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Review Article

Modulation of dendritic cell immune functions by plant components

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ABSTRACT

Dendritic cells (DCs) are the key linkage between innate and adoptive immune response. DCs are classified as specialized antigen-presenting cells that initiate T-cell immune responses during infection and hypersensitivity, and maintain immune tolerance to self-antigens. Initiating T-cell immune responses may be beneficial in infectious diseases or cancer management, while, immunosuppressant or tolerogenic responses could be useful in controlling autoimmunity, allergy or inflammatory diseases. Several types of plant-derived components show promising properties in influencing DC functions. Various types of these components have been proven useful in clinical application and immune-based therapy. Therefore, focusing on the benefits of plant-based medicine regulating DC functions may be useful, low-cost, and accessible strategies for human health. This review illustrates recent studies, investigating the role of plant components in manipulating DC phenotype and function towards immunostimulating or immunosuppressing effects either *in vitro* or *in vivo*.

1. Introduction

Dendritic cells (DCs) are professional antigen-presenting cells that provide a link between the innate and the adaptive immune responses. DCs stimulate adaptive immune response by activating T lymphocytes, inducing an effector response or tolerance depending on the DC differentiation level. In addition, DCs play a crucial role in immunosuppression and maintain tolerance against self-antigens. Therefore, DCs have become a key target for research activities focused on manipulating DCs to obtain novel biological modifiers that can be used for the treatment or management of different infectious and immune-related diseases. Herbal plants offer a wide range of medicinal components that have proved beneficial in treating different diseases worldwide.

Several plant-derived components may have immunostimulatory, immunosuppressive, and/or anti-inflammatory activities depending on the plant type and extraction method. Most of these therapeutic plants may be effective in modulating DC activities and considered as an alternative tool for treatment. Therefore, I present the findings of recent studies investigating the role of plant components in manipulating DC functions either *in vitro* or *in vivo*.

2. Modulation of DC activities

DCs are a heterogeneous population of immune cells, comprising different subsets that can be distinguished by their phenotypic and functional properties. Functional properties include the ability to upregulate specific

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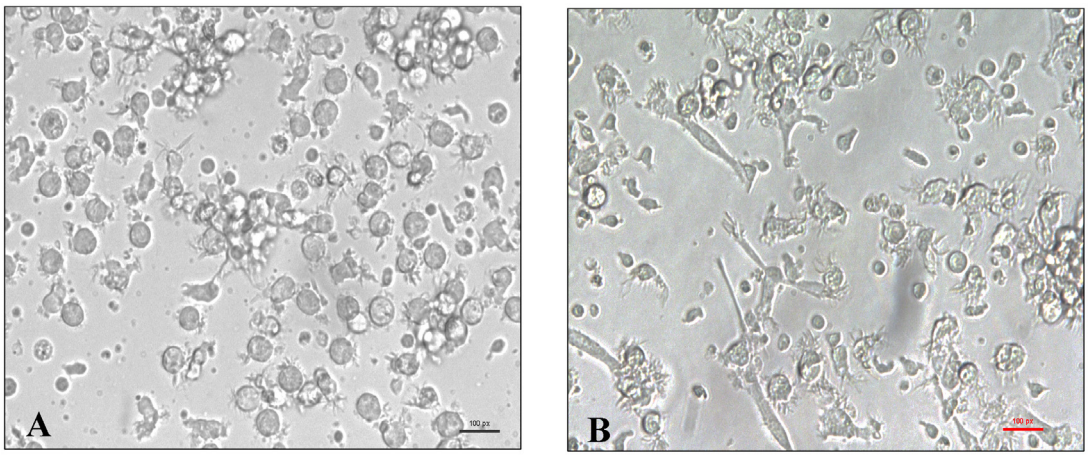

Fig. 1. (A) Morphology of immature DCs generated from peripheral blood monocytes cultured in RPMI-1640 medium supplemented with granulocyte–macrophage colony-stimulating factor and interleukin-4 for 7 days. (B) Immature DCs stimulated with 1 μg/mL lipopolysaccharide for 24 hours showed long cytoplasmic veils typical for mature DCs. Cells were photographed using a digital camera assembled on a bright field inverted microscope. Original magnification was 40×. (Unpublished data, Immunology Unit, King Fahad Medical Research Center, KAU, Jeddah, Saudi Arabia.).
DC = dendritic cell.

maturation markers and the capacity to stimulate naïve T cells. The maturation status of DCs may be responsible for either induction of immunity or tolerance. The process of DC maturation is highly regulated and results in conversion of immature DCs in the periphery into fully competent antigen-presenting cells. During conversion, DCs undergo a number of phenotypical and morphological changes (e.g., formation of dendrites; Fig. 1). In addition, there are reallocation of major histocompatibility complex (MHC) molecules from intracellular endocytic compartments to the DC surface; downregulation of antigen internalization; an increase in the surface expression of co-stimulatory molecules; cytoskeletal reorganization; secretion of chemokines, cytokines, and proteases; and surface expression of adhesion molecules and chemokine receptors [1,2]. This process can be induced by a variety of infectious agents, cytokines, and natural products. Several researchers have studied the impact of various natural product extracts during the recent years.

