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THERAPEUTIC PROPERTIES OF MEDICINAL PLANTS: A REVIEW OF THEIR IMMUNOLOGICAL EFFECTS (PART 1)

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ABSTRACT

Many previous studies showed that medicinal plants possessed immunological effects. These plants included: *Agrimonia eupatoria*, *Alpinia galanga*, *Althaea officinalis*, *Althaea officinalis*, *Althaea rosea*, *Avena sativa*, *Bauhinia variegata*, *Betula alba*, *Brassica rapa*, *Bryophyllum pinnatum*, *Caesalpinia cristaCalendula officinalis*, *Calotropis procera*, *Canna indica*, *Capsicum annuum*, *Capsicum frutescens*, *Carthamus tinctorius*, *Carum carvi* and *Cassia occidentalis*. This review was designed to highlight the immunological effects of these medicinal plants.

Key words: Medicinal plants, Immunological, Pharmacognosy, Pharmacology, Therapeutics.

INTRODUCTION

Plants remain the basis for a large proportion of the commercial medications used today for the treatment of heart disease, high blood pressure, pain, asthma, cough, gastrointestinal and other problems [1]. However, plants are a valuable source of a wide range of secondary metabolites, which are beside their use in medicine, they are also used as agrochemicals, flavours, fragrances, colours, biopesticides and food additives [2-51]. Recent studies showed that many medicinal plant possessed immunological effects. This study will highlight the immunological effects of the medicinal plants.

Agrimonia eupatoria

An aqueous ethanol extract of the herb was tested for immunomodulative activity in the peritoneal cavities of mice. Immunostimulant activity resulted in an increase in phagocytic activity and increases in the activities of lysozyme and peroxidase [52]. The antioxidative properties of aqueous plant extracts were evaluated using common methods such as the Rancimat and 2,2'-diphenyl-1-picrylhydrazyl (DPPH) free radical method. Moreover, a voltammetric procedure based on the protective effect of antioxidants against the oxidative DNA damage was employed using a disposable DNA biosensor fabricated as a screen-printed electrode chemically modified by calf thymus double stranded (ds) DNA [53].

Alpinia galanga

The flavonoid fraction of *Alpinia galanga* Linn. extract significantly stimulated (P <0.001) T cell proliferation and splenocyte proliferation in mice spleen at a dose of 100 mg/kg body weight of mice. The aqueous fraction had a lower stimulatory effect than the flavonoid fraction. The antioxidant level of the spleen cells also increased following treatment with the flavonoid fraction. Hot water soluble polysaccharide extract of *A. galanga* rhizome possesses a marked stimulating effect on the reticulo endothelial system (RES) and increased the number of peritoneal exudates cells and spleen cells of mice [54]. 1'S-1'- acetoxychavicol acetate and 1'S-1'-acetoxyeugenol acetate from aqueous extract of rhizome inhibited the release of hexosaminidase and the antigen-IgE-mediated TNF-alpha and IL-4 production in passive cutaneous anaphylaxis reactions in mice [55]. 1'-acetoxychavicol acetate and the related compounds in the rhizomes of *Alpinia galanga* exerted antioxidative activity [56]. The antioxidant activity of *Alpinia galanga* extracts and essential oil *was* determined using the 2,2-diphenyl-1-picrylhydrazyl (DPPH) and oxygen radical absorbance capacity (ORAC) methods. The ethanolic extract showed the highest DPPH free radical scavenging ability as well as the highest ORAC value when compared to the water extract and the essential oil [57]. Ethanolic extract of *Alpinia galanga* showed a potent scavenging activity by

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DPPH method with the IC 50 value of 69.5±1.375 µg/ml, by lipid peroxidation method with the IC 50 value of 77±1.876 µg/ml, hydrogen peroxide radical scavenging activity with the IC 50 value 55±1.59 µg/ml, and ABTS radical scavenging method with the IC_{50} value 0.086±1.10 µg/ml [58]. Acetoxychavicol acetate of *Alpinia galanga* exhibited potent antioxidant activity, increased cell apoptosis and decreased cytokine production by T helper cells [59, 60] .

