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Review Article

Immuno-modulating Properties of Aloe Vera and its Efficacy in Immune Mediated Disorders

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ABSTRACT

Introduction: Aloe produces immune-modulation as it can suppress as well as stimulate the selected sites of the immune system at the same time. The polysaccharide gets attached to the receptors for macrophages that lead to the stimulation of cytokine production. In addition, there is activation of cell mediated immune response too. Aloe has been noted to increase the peripheral percentage of CD4 and CD8 cells, activation of the NF-κB protein and stimulation of interleukin production.

Methodology: In this cross-sectional survey, literature was searched using two search engines: Pubmed and Google Scholar. Pubmed using MesH terms was used as the first option for validation of the systematic review process and the process was further refined using google scholar

Result: Immune-modulation by aloe results from its effect on the T cells, complement system, cytokines as well as the No synthesis. The modulation can be used as a therapeutic benefit for disorders triggered by an abnormal immune response e.g., multiple sclerosis, hyperthyroidism, psoriasis, lichen planus etc.

Conclusion: The efficacy and utility of aloe in auto-immune disorders offers promising range of properties that may help improve the treatment outcomes of immune mediated disorders.

Key words; Aloe Vera, Immune-modulation, Processed aloe gel (PAG), NF-Kb, Cytokines, Auto-immunity.

Introduction

Aloe vera chemically known as Aloe barba-densis Miller is part of a family of herbs known as Asphodelaceae (Liliaceae)[1]. These plants are widely available worldwide[2]. Name of the herb is a derivative of an Arabic word "Alloeh" means "shining bright" and a word in Latin "vera" means "truth"[3]. Medicinal value of Aloe Vera dates back to the Egyptian era. It was used for many allopathic purposes and was called the "plant of immortality"[4]. Evidence has been collected on Sumerian clay tablets from 2100 BC found in the city of Nippur. Tablets have been created at the time of the King of Akkad and talk about the medicinal properties of this plant [5, 6].

There are about 200 different types of chemical substances present in aloe leaf gel[7]. Substances vary from minerals, amino acids especially arginine, Vitamin A, B complex and C, enzymes including amylases, catalases, lipase and peroxidases.

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It also has a wide range of medicinal properties e.g. sterols, salicylic acid, anthraquinones, saponins etc[8]. The intricate structure of this plant offers a variety of properties to it. Vitamin content is responsible for the anti-oxidant and anti-inflammatory effects[9]. It produces an analgesic effect that is associated with the presence of anthroquinones such as auxins and giberrelins and bradykinin[10]. This anthroquinone also contains anti-bacterial properties. These properties make aloe vera a potential treatment for dermatitis, skin infections such as psoriasis and rashes[11]. It has a potential in the therapy for systemic disorders including diabetes, carcinomas, GI disorders and a wide range of immunological disorders e.g. systemic lupus erythematosis, multiple sclerosis etc[12].

Methodology

In this cross sectional survey from Feb 2021 to April 2021, literature was searched using two engines for searching, Pubmed and Google Scholar. Pubmed using MesH terms was used as the first option for validation of the systematic review process and the process was further refined using google scholar. Both the databases are able to combine large amounts of data and provide statistics based on various

bibliographic indicators. The review process continued to refine some keywords and other search results. Summaries were analyzed for the keyword-based research, submitted selected documents, and were grouped into the final version of the software management system. Full downloaded documents were carefully read and the writing process began. During the writing phase, some searches were performed using Google Scholar in each category / section to access missing information.

The impact of Aloe Vera on humoral and cell-mediated immunity:

Aloe produces immune-modulation as it can suppress as well as stimulate the selected sites of the immune system at the same time, hence containing immune-modulatory action in the doses of 300-500mg/kg. The immune modulatory property of aloe is attributed to a polysaccharide called "acemannan"[13]. The polysaccharide gets attached to receptors for macrophages that lead to the stimulation of cytokine production. There is also activation of cell-mediated immune response. Aloe has been noted to increase the peripheral percentage of CD4 and CD8 cells, activation of the NF-κB protein and stimulation of interleukin production[14].