2.1. Plant components modulating DC differentiation and maturation

Different types of plants and plant components were shown to induce DC differentiation either *in vitro* or *in vivo* including pinecone extract [3], the traditional Japanese herbal plants kampo and Hochu-ekki-to (HOT) [4], and the water soluble extract of fern *Polypodium leucotomos* named Anapsos [5]. Anapsos especially was found to enhance production of interleukin (IL)-1α, IL-1β, and tumor necrosis factor α proposing a stimulation of monocytes and DCs *in vitro*. In addition, *Astragalus mongholicus* polysaccharide isolated from one of the Chinese herbs was found to enhance the co-expression of CD-11c and MHC class II molecules on murine bone marrow (BM)-derived DC (BMDC) surfaces, reduce fluorescein isothiocyanate–dextran uptake, and produce a higher level of IL-12 than untreated DCs, suggesting that it modulates DC maturation [6].

Moreover, some plant components were reported to induce both the differentiation and maturation of DCs *in vitro*, such as lupane acetate of cortex periplocae [7], the aqueous and organic fractions from *Petiveria alliacea* [8], acidic polysaccharide isolated from ginseng (*Panax ginseng* Meyer) [9], and *Lycium bararum* polysaccharide (LBP) extracts [10]. One interesting study on LBP demonstrated its ability to induce phenotypic and functional maturation of DCs [11]. The therapeutic effects of LBPs were related to their ability to induce DC maturation through Toll-like receptor (TLR)2- and/or TLR4-mediated nuclear factor (NF)-κB signaling pathways [12]. Likewise, *Achyranthes bidentata*, a traditional Chinese medicine also provides phenotypic and functional maturation of murine DCs, suggesting that it may be used to boost immune responses [13]. Similarly, the polysaccharide obtained from a Chinese medicinal herb, Zhu Ling [the sclerotium of *Polyporus umbellatus* (Per) Fr], was found to induce the activation and maturation of murine BMDCs through TLR4 [14].

Some plant extracts were found to interfere with DC differentiation and maturation, as shown by the exposure of monocytes to areca nut extracts. These extracts did not effect the expression of HLA-DR and CD11c, but markedly decreased the proportion of CD40-positive cells, expression of CD86, and IL-12 production. Curcumin was found to induce an immunosuppressant effect on DCs and prevent response to lipopolysaccharide (LPS) by blocking of maturation markers, cytokines, chemokine expression, and endocytosis [15]. Moreover, fisetin, a flavonoid commonly present in fruits and vegetables, in addition to TongXinLuo, *Semen cuscutae*, and *Acanthopanax koreanum*, a traditional Chinese medicine, impair functional maturation of DCs [16–19]. Acetylcorynoline component derived from *Corydalis bungeana* herbs was also reported to work as a potent immunosuppressive agent through its ability to alter of DC maturation and function [20].

2.2. Activities of stimulated DCs

2.2.1. Activation of T cells

The ability of matured DCs to activate T-cell responses was studied by various research groups that found that some plant components lead to the stimulation and upregulation of several chemokine and cytokine genes [21]. A mixture extracted from the butanol fraction of a stem and leaf extract of *Echinacea purpurea* had a significant influence on mouse BMDC phenotype and maturation. These effects coincide with induction of metabolism-, cytoskeleton-, or NF-κB signaling-related proteins. Flow cytometric analysis showed that the polysaccharide-rich root extract increased the expression of MHC class II, CD86, and CD54 surface markers, whereas the alkylamide-rich leaf extract inhibited the expression of these molecules. Moreover, the leaf but not root extract inhibited the antigen-specific activation of naive $CD4^+$ T cells [22,23]. The effect of *Plantago asiatica* L. (ES-PL) seeds, a traditional Chinese medicine, was found to increase levels of MHC class II molecules and major co-stimulatory molecules on DCs, suggesting it may enhance antigen presenting abilities to primed T lymphocytes indicating functional maturation of DCs [24]. BRC-301 (a polyherbal extract), BRC-304 (a mixture of vitamins, minerals, antioxidant enzymes, botanical extracts, and carotenoids), and BRC-306 [a trademarked blend of *Uncaria tomentosa* (cat's claw) and Phytolens] were found to affect the innate responsiveness of murine DCs and enhance their ability to stimulate T-cell-mediated immunity [25].