Althaea officinalis

Althaea-mucilage O, an acidic polysaccharide isolated from marshmallow root, has been demonstrated to have an anti-complement activity on normal human serum in concentrations of 100 – 1000 ug/ml [61]. An extract (extraction medium 45 % 1,3-butylene glycol solution) of marshmallow root was found to inhibit intracellular calcium mobilisation in normal human melanocytes activated by endothelin-1, and to strongly inhibit endothelin-1-induced proliferation of melanocytes. The extract can diminish the physiological effect of endothelin-1 on normal human melanocytes following UVB irradiation [62]**.** Scopoletin produced dual action on tumoral lymphocytes exhibiting both a cytostatic and a cytotoxic effect on the cell , and also exert apoptosis. Proliferation of normal T lymphocytes was found due to the interaction with kinase C (PKC) protein. It indicates that scopoletin may be a potential anti-tumoral compound [63].

Althaea rosea

Water extract of *Althaea rosea* produce the following effects on immune system [64]

1- Induced a transient non-specific polyclonal response indicated by the production of IL-4 in treated, non-immunized mice.

2- Initially boosted the production of anti-EA antibodies and IL-4, a T- helper 2 cytokine.

3- Suppress production of gamma-interferon, a T- helper 1 cytokine.

Avena sativa

β- glucan helped neutrophils to reach the site of infection more rapidly and enhanced their ability to eliminate the bacteria [65]. The different immunological aspects of β-glucans derived from different food sources (oat, barley and shiitake) was examined on phorbol myristate acetate (PMA)-differentiated THP-1 macrophages. Inflammation-related gene expression kinetics (IL-1β, IL-8, nuclear factor kappa B [NF-κB] and IL-10) were evaluated after 3, 6 and 24 h of stimulation with 100 µg/ml β-glucan. All tested β-glucans were mildly up-regulated the observed inflammation-related genes with differential gene expression patterns. Similar gene expression kinetics, but different fold induction values, was found for the crude β-glucan extracts and their corresponding commercial forms. Pre-incubation of THP-1 macrophages with β-glucans prior to lipopolysaccharide (LPS) exposure decreased the induction of inflammation-related genes compared to LPS treatment. No production of nitric oxide (NO) and hydrogen peroxide was detected in β-glucan stimulated THP-1 macrophages. Phagocytic activity was not differ after stimulation by β-glucan samples. Based on these in vitro analyses, β-glucans have varying levels of immunomodulating properties, which are likely related to structure, molecular weight and compositional characteristic of β-glucan [66].

Bauhinia variegata

The ethanolic extract of the stem bark of *B. variegata* showed immunomodulatory activity on the primary and secondary antibody responses. It was also increased phagocytic index and percentage neutrophil adhesion [67].

Betula alba

Betulinic acid, a pentacyclic triterpene isolated from the bark of white birch *Betula alba* exerted many immunological effects. It was found that betulinic acid administered orally five times at the dose of 0.5 mg/kg increased the total number of thymocytes, splenocytes, lymphocytes of mesenteric lymph node cells, and the weight ratio of the spleen and mesenteric lymph nodes in non-immunized mice. Betulinic acid also changed the percentage of T cell subsets in the thymus and T and B lymphocytes in peripheral lymphatic organs. The effects of betulinic acid on T and B cell subpopulations depended on the dose applied. The strongest stimulating effect of betulinic acid was observed when the drug was administered at the dose of 0.5 mg/kg. Five exposures to betulinic acid (0.5 mg/kg) decreased the percentage of immature CD4+ CD8+ thymic cells with corresponding increases in the percentage and absolute count of mature, single-positive CD4+ thymocytes and decreased the percentage and total count of CD3+ splenocytes and mesenteric lymph node cells with corresponding decreases in the percentage and absolute count of CD4+ and CD8+ cells. Multiple administration of betulinic acid at the investigated doses augmented the percentage and absolute count of CD19+ cells in the peripheral lymphatic organs. Moreover, betulinic acid at the dose of 5 mg/kg administered prior to SRBC immunization increased the number of plaque forming cells (PFC) but decreased the production of anti-SRBC antibodies in red blood cells (SRBC)-immunized mice on day 4 after priming [68].