The effect of aloe on immune mediation shows an enhanced expression of the genes encoding CD4 and CD8 receptors on the surface of the cells[15]. Expression of the gene encoding IFN- which is synthesized by stimulation via T and B cells, is also enhanced. In addition the evidence from the experimental studies revealed that doses of aloe higher than 500mg/Kg had a predominant immunosuppressive effect rather than immune-modulatory action. The dose dependent effect on immune system was strengthened further by a decrease in the expression of receptors for both CD-4 and CD-8 cells at higher doses. Therefore, the effects of aloe vera on the immune system are dose dependent and vary from immune-modulation to suppression[16].

Therapeutic Application of Aloe Vera in Multiple Sclerosis

Multiple sclerosis is a chronic disease mediated via auto-immune trigger that leads to de-myelination of the nerve sheaths[17]. The pathogenic stimulus is the activation of mono-nuclear cells. The main cell lines involved are both CD4 and CD8 T cells as well as B cells[18]. This results in the secretion of chemical mediators including cytokines, components of the complement system and reactive oxygen species, all of which de-myelinate the neuronal sheaths[19]. Experimental autoimmune encephalomyelitis (EAE) has been utilized for studies on multiple sclerosis[20]. The auto-antigens include antigens against myelin sheath, myelin proteins and myelin oligodendrocyte glycoprotein. Aloe Vera experimentally proves to suppress the immune response of the pro-inflammatory helper T cells, which if left unchecked ultimately leads to the initial appearance of the disease[21]. Aloe decreases the activation of main cytokines that trigger the sclerosis including IFN-γ[22]. The levels of the oxidative stress inducing Nitric Oxide (NO) are also reduced as it is stimulated via IFN-γ. NO potentially leads to oligodendrocyte de-myelination and acts as a part of cascade of reactions de-myelinating the nerve sheath. In addition NO blocks the neuronal conduction producing a neuronal blockade[23]. These findings warrant further investigations for the utility of Aloe vera as a potential candidate therapeutic strategy against not only the treatment but also prevention of multiple sclerosis.

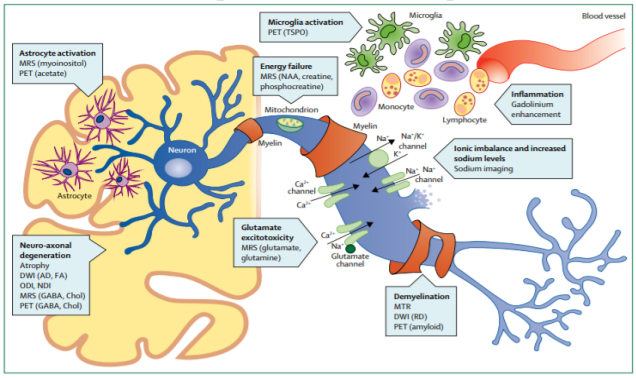

Fig 1 – Patho-physiology of demyelination in multiple scerosis[19]

Aloe Vera in hyperthyroidism:

Aloe Vera contains anti-oxidative properties and regulates lipid and glucose metabolism in the body[24]. In this regards its efficacy has been experimented in thyroid disorders. The crude aloe extract decreases the level of thyroid hormones in experimental animals[25]. Experimental studies show low levels of T3 as well as inhibition of conversion of T4 into T3 peripherally[26]. The G6 phase in glucose synthesis is directly regulated via the thyroid hormone and is therefore an indicator of the thyroid hormone levels. Aloe decreases the G6 phase activity hence solidifying its anti-thyroid action[27].

Hyper-thyroid disorders deplete the body of lipid stores and decrease cholesterol and triglyceride levels. The use of aloe raises serum cholesterol as well as

triglyceride levels that are noted to be low prior to the administration of aloe vera[28]. Increased secretion of the thyroid hormones leads to hepatocyte damage, raising serum AST and ALT. However, the administration of aloe showed significant mitigation in the increased activities of the hepatic enzymes. Hyperthyroidism increases the mitochondrial consumption of oxygen hence producing oxidative stress. The reactive species of oxygen produced exhibit lipid peroxidation and cellular damage. The administration of aloe in these states decreases the markers indicating oxidative damage and at the same time the levels of anti-oxidants such as glutathione is significantly increased[29]. In addition aloe also reduces the levels of TNF alpha along with interleukin-6 that are enhanced following the oxidative stress in hyperthyroid states.