2.2.2. Activation of B cells

Fermented Noni Exudate, a traditional medicine, activates DCs to stimulate B-cell differentiation and immunoglobulin class switching [26].

2.2.3. Induction of cytokine secretion

An *in vitro* study of okra (*Abelmoschus esculentus* L.) extract on DCs derived from rat bone marrow hematopoietic cells (BMHCs) showed that *A. esculentus* L. polysaccharides displays DC stimulatory effects demonstrated by upregulation of the MHC class II and CD80/86 expression, reduced endocytosis activity, and increased levels of T helper (Th)1 cytokines IL-12 and interferon (IFN)-γ [27]. Further study on a Chinese tonifying herb, named *Cordyceps sinensis* showed activation of DCs toward a Th1-type immunity, whereas in a potential inflammatory reaction, it reduced the over-reactivity of stimulated Th1 immunity and shifted activation toward a Th2 response [28].

A variety of the Japanese soybean, Glycine max cv. Kurosengoku (Kurosengoku) extracts trigger the production of IL-12 from DCs mediated by TLR4 and TLR2 and sequentially induced IFN-γ production [29]. Triterpene esters, uncarinic acid C (1) and uncarinic acid D (2) obtained from the hooks of *Uncaria rhynchophylla* were found to activate cytokine production of human DCs towards Th1 [30]. Also, purified galactomannan from *Caesalpinia spinosa* induced phenotypic maturation in monocyte-derived DCs (MDDCs) revealed by increased expression of maturation markers, reduced antigen uptake, and increased protein and mRNA levels of proinflammatory cytokines [31].

2.3. Activities of immunosuppressant DCs

It was found that modulating DCs by natural plant products that inhibit DC maturation might alter immune-mediated inflammatory reactions *in vivo* and induce immunoregulatory responses, suggesting that it can be used as a valuable strategy to prevent inflammation associated with inflammatory diseases.

2.3.1. Inhibition of T-cell activation

Several lines of evidence support the immunosuppressive properties of resveratrol, a natural polyphenol present in grapes and grape products such as wine, which inhibited expression of co-stimulatory molecules (CD80 and CD86), suppressed the capacity of BMDCs to produce intracellular IL-12 p40/p70 and IL-12 p70, increased antigen capturing and endocytosis, and reduced stimulation of naive allogeneic T-cell proliferation. These data indicated therapeutic use of resveratrol for chronic immune and/or inflammatory diseases [32].

Recently, Gold Lotion, a formulated product prepared from the peels of six citrus fruits, displayed immunomodulatory effect on LPS-stimulated mouse BMDC maturation and function by significantly decreasing production of proinflammatory cytokines and chemokines, inhibiting expression of maturation markers, increasing phagocytic ability, and reducing the propensity to stimulate autologous $CD4^+$ and $CD8^+$ T-cell proliferation [33]. *Ziziphora tenuior* L. (Kakuti in Persian) a traditional medicine for treatment of gastrointestinal disorders was found to stimulate CD40 expression on DCs and cytokine production at low concentrations; however, it can prevent T-cell stimulation of DCs at high concentrations [34]. Likewise, extract of *Chrysanthemum coronarium* L. induces DC maturation and production of IL-12 [35]. Triptolide isolated from Chinese herbal medicine demonstrated T-cell suppression and inhibition of DC maturation [36]. The hydroethanolic extraction of turmeric was also found to reduce the activation of human DCs in response to inflammatory cytokines, and to inhibit DC ability to stimulate the mixed lymphocyte reaction [37]. Similarly, ethanolic root extract of *Cichorium intybus*, a traditional medicine, was found to inhibit T-cell proliferation, while low concentrations can modulate cytokine secretion toward a Th1 pattern as shown by increased production of IFN-γ [38].

2.3.2. Modulation of cytokine secretion

Arctium lappa fruit extract was found to inhibit IL-6 and TNF-α concentration generated by DCs [39]. A recent study documented the effect of Saucerneol D, a lignan constituent of *Saururus chinensis* plant, on BMDCs, which decreased expression of maturation proteins (MHC I/II, CD40, CD80, and CD86), inflammatory mediators (NO, IL-12, IL-1β, and TNF-α), and inhibition of allogenic T-cell activation [40]. Birch bark extracts from *Betula pubescens* ethanolic extract lower DC production of IL-6, IL-10, and IL-12p40 and expression of CD83, CD86, chemokine CC receptor 7, and Dendritic Cell-Specific Intercellular adhesion