Brassica rapa

The effects of chloroform, ethyl acetate and methanolic extracts of *Brassica rapa* were investigated on cell-mediated immune response in mice. Chloroform, ethyl acetate and methanolic extracts of *Brassica rapa* glands were prepared by maceration method. Sheep red blood cell (SRBC) was injected (sc, 1×10^8cells/ml, 0.02 ml) and 5 days later, different extracts (10, 100 and 500 mg/kg),

betamethasone (4 mg/kg) and Levamisol (4 mg/kg) as a positive control and normal saline as a negative control were given ip. After 1 h SRBC was injected to footpad (sc, 1×10^8 cells/ml, 0.02 ml) and footpad swelling was measured up to 72 h. To investigate the effects of *B. rapa* on innate immunity the same procedure was used, but animals only received one injection of SRBC 1 h after ip injection of test compounds. The results showed that SRBC induced an increase in paw swelling with maximum response at 6-8 and 2-4 h for innate and acquired immunity, respectively. Betamethasone inhibited and levamisol increased paw thickness in both models. In both innate and acquired immunity models, chloroform, ethyl acetate and methanolic extracts of *B. rapa* glands significantly and dose-dependently reduced paw thickness. Ethyl acetate extract showed better effect [69].

Bryophyllum pinnatum

Mice treated daily with oral *B. pinnatum* during hypersensitization with ovalbumin were protected against death. Oral protection was accompanied by a reduced production of OVA-specific IgE antibodies, reduced eosinophilia, and impaired production of the IL-5, IL-10 and TNF- α cytokines. Oral treatment with the quercitrin flavonoid isolated from plant extract prevented fatal anaphylaxis in 75% of the animals. These findings indicated that oral treatment with *Bryophyllum pinnatum* effectively downmodulates pro-anaphylactic reactions inducing immune responses [70]. The aqueous extract of leaves causes significant inhibition of cell-mediated and humoral immune responses in mice .The spleen cells of animals pretreated with plant extract showed a decreased ability to proliferate in response to both mitogen and antigen in vitro as well as, the specific antibody responses to ovalbumin were also significantly reduced by treatment [71].

Caesalpinia crista

The aqueous extract of *Caesalpinia crista* seeds was tested for its effect on cell mediated and humoral components of the immune system in rats. Administration of *Caesalpinia crista* seed extract produced an increase of 93.03 ± 4 mean hemagglutinating antibody titer and a change of 0.56 ±0.058 mm in delayed type hypersensitivity as compared to control at a dose of 400 mg/kg bw [72]. The immunomodulatory activities of ethanolic extract of *Caesalpinia crista* seeds were tested via neutrophil adhesion test, haemagglutinating antibody titer, delayed-type hypersensitivity response, phagocytic activity and cyclophosphamide-induced myelosuppression. Oral administration of ethanolic seed extract of *Caesalpinia crista* (200-500 mg/kg) evoked a significant increase in percent neutrophil adhesion to nylon fibers, as well as a dose-dependent increase in antibody titer values, and potentiated the delayed-type hypersensitivity reaction induced by sheep red blood cells. Also it prevented myelosuppression in cyclophosphamide treated rats with a good response towards phagocytosis in carbon clearance assay [73].

