# Plant Derived Bio-actives for the Suppression of Immune Response: A Review

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***Abstract*- The present review deals with the potential of herbal products in suppression of immune system, in autoimmune diseases and in inflammatory diseases. Humans have been using herbal plants to treat many diseases for centuries as complementary medicine. More than 2000 herbs are present in nature, but a little have been sufficiently studied by humans to cure or treat medical illness and numerous of them are remained uninvestigated. Immuno-suppression refers to slowdown the response of over reactive immune system. Over reactive immune system may leads to allergic reactions, graft rejections, inflammation and many more medical conditions. It may be genetic or some time occurs in response of a medical illness. Numerous plant derived bio-actives have been used as immuno-suppressants by our ancestors. These plants works as immunosuppressant by inhibiting the cellular and humoral immunity, but each plant targets different cellular receptor inhuman body. Bioactives such as Plumbagin inhibits T-cells proliferation, 8- gingerol suppress the production of cytokines IL-1, IL-6 and Xanthohumolinhibits the mitogen and allogen induced proliferation of T cells.**

***Keywords*-** Herbs, immune system, Immuno-suppressants, autoimmune disease

## I. INTRODUCTION

According to WHO, around one third of world's population relies upon herbal plants for maintenance of its health [1]. Natural herbs provide different kind of pharmacological activity, of which immunosuppressant is also one. The medicinal activity of plant is due to presence of a particular bioactive component in it. These natural herbs can be used as alternative to conventional allopathic chemotherapy, which only provides symptomatic relief with lots of +- adverse effects [2]. Due to this, the need for discovery of alternative therapy increases. Herbs are quite safe in terms of adverse effect with cost effectiveness [3]. This review article discusses the potential of different medicinal plants in suppression of immune systems.

## II. IMMUNE SYSTEM AND IMMUNITY

The immune system has two types of defense mechanisms, innate immunity also called as natural immunity and adaptive immunity also called as acquired immunity which provide protection from external environmental particles such as microorganisms, cancer cells, toxins etc.[4], [5], [6]. Innate immunity works as first line of defense against invading pathogens [7], [8]. It is antigen-independent [9] and works through phagocytosis. Adaptive immunity on the other hand is second line of defense which is antigen dependent [10]. It only activates when innate immune system is insufficient to provide protection from invading antigen. Adaptive immunity is based on release of some special structural components in response of a particular antigen, which are called as antibodies. It is mediated by T lymphocyte (thymus cells) and B lymphocyte (bone-marrow cells) [11]. Adaptive immunity is further subdivided into cellular (cell-mediated) and humoral (antibody-mediated) immunity [12]. Cellular immunity involves the activation of cytotoxic T-cells also called as killer cells [13] and humoral immunity involves the activation of B cells as shown in figure 1[14], [15]. Both T and B cells include CD8 killer cells, which are cytotoxic to tumors, CD4 helper cells [16], which only activate after the interaction with major histo-compatibility complex (MHC). CD4 cells regulate B cell and CD8 cells function, and antigen presenting B cells (APC) and thus produce antibodies [17].