Receptor of the thyroid hormone (TSHR) is the main auto-antigen that transmits the major tropic stimuli to thyroid leading to synthesis and release of the thyroid hormones. Aloe has the ability to decrease the expression of TSHR hence decreasing the thyroid activity. Aloe administration also leads to improved histology of the thyroid gland proving its effectiveness in controlling the hyper-thyroid states[25].

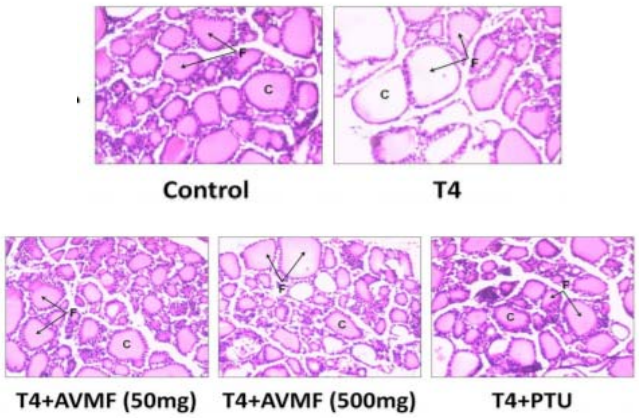

Fig-2 – Hist-pathological changes in the thyroid in hyper-thyroid mice vs protective effects of aloe in comparison with PTU[25]

Microscopic analysis of hyperthyroid mice was compared against aloe gel and propyl-thiouracil. The distorted structure of the follicles, flattening of the epithelial lining the follicles as well as the decreased epithelial thickness observed in the hyper-thyroid mice were all reversed and normal architecture was observed in aloe and PTU groups with similar efficacy[25].

Aloe Vera in Psoriasis:

Psoriasis is an inflammatory disease caused by the activity of T cells. T cells stimulate the release of cytokines following activation by stimuli from natural substances. Activated T cells lead to the development of an inflammatory response[30].

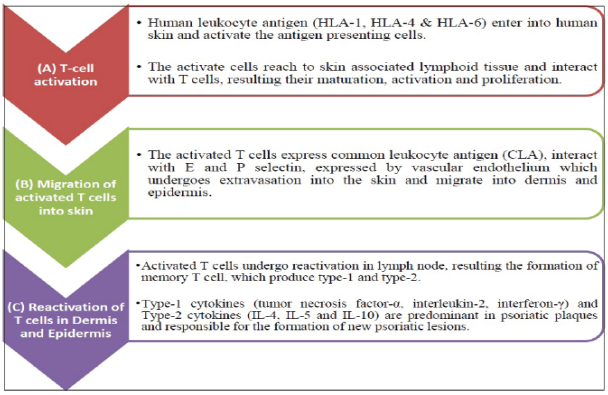

Fig 4 – Pathogenesis of Autoimmune Psoriasis[31]

Immuno modification by aloe vera due to macrophage and lympohocyte activation may be helpful in psoriasis therapeutics. Aloe also increases collagen activity hence enhancing wound healing and hydration. Clinical studies have shown a steady decrease in skin degeneration, as well as a decrease in infiltration and erythema. Symptom management varies from minor development to marked improvement in various subjects[32].

According to already known experimental data, it is safe to say that aloe vera has many anti-pathophysiological processes involved in psoriasis and therefore can be used for therapy in addition to further treatment options[33,34].

Aloe Vera in Lichen Planus:

Oral lichen planus is a chronic ailment that forms lesions in the oral mucosal surfaces[35]. This form of the disease is difficult to treat and does not respond well to the current available therapeutics. The pathological mechanism involved in the disorder is an immune response mediated via the stimulation of T cells. The CD-8 variety of cells thus activated produce apoptotic lesions in the epithelium. Production of the cytokines especially IL 2 along with TNF alpha is also up regulated [36].

Aloe vera suppresses the immune inflammatory response via interference with the cycloxygenase pathway responsible for the formation of the mediators of inflammation[37]. In addition the anti-inflammatory potency is further enhanced by the reduction in the

adhesive capacity of the leukocytes and TNF by aloe. These effects have experimentally shown positive beneficial effects of aloe in early wound healing of lichen planus lesions[38].

