules caused them to feel tired, slightly painful in the stomach, and some joint discomfort. The U.S. Food and Drug Administration (FDA) still haven't authorised *w. Somnifera*, and it hasn't been used extensively in clinical trials to treat illnesses. The effectiveness, mechanism, and long-term consequences of this medication have not been completely addressed in any clinical trials that have been conducted. In addition, there is disagreement on the proper dosages and length of treatment for *w. Somnifera*, suggests that further clinical trial research is required. Also, there have only been a few research looking into how *w. Somnifera* could interact with other medications.

Overall, there are significant gaps regarding the therapeutic use of *w. Somnifera* as a botanical medication, despite the fact that it causes numerous positive effects and lessens the severity of various ailments. These information gaps need to be filled by clinical investigations that define the mechanisms, suitable dosages, duration, and long-term adverse effects of *w. Somnifera*.

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