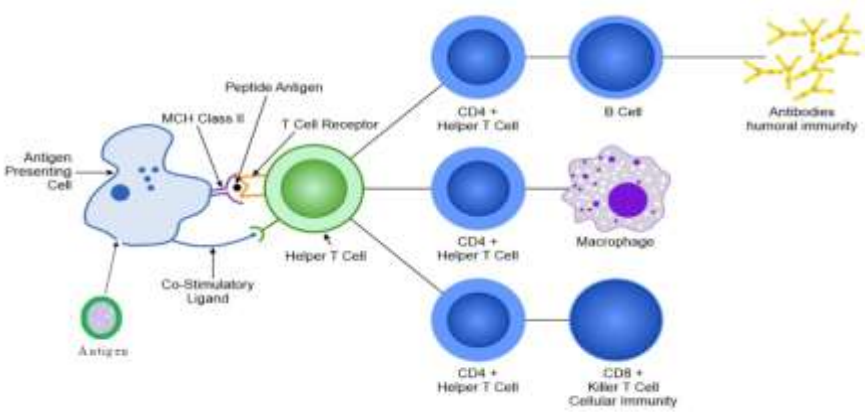


Figure 1: Mechanism of immune response

## III. WHAT IS THE NEED OF IMMUNO-SUPPRESSANTS?

Sometimes our immune system does not work properly, which may be genetic or acquired by a medical condition. The insufficient working of immune system may lead to immune-deficiency or hyper immune-activity. This hyperactivity/over reactivity turns into allergic reactions, into graft rejection of organ transplantation or into autoimmune diseases (psoriasis, rheumatoid arthritis, lupus) [18]. So, to contain these reactions, there is a high need of immuno-suppressants. Every immuno-suppressant drug has different mechanism of action, but all of them work by a common action of inhibiting cytokine production, cell activation/proliferation and/or differentiation [19].

## IV. MECHANISM OF NATURAL HERBS AS IMMUNE-SUPPRESSORS

1. Xanthohumol (XH), theactive bio-active compounds present in the Humulus lupus L. of Cannabaceae family is most commonly used as immunosuppressant. Xanthohumol works by inhibiting the mitogen and allogen induced proliferation of T cells, bygenerating cytotoxic lymphokine-activated killer cells and producing Th1 type cytokines [20].


Figure 2: Structure of Xanthohumol

2. Plumbagin, a bioactive constituent of Plumbago zylanica gives immunosuppressive effects by inhibiting activation and proliferation of T lymphocytes, by inhibiting IL-2/IL-4/IL-6/IFN-γ production and by suppressing nuclear factor-κB (NF-κB) [21].

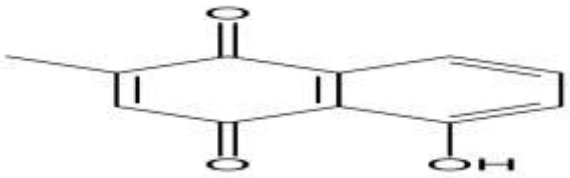


Figure 3: Structure of Plumbagin

3. Piperlongumine (PL), a pharmacological active constituent derived from the Piper longum Linn. plant shows promising immunosuppressant properties. It works by inhibiting the T cells/antigen presenting cell immune synapse formation, by co-stimulation-induced up-regulation of cluster of differentiation 69 (CD69)

and cluster of differentiation 25 (CD25), T cell proliferation and the secretion of pro-inflammatory cytokines [22].

Figure 4: Structure of Piperlongumine

4. Curcumin, a pharmacologically active constituent derived from the Curcuma longa Linn, shows promising immunosuppressant properties. It works by regulating inflammatory cytokines such as IL-1beta, IL-6, IL-12, TNF-alpha [23], [24].It also suppresses NF-κB pathway to decrease inflammation [25].

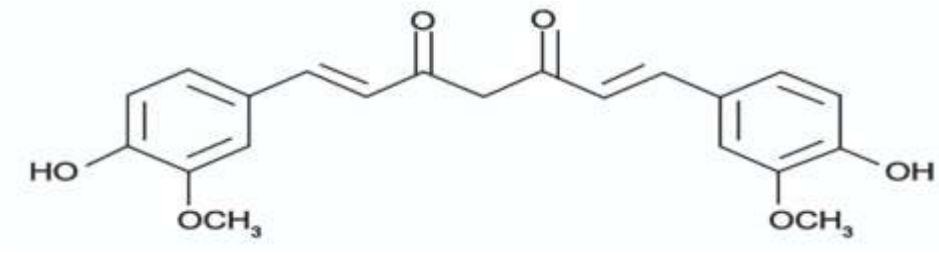


Figure 5: Structure of Curcumin

5. 8- Gingerol, the active pharmacological constituent present in Zingiber officinalis shows immunosuppressive effect [26] by inhibiting production of cytokines IL-1, IL-6 and bydecreasing the percentage of CD19 B cells and CD3T cells. It alsosuppresses the concanavalin A (ConA) and lipopolysaccharide (LPS) induced splenocyte proliferation in vivo [27], [28].