Calendula officinalis

The polysaccharides isolated from an aqueous extract of Flos Calendulae enhanced phagocytosis in human granulocytes *in vitro* in the colloidal carbon clearance test. The polysaccharides isolated from flowers aqueous extract also enhanced phagocytosis when administered (10 mg/kg bw) intraperitoneally to mice. On the other hand, intraperitoneal administration of unsaponifiable fraction (0.5 ml) of a hydroalcoholic extract of the flowers also stimulated phagocytosis in mice inoculated with *Escherichia coli* [74-76].

Calotropis procera

The immunological potential of the latex of *Calotropis procera* against sheep red blood cells (SRBC) as antigen was investigated in Wistar albino rats by studying cell-mediated, delayed type hypersensitivity reaction (DTH), humoral immune response, macrophage phagocytosis and *E. coli* induced bacteremia sepsis. The latex was fractionated according to water solubility and molecular size of its components. The fractions were named as non-dialyzable latex (NDL) which corresponding to the major latex proteins, dialyzable latex (DL) corresponding to low molecular size substances and rubber latex (RL) which was highly insoluble in water. The HA titer levels were quantified by primary and secondary humoral immune response in rats. The fractions induced production of antibodies titer level significantly ($p<0.05$) in response to SRBC. In addition immunostimulation was counteracted by up regulating macrophage phagocytosis in response to carbon particles. Rats received NDL fractions by oral route displayed considerable immunological response. Oral administration of NDL fractions, dose dependently increased immunostimlatory responses. DTH reaction was found to be augmented significantly ($p<0.05$) by increasing the mean foot pad thickness after 48h. In the survival study, control group I and negative control group II in *E. coli* induced peritonitis has shown 50% and 66.6% mortality, while pretreated groups with NDL has reduced mortality in rats injected with 1×10^8 *E. coli* intraperitoneally from 0.0% - 16.6% [77]. The immunomodulatory functions of the water-soluble *C. procera* extract (CPE) was investigated via determination of its ability to activate macrophages-effector cells in inflammatory and immune responses. Intraperitoneal injection of CPE in mice (2 mg/mouse) induced migration of macrophages to the intraperitoneal cavity. The direct effects of CPE on macrophages were then assessed by measuring the production of nitric oxide (NO) as an indicator for macrophage activation. Addition of CPE (1-10 microg/ml) to the culture medium of the murine monocyte/macrophage cell line RAW264.7 caused an increase in NO production in a time- and dose-dependent manner. CPE-elicited NO production was blocked by application of an inhibitor of inducible nitric oxide

synthase (iNOS). Expression of iNOS mRNA was induced by treatment of cultured macrophages with CPE. Injection of CPE in mice also resulted in an increase in plasma NO level [78]. The hexane, ethyl acetate, and dichloromethane crude extracts of *C. procera* (250 and 500µg/mL), showed toxicity to human macrophages (U-937). However, methanol and aqueous extracts were less toxic up to >2000µg/ml. The lower concentrations (100-12.5µg/ml) were devoid of toxic effects and morphological changes of cells. However, various toxic effects were observed in the *C. procera* crude extracts in a dose-dependent manner compared to control cells [79].

Canna indica

The effect of *Canna indica* ethanolic extract (CIE) on productions of nitric oxide (NO), prostaglandin E2 (PGE2), and interleukin-1β (IL-1β) in lipopolysaccharide (LPS)-induced RAW 264.7 macrophages was investigated. In addition, the effects of CIE in high glucose (HG)-induced U937 monocytes on mRNA expressions of IL-8 and monocyte chemoattractant protein-1 (MCP-1), and regulation of mitogen-activated protein kinase (MAPK) pathways were also identified.CIE was found to inhibit the production of inflammatory mediators including NO, IL-1β, and PGE2 from LPS-induced RAW 264.7 macrophages. The increases in HG-induced mRNA expressions of IL-8 and MCP-1 were also significantly inhibited by CIE. Stimulation of HG in U937 monocytes resulted in activation of p38 MAPK, ERK1/2, and JNK. However, CIE treatment significantly decreased phosphorylation of p38 MAPK, ERK1/2, and JNK [80].

