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Role of Ashwangandha (Withania Somnifera) in Immune Modulation: Proposed Influence in Immune-Regulation

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Role of Ashwangandha (*Withania somnifera*) in immune modulation: Proposed influence in Immune-regulation

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Abstract: The immune system evolved to protect organisms from an infinite variety of disease-causing agents but to avoid harmful responses to self. However, such a powerful defense mechanism requires regulation. Immune regulation includes homeostatic and cell-mediated targeted mechanisms to the activation, differentiation and function of antigen-triggered immuno-competent cells and immuno-regulatory cells. The regulation of the immune system has been a major challenge for the management of autoimmune disorders, tumor immunity, infectious diseases and organ transplants. However, immuno-modulatory procedures used by modern medicine to induce immunoregulatory function have deleterious side effects. Ashwangandha (*Withania somnifera*), an herb used in Ayurvedic medicine is being tested and used in experimental and clinical cases with potential immuno-modulatory functions without any side effects. Here we propose future usages of Ashwangandha for immuno-regulatory function in translational research.

Ashwangandha: an immunoregulatory herb

Immune protective mechanisms include the elaboration of potent inflammatory molecules, antibodies, and killer cell activation — which together not only destroy invading microorganisms, pathogenic autoreactive cells, and tumors, but also may mortally injure normal cells. Accordingly, the immune response is tightly regulated by immuno-regulatory cells, cytokines and external influences.

Withania somnifera Dunal (Ashwagandha), also known as Indian ginseng, belongs to the family Solanaceae, which is distributed throughout India. It is widely used in the Ayurvedic system of medicine to treat tumors, inflammation, arthritis, asthma, and hypertension (1). Ashwangandha has been used as an immunostimulant and as a dietary supplement (1, 2). Although it has been reported to selectively enhance T helper 1 (Th1) immune responses (2, 3), Ashwangandha also has anti-inflammatory function (4).

Understanding the immuno-modulatory mechanisms of Ashwangandha can provide insight into immune function and regulation that could further help in immunoregulatory procedures. Chemical investigation with the extract of roots and leaves of *Withainia somnifera* (WS) have yielded bioactive withanolides, which inhibit cyclooxygenase enzymes, lipid peroxidation, and the proliferation of tumor cells (reviewed in 5). It has been reported that WS extract preferentially reduces inflammatory processes by inactivating nuclear factor-kappaB (NF-kB) activation, by inducing cellular death by apoptosis, inhibiting inflammation and abolishing osteoclastogenesis through suppression of NF-kB activation and NF-kB-regulated gene expression (5). Similar studies show that the leaf extract of WS, as well as its major constituent withaferin A (WA), potently inhibits NF-kB activation by preventing the tumor necrosis factor-induced activation of I-kappaB kinase beta (6). This study indicates that pure WA or WA-enriched WS extracts can be considered as a novel class of NF-kB inhibitors, which hold promise as novel anti-inflammatory agents for the treatment of various inflammatory disorders and/or cancer. It has been proposed that the antiproliferative, proapoptotic, anti-invasive, antiosteoclastogenic, antiangiogenic, antimetastatic, radiosensitizing, antiarthritic, and cardioprotective effects assigned to withanolide may be mediated in part through the suppression of NF-kB and NF-kB-regulated gene products (5).

Recently, withaferin A (made from the crushed air-dried leaves of *Withania* somnifera *Dun.*) was used to induce apoptosis in parasitic protozoa *Lesihmania donovani,* which acts as a novel protein kinase inhibitor and it is facilitated by apoptotic topoisomerase I-DNA complex (7). The anti-microbial effect of WS was also shown in a prophylactic administration of WS extract, which increases host resistance in *Listeria monocytogenes*- infected mice (8). Moreover, the therapeutic role of *Withania* has potential usage in inflammation and the patho-physiology of immune regulation. In summary the potential roles of Ashwangandha in immune modulation is shown in Fig. 1 along with its curative usage for different diseases.

Ashwangandha: the future candidate for experimental and clinical immunology research

The future lines of basic and translational research with *Withania* must enroll the investigation for immunoregulatory cells, which are the cellular feedback regulators of an immune response.

The involvement of such immuno- regulatory cells induced by WS might have several functions: such as regulating antigen presentation and an immunosuppressive microenvironment along with a physiological cytokine milieu for an effector T cell function. It is intriguing that the treatment of *Withania* induces a Th1 cell-mediated immune response and an elevation of IgG2a- mediated humoral immune responses (2, 3). In addition, the aqueous suspension of WS shows anti-inflammatory and immunosuppressive effects by inhibiting the complement system, mitogen- induced lymphocyte proliferation and delayed type hypersensitivity (DTH) in rats (4). Although in this investigation no effect on the humoral response was observed, others have reported elevated levels of IgG2a over IgG1 in the WS- treated BALB/c mice (3). There may be differential effect(s) and/or alternative responsiveness of WS treatment between mouse strains and rats for immune activation versus suppression. Accordingly, a comparative study of different forms of WS extract is warranted towards the understanding of respective immune modulation in different contexts. The induction of regulatory T cells (Treg) and the immune suppression of effector T cell functions have been reported by others and us in tumor immunity (9-12) and ocular immune privilege (13, 14). However, the effect of *Withania* on the immuno-regulatory cellular response has not been tested yet. Accordingly, this natural product is a future candidate that might address the cross-talk between the effector immune cell response and the influence of a Treg response.