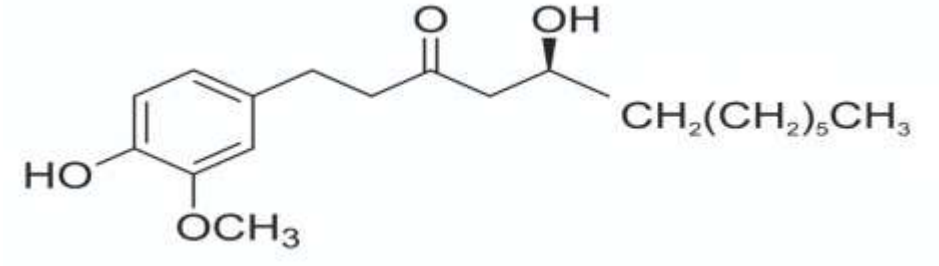


Figure 6: Structure of 8-Gingerol

6. Epigallocatechin-3-gallate, a polyphenol, an active pharmacological constituent of green tea [29] treats the autoimmune arthritis by decreasing the production of IFN-γ, IL-6 and TNF-α. It also suppressesT cell proliferation and relative frequencies of CD4 T cells, CD8 T cells and B cell subsets including marginal zone B cells, T1 and T2 transitional B cells, while increasing the frequency of $CD4^+$ $Foxp3^+$ regulatory T cells (Tregs) and indoleamine-2,3-dioxygenase (IDO) expression by $CD11b^+$ dendritic cells (DC) [30].

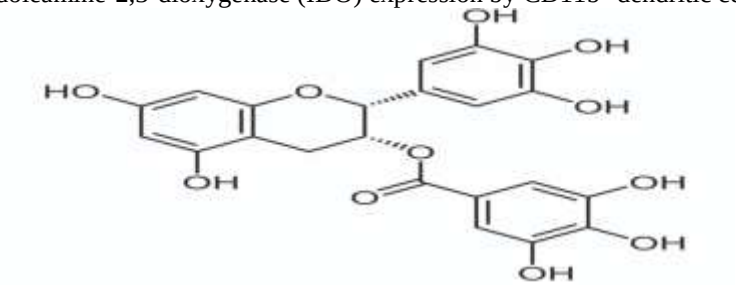


Figure 7: Structure of Epigallocatechin-3-Gallate

7. Salicin, an active pharmacological active constituent of white willow bark suppresses the immune system by suppressing the TNF-α-induced cellular senescence in human [31].

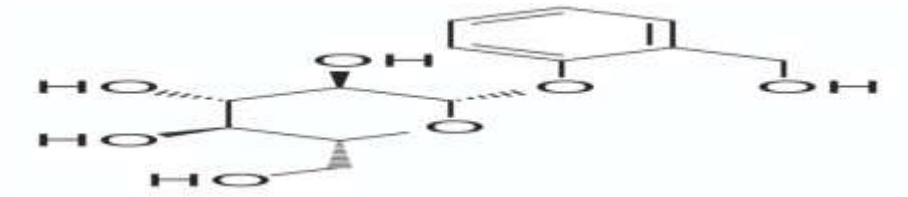

Figure 8: Structure of Salicin

8. Silymarin, a polyphenolic flavono-lignan, an active constituent of Silybum marianum is a potent inhibitor of immune system [32]. It suppresses the immune system by inhibiting T cell proliferation, transcription factor NF-kB and pro-inflammatory cytokine secretion [33]. It also suppresses the mTOR signalling pathway in human activated T lymphocytes in vitro [34].