Capsicum annuum* and *Capsicum frutescens

The immunological effects of red pepper (*Capsicum annuum* Lin.) extracts (capsicum extract) and its main pungent capsaicin was investigated on T helper 1 (Th1) and 2 (Th2) cytokine production in cultured murine Peyer's patch (PP) cells *in vitro* and *ex vivo*. Direct administration of capsicum extract (1 and 10 mug/ml) and capsaicin (3 and 30 muM) resulted in suppression of interleukin (IL)-2, interferon (IFN)-gamma, IL-4 and IL-5 production. In an *ex vivo* experiment using PP cells removed from the mice after oral administration of capsicum extract (10 mg/kg/day for 4 consecutive days), IL-2, IFN-gamma and IL-5 increased in response to concanavalin A (Con A). Oral administration of 3 mg/kg/day capsaicin, also enhanced IL-2, INF-gamma and IL-4 production in response to Con A stimulation but did not influence the production of IL-5. Orally administered capsazepine (3 mg/kg/day), a selective transient receptor potential vanilloid 1 (TRPV1) antagonist, slightly enhanced IL-2 production also irrespective of Con A stimulation. The capsaicin-induced enhancement of both IL-2 and IFN-gamma production was not reduced by oral administration of capsazepine (3 mg/kg/day), suggesting a TRPV1 receptor-independent mechanism. Flow cytometric analysis revealed that the population of CD3(+) cells in the PP cells was significantly reduced while CD19(+) cells increased after oral administration of capsicum extract (1 and 10 mg/kg/day) and capsaicin (0.3 and 3 mg/kg/day). Capsazepine (3 mg/kg/day) weakly but significantly reversed these effects. Orally administered capsicum extract and capsaicin did not change the T cell subset (CD4(+) and CD8(+), Th1 (IFN-gamma(+) and T2 (IL-4(+) ratio [81]. It appeared that dendritic cells, a key cell type in immune responses, have the receptor for capsaicin, and engagement of this receptor has powerful immune consequences. The intratumoral administration of capsaicin into a preexisting tumor results in retarded progression of the injected tumor regardless of whether the tumor is at its early or late stage. Furthermore, it leads to significant inhibition of growth of other, uninjected tumors in the same animal. Capsaicin-elicited immunity is shown to be T cell-mediated and tumor-specific [82]. Vanilloid receptor 1 (VR1) is expressed on immune cells. VR1 can regulate immunological events in the gut in response to its ligand Capsaicin (CP). Oral administration of CP attenuates the proliferation and activation of autoreactive T cells in pancreatic lymph nodes (PLNs) but not other lymph nodes. Engagement of VR1 enhances a discreet population of CD11b(+)/F4/80(+) macrophages in PLN, which express anti-inflammatory factors interleukin (IL)-10 and PD-L1. This population is essential for CP-mediated attenuation of T-cell proliferation in an IL-10-dependent manner [83]. The effect of a methanolic *C. annuum* L. extract (CAE) was investigated in mice model of ovalbumin-induced allergic airway inflammation. Animals were treated with CAE by oral gavage before ovalbumin challenge. Oral treatment with CAE significantly reduced the pathophysiological signs of allergic airway disease, including increased inflammatory cell recruitment to the airways, airway hyper-responsiveness, and increased levels of T-helper type 2 cytokines. Reactive oxygen species were also decreased in cells from broncho-alveolar lavage fluid. In addition, the administration of CAE attenuated ovalbumin-induced increases in NF-κB activity in lungs [84]. Treatment with capsicum oleoresin of lactating dairy cows increased the relative proportion of lymphocytes compared with the control. It also increased the proportion of total CD4(+) cells and total CD4(+) cells that co-expressed the activation status signal and CD25 in blood. The percentage of peripheral blood mononuclear cells (PBMC) that proliferated in response to concanavalin A and viability of PBMC were not affected by treatment. Cytokine production by PBMC was not different between control and capsicum oleoresin treated cows. Expression of mRNA in liver for key enzymes in gluconeogenesis, fatty acid oxidation, and response to reactive oxygen species were not affected by treatment. No difference was observed due to treatment in the oxygen radical absorbance capacity of blood plasma [85]. The effects of 10 mg/kg Capsicum oleoresinon on growth performance and immune responses was studied in weaned pigs