Finally, investigations into the use of preparation of *Withania somnifera*, in concert with the holistic Ayurvedic approaches to treat immunoregulatory disorders may impact on several forms of autoimmune diseases, tumor progression, parasitic infection, inflammation, organ transplantation and stress.

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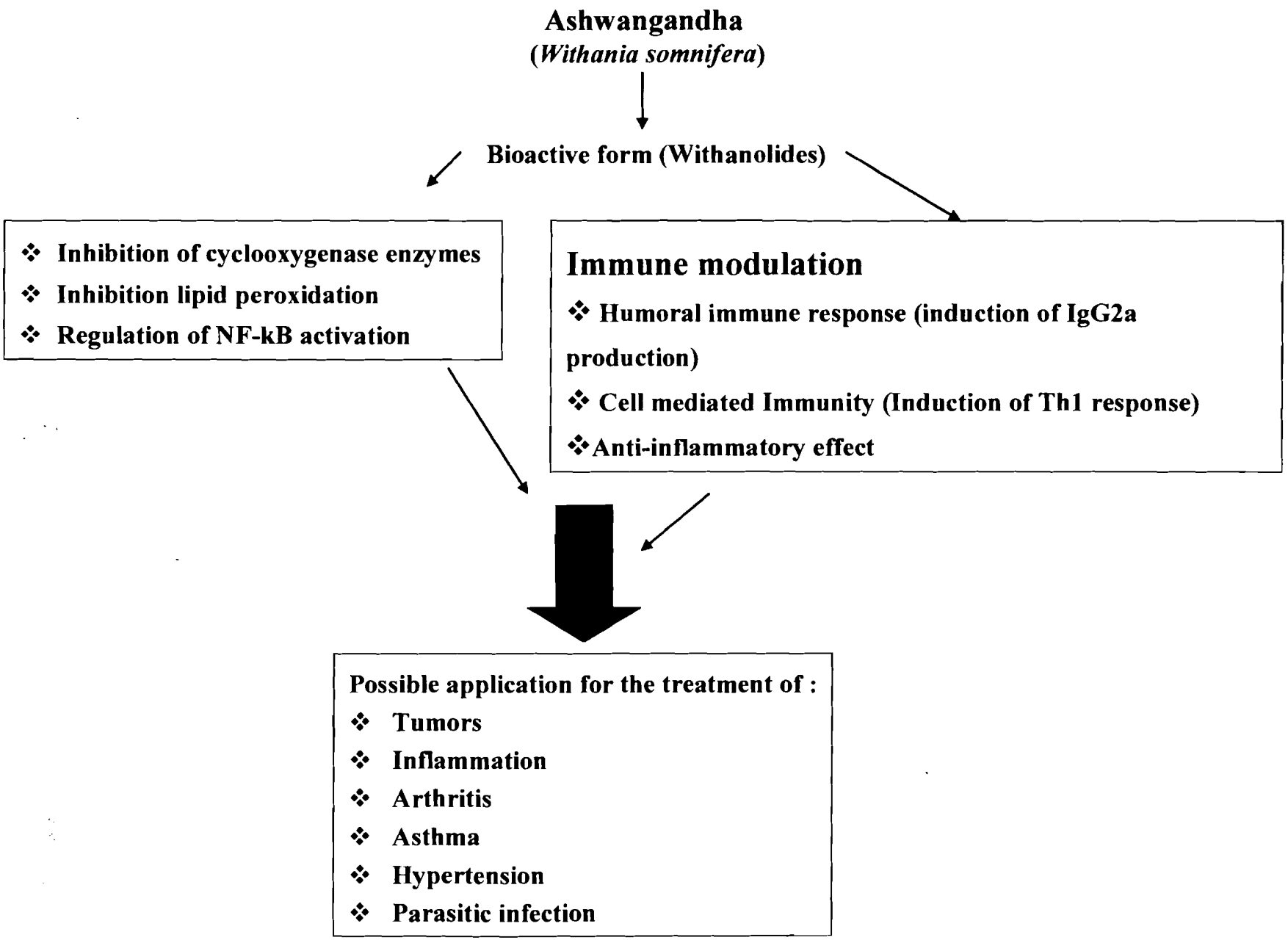

Fig.1. Effect of Ashwangandha (*Withania somnifera*) in the cellular and biochemical function(s) as an immune-modulator and its usage for the treatment of different diseases