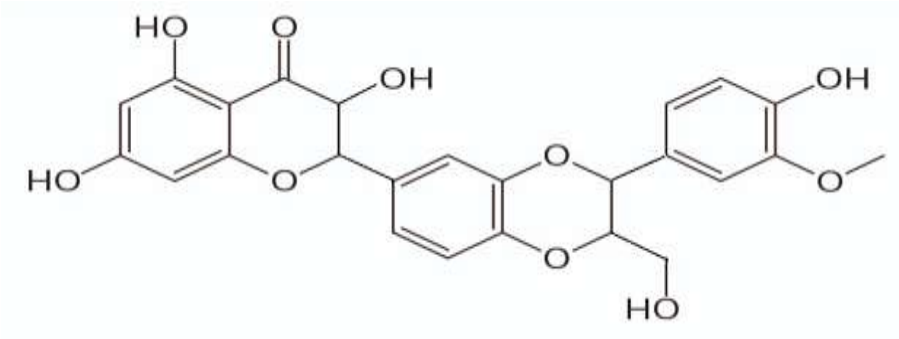

Figure 9: Structure of Silymarin

9. Withaferin A (WA) a steroidal lactones obtained from Withania sominifera showsimmune-suppresant effect by inducing oxidative stress byincreasing the basal ROS levels and blockage of NF-κB pathway [35]. It also inhibits the up-regulation of T-cell (CD25, CD69, CD71 and CD54) and B-cell (CD80, CD86 and MHC-II) activation markers and secretion of Th1 and Th2 cytokines [36], [37].

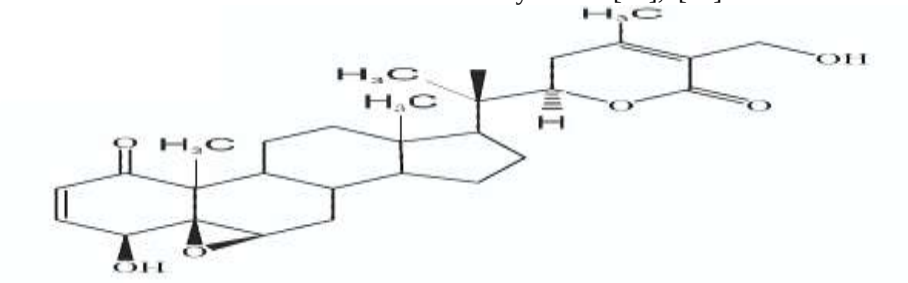

Figure 10 : Structure of Withaferin A

10. Berberine, an active constituent isolated from Berberis aristata works by inhibiting IL-2 induced T cell proliferation andtheproduction of IFN.sub.γ T cells [38], [39].

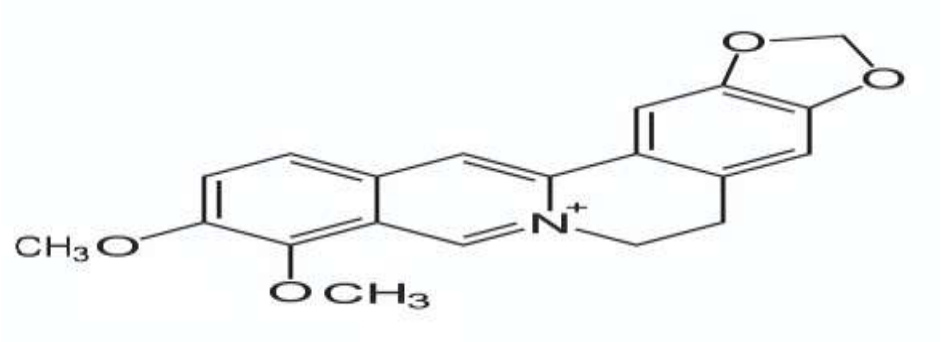


Figure 11: Structure of Berberine

11. Ginsenoside-Rd, an active constituentisolated from Panax ginseng inhibit the immune response bysuppressing the alloantigen-specific production of Th1 cytokines IL-2 and IFN-γ as well as pro-inflammatorycytokines TNFα and IL-12.It also markedly inhibits the concanavalin A (ConA)-induced T lymphocytes proliferation [40] , [41].