experimentally infected with porcine reproductive and respiratory syndrome virus (PRRSV). The results indicate that supplementation with capsicum oleoresin reduces the adverse effects of PRRSV by improving the immune responses of pigs [86]. Hot water-soluble crude polysaccharide (HCAP-0) that was obtained from the fruits of *Capsicum annuum* showed potent anti-complementary activity. The activity was unchanged by pronase digestion, but decreased by periodate oxidation. The HCAP-0 was fractionated by DEAE ion-exchange chromatography to give two major fractions, HCAP-II and III. These two fractions were finally purified by gel filtration to give HCAP-IIa, HCAPIIIa1, and IIIa2 fractions that had high anticomplementary activities. The HCAP-IIIa1 and IIIa2 consisted of homogeneous polysaccharides. The anticomplementary activities were unaffected by treatment with polymyxin B, indicating that the modes of complement activation were not due to preexisting lipopolysaccharide [87].

Carthamus tinctorius

The polysaccharide of *Carthamus tinctorius* modulated immune function in mice [88]. Safflower yellow (SY) produced declines in both nonspecific and specific immune functions. Administration of safflower yellow (SY) ip 50-450 mg/kg/day for 6-8 days in mice decreased serum lysozyme concentration and phagocytosing functions of both peritoneal macrophages and peripheral leukocytes; diminished the production of plaque forming cells, specific rosette forming cells, and antibody production; inhibited delayed type hypersensitivity reaction and the activation of T suppressor cells elicited by supraoptimal immunization. *In vitro* experiments showed inhibitory effects on [3H]TdR incorporation during human peripheral T- and B-lymphocyte proliferation by SY 0.03-3.0, 0.1-2.0 mg/ml respectively, murine mixed lymphocyte culture response and the production of interleukin-2 by SY 0.1-2.5 mg/ml. In conclusion, SY produced declines in both nonspecific and specific immune functions [89]. *N*-(*p*-coumaroyl)serotonin and *N*-(*p*-coumaroyl) tryptamine, active ingredients in CT, were shown to strongly inhibit the production of proinflammatory cytokines (IL-1α, IL-1β, IL-6, IL-8 and TNF- α) from lipopolysaccharide-stimulated human monocytes. HSYA treatment increased adhesion potency (HSYA dose 1.01 x 10^{-4} mol x $L^{-1)}$, free calcium concentration (HSYA dose 3.1 x 10^{-5} mol x $L^{-1)}$, TNF-alpha and IL-6 mRNA expression elevation (HSYA dose 5.2 x 10^{-5} mol x L^{-1}) induced by LPS . HSYA also inhibited NF-kappaB p65 subgroup nuclear translocation (HSYA dose 5.2 x 10^{-5} mol x L^{-1}) [90].

Carum carvi

The effects of caraway hydroalcoholic extract (CHE) and its essential oil (CEO) were investigated in an immunological model of colitis in rats induced by trinitrobenzene sulfonic acid (TNBS). Different doses of CHE (100, 200, 400 mg/kg) and CEO (100, 200, 400 µl/kg) were administered orally and also doses of CHE (100, 400 mg/kg) and CEO (100, 400 µl/kg) were given intraperitoneally. Administration of the doses started 6 h after induction of colitis and continued daily for 5 consecutive days. CHE and CEO at all tested doses were effective in reducing colon tissue lesions and colitis indices and the efficacy was nearly the same when different doses of plant fractions were administered orally or intraperitoneally [91].