Table 1 – Summary of mechanisms of aloe therapeutics in various auto-immune disorders

Sr#	Auto-immune Disorder	Mechanism of Aloe vera
1.	Multiple Sclerosis	• Suppression of immune response of the pro-inflammatory helper T cells • Decreased IFN-γ production • Decreased NO synthesis
2.	Hyperthyroidism	• Decreased levels of T3 • Inhibition of conversion of T4 into T3 peripherally • Decreased expression of TSHR
3.	Psoriasis	• Macrophage and lymphocyte activation • Increased collagen activity • Decreased erythema and cellular infilteration
4.	Lichen Planus	• Inhibition of arachidonic acid metabolism • Decreased adhesion of leukocytes and TNF alpha

Discussion

Aloe Vera gel is one of the most effective and powerful agents with various therapeutic benefits in addition to its unique set of properties[49]. Aloe contains polysaccharides that cause immune-modulation, including acetylated-mannan, gluco-mannan, and galacto-galacturan. Acemannan, a combination of long polymer chains linked to acetylated galacto-mannan, can be the most common body polysaccharides[39]. Studies involving the molecular structure reveal that its metabolism is characterized by the ion of aloe that range in size from 5kDa to 400kDa[40], whereas chemicals smaller than this level, show less fluctuations in the immune system[41].

When applied to experimental mice, acemannan which is a D-isomer mucopolysaccharide in aloe vera leaves with potential immunostimulant, antiviral, antineoplastic, and gastrointestinal properties. is seen to either completely heals or significantly ameliorates the skin reactions induced by radiation[42]. Acemannan is also effective in treating spinal cord fibrosarcomas[43]. Many of the immune-modulating properties of acemannan are brought about via macrophage activation. Acemannan leads to stimulation of macrophages and produces cytokines involved in inflammation such as IL-6 and TNF-a, increases NO production by macrophages, and regulates phagocytic activities of macrophages. Acemannan also promotes hematopoiesis and causes the maturation of immature dendritic cells[44]. Numerous studies have investigated the physical activity of Aloe vera in vitro through cell cultures, in vivo with intraperitoneal or intramuscular administrative routes and with Processed Aloe vera gel (PAG) [45,46,47].

Modulation of the immune system is produced directly by aloe gel by the action of the complement system, T lymphocytes and cytokines[48,49]. These actions provide benefits such as the treatment of autoimmune conditions, anti-inflammatory action and anti-oxidant activities[50]. Aloe demonstrates improvement in wound healing of immune suppressed and diabetic lab animals[51]. The inhibition of inflammation is designed to be the result of the inhibition of the cyclo-oxygenase pathway of arachidonic acid metabolism. Jotsana et al reported that macrophages and the total number of white blood cells increased significantly in aloe vera administration[52]. Activated macrophages trigger the immune response that leads to the activation of NO cytokines including TNF-α, interleukin-1 and / or interleukin-6. Studies have shown immune modulating properties of aloe vera extracts in experimentally induced UV stress in laboratory animals[53]. Radiation induced changes in the morphology of langerhans and dendritic cells in the skin are blocked by aloe.

Glyco-proteins and poly-saccharides present in aloe vera act against various cancers[54]. Compounds in the aloe gel bring about immune modification that provide anti-carcinogenic benefits and in addition enhance the efficacy of other anti-cancer drugs[55].

Aloe vera contains many antioxidants such as anti-tocopherols, caro-tenoids, ascorbic acid, flavonoids, tannins, vitamin C and vitamin E. Anti-oxidant properties of the products of aloe (leaf and flower) have been reported by Lopez et al[56,57]

Conclusion

Immune modulation offered by Aloe can be used for therapeutic benefit in disorders triggered by an abnormal immune response e.g. multiple sclerosis, hyperthyroidism and dermatological conditions including psoriasis and lichen planus.

Recommendations

The utility of aloe in auto-immune disorders further needs to be solidified and investigated as the plants offers promising range of properties that may help improve the treatment outcomes of immune mediated disorders.

Conflicts of Interest: None

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