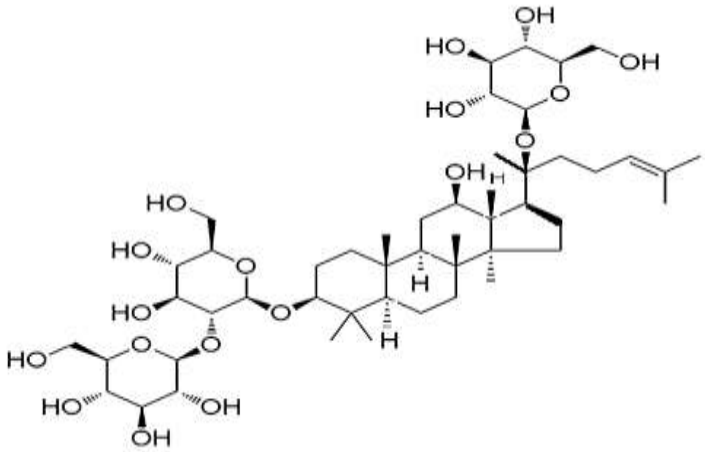


Figure 12 : Structure of Ginsenoside-Rd

12. Emodin isolated fromRheum palmatum Linn. [42], inhibits the alloimmune responses by suppression of lymphocyte proliferation, and by blockage of mTOR signaling. It also prolongesthe MST of skin grafts and decreasesthe production of serum IL-2 [43] , [44].

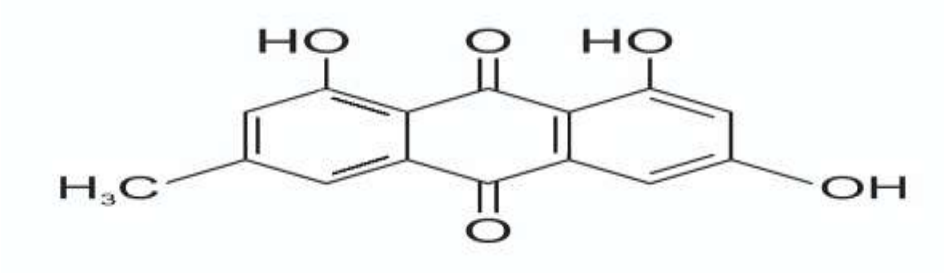


Figure 13: Structure of Emodin

13. 6,7-dimethoxy coumarin (Scoparone) isolated from Artemisia scopariaexertsimmunosuppressive effect through inhibition of protein tyrosine kinase and release of arachidonic acid metabolites [45], [46].

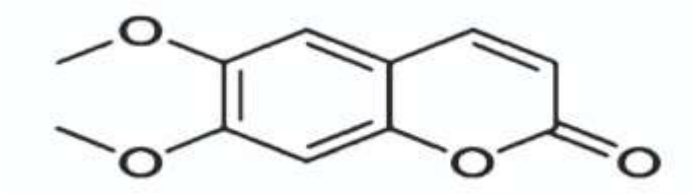

Figure 14: Structure of Scoparone

14. Capsiate and its dihydroderivativesare the major capsaicinoidsderived from Capsicum annuum. Theyinhibitthe activation of T cells including CD69, CD25 and ICAM-1 cell surface expression [47], [48].

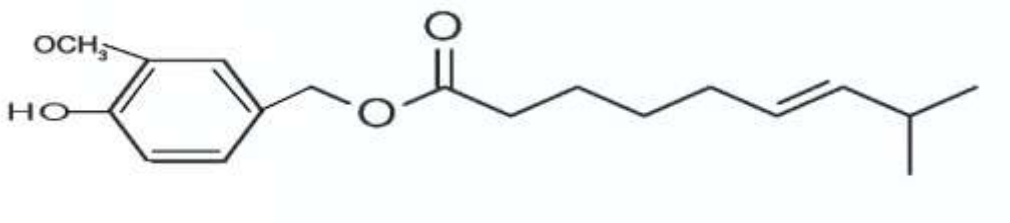


Figure 15 : Structure of Capsiate

## V. CONCLUSION

Herbal medicines have been used for centuries as complementarymedicines in the suppression of immune response. A number of plant derived bioactives have been isolated with potential immunosuppressant activity, that can form the basis for further research. These bioactives can be used as an effective alternative to conventional allopathic medicines in terms of low cost, high saftey, and high efficacy.

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