Cassia occidentalis

The protective effect of *Cassia occidentalis* against cyclophosphamide (CP)-induced immunosuppression was evaluated in animal models. Swiss albino male mice were treated orally with the aqueous extract of *C. occidentalis*, 100 mg/kg, body weight, for 14 days. Cyclophosphamide was given intraperitoneally in a single dose of 50 mg/kg bw. Body weight, relative organ weight, lymphoid organ cellularity, hemagglutination titre (HT), plaque forming cell (PFC) assay and quantitative hemolysis of SRBC (QHS) were studied in these animals. CP showed suppressive effects on lymphoid organ weight and cellularity and other parameters of humoral immunity. Plant extract treatment itself produced no toxicity. The administration of plant extract to CP-exposed animals resulted in improved humoral responses. *C. occidentalis* treatment significantly ($P<0.01$) enhanced PFC response in CP-treated animals. In QHS assay, *C. occidentalis* also showed protection in CP-treated animals. Bone marrow cell counts, which were reduced in CP-treated animals, were reversed significantly ($p<0.01$) to normal levels in CP + plant extract group animals [92]. The effects of *Cassia occidentalis* (CO) on rat mast cell degranulation inhibition and human red blood cell (HRBC) membrane stabilization were studied *in vitro*. The anti lipid peroxidant effects of CO were also studied *in vitro*. Effect of CO on carrageenan-induced mouse paw oedema inhibition was also assessed. CO significantly decreased maximum protection of 80.8% at 15 microg/ml. The extract also caused significant reduction in malondialdehyde (MDA) levels of murine hepatic microsomes at 100 microg/ml (56%) and significantly reduced carrageenan induced inflammation in mice at a dose of 250 mg/kg [93]. The effects of the treatment with seeds of *C. occidentalis* and its external tegument fraction (TE) on the development of chicks and their lymphoid organs bursa of Fabricius and spleen were studied. Chicks that received a commercial ration with 1% TE had reduced body and lymphoid organ weights. The bursa of Fabricius presented reduction in the diameters of the follicles, and in the thickness of the cortical and medullary regions. The spleen presented depleted lymphoid tissue in the white pulp. These results indicate that the active principle of *C. occidentalis* is more concentrated on its TE fraction, and that it can cause weight loss as well as alterations in the lymphoid organs in chicks [94]. The possible immunotoxic

effects of *Cassia occidentalis* (Co) seeds were studied through incorporated of seeds in broiler chicken rations at different concentrations (0.0%, 0.25%, 0.50% and 0.75%), for 28 or 42 days. The innate immune function (macrophage activities of spreading, phagocytosis, peroxide and nitric oxide production) and acquired immune function (humoral and cellular immune responses), as well as lymphoid organ weights and pathology were evaluated. There was enhanced macrophage activity, increased hydrogen peroxide production ($P<0.05$) in cells of birds given 0.75% Co, but there were no other pro-inflammatory effects. Birds receiving 0.75% of Co in ration for 42 days gained less weight ($P<0.01$), and showed a decrease in relative weight of the bursa of Fabricius ($P<0.05$) and spleen ($P<0.01$). In addition, morphological changes were also noted in these lymphoid organs, with depletion of lymphoid cells on the spleen and bursa of Fabricius, resulting in lower relative weight of both lymphoid organs. No impairment of humoral immune response against Newcastle disease and in cellular immune response after a phyto-haemagglutinin challenge was recorded. The authors postulated that mitochondrial damage and related apoptosis may be responsible for the enhanced peroxide production and the reduced relative weight of the bursa of Fabricius and spleen [95].

CONCLUSION

The paper reviewed the immunological effects of the medicinal plants to open the door for their utilization in medical applications as a result of effectiveness and safety**.**

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