molecule-3-Grabbing Non-integrin (DC-SIGN) in contrast to control DCs [41]. Likewise, aqueous extract from *Achillea millefolium* reduces the ability of DCs to induce a Th17 response [42]. Luteolin, a flavonoid found in various herbal extracts, was found to block LPS-induced NF-κB signaling and proinflammatory gene expression in intestinal epithelial cells and DCs [43]. *Panax notoginseng* extract, a traditional Chinese herbal medicine, was also found to inhibit TLR-activated DCs, leading to inhibition of the production of inflammatory cytokines and innate immune responsiveness [44]. Additionally, the effects of apple polyphenol extract and procyanidin induced downregulation of HLA-DR (MHC class II), suggesting immunomodulatory properties [45]. Furthermore, several active compounds isolated from leaves and stems of plant such as *Desmodium caudatum*, *Astragalus membranaceus*, *Cassia alata*, *Eleusine indica*, *Carica papaya*, *Eremomastax speciosa*, and *Polyscias fulva* showed inhibitory effects on LPS-induced inflammatory cytokines from DCs, suggesting their anti-inflammatory potential [46,47].

2.3.3. Induction of regulatory DCs

Treatment with cinnamon extract inhibited maturation of DCs and stimulated regulatory DCs, and expressed high levels of immunoregulatory cytokines IL-10 [48]. Ethyl acetate extract from *Urtica dentate* showed anti-allograft rejection by enhancing regulatory T-cell differentiation, inhibition of Th1 cytokines and increased Th2 cytokines, suggesting it is beneficial in autoimmune disease treatment [49].

2.4. Clinical applications of DCs

2.4.1. Cancer treatment

DCs display a key role during the initiation of specific immune responses required for anticancer immunity. DC functions are often altered in cancer patients; therefore, immunomodulation of DC function is suggested as a key event in cancer prevention and treatment. Consequently, several studies have been performed to investigate the role of plant products or extracts on the behavior of DCs toward cancer cells [50].

2.4.1.1. Human trial studies. Li et al [51] showed that injecting Shenqi Fuzheng Chinese herbal medication during chemotherapy of breast cancer patients induced DC activation. Likewise, combined treatment of Chinese herbal medicine, Lingdankang Composite and DC-cytokine-induced killer cells, was effective in clearing molecular biological remission in leukemia patients [52]. Tolerogenic DCs, which may be involved in induction of regulatory T cells was found to be reduced by Neem leaf glycoprotein in cervical cancer stage IIIB (CaCx-IIIB) patients [53]. Chinese herb *Ganoderma lucidum* showed immunomodulatory effects mediated by DCs [54]. Further studies also indicated that *Astragulus* membranes induced DC maturation *in vitro* and enhanced antigen presentation in children with acute leukemia. In addition, DCs exposed to Amomi Semen extract exhibited activated phenotypes, secreted IL-12p70, and inhibited the growth of tumor cells [55]. Recently, effective stimulation of intercellular adhesion molecule 1 expression in primary DCs was also achieved by the glycolipid mixture containing β-glucosylceramides purified from Juzen-taiho-to herb that used in East Asia for cancer patients [56].

2.4.1.2. In vitro studies. Fermented mistletoe extract significantly enhanced maturation of immature DCs, as showed by upregulation of CD83, CD80 and CD86, as well as HLA class I and II molecules on these cells [57]. Likewise, different molecular weight fractions of pine cones (termed poly-phenylpropanoid polysaccharide complex) extract were introduced to murine BMDCs and human monocyte U937 cells, resulting in enhanced maturation of murine DCs and inhibiting growth of human cancer cell lines, indicating the efficacy of this extract in cancer treatment [58]. Mucuna (*Mucuna pruviens* var. utilis) biologically active component was found to induce DC differentiation and maturation as well as apoptosis in human cancer cell lines [59]. Similarly, heat-stable extract from azuki bean (*Vigna angula*) encouraged differentiation of immature DCs and suppressed the growth of human leukemia U937 cells, through induction of apoptosis [60]. *Ocimum basilicum* polysaccharide extract (basil polysaccharide) and curcumin regulated invasion of ovarian cancer cells and human monocyte-derived DCs by markedly downregulating osteopontin, CD44 and matrix metalloproteinase-9 expression [61].

2.4.1.3. In vivo studies. Numerous studies were performed on animal models to emphasize the effect of different plant products on DCs toward tumor suppression. *Astragulus* injection modulated action of DCs and resulted in inhibition of tumor metastasis in mice with metastatic lung cancer [62]. Another study using H22-bearing mice indicated a significant decrease in DCs in the tumor microenvironment, while treatment with LBP increased the number of DCs associated with enhanced anti-tumor function of the immune system [63]. Furthermore, an alcoholic extract of *Tinospora cordifolia* boosts the differentiation of tumor-associated macrophages to DCs in response to granulocyte–macrophage colony-stimulating factor, IL-4, and TNF, and led to enhanced tumor cytotoxicity and production of tumoricidal soluble molecules and increased survival of tumor-bearing mice [64]. The extract of *Larix leptolepis*, one of the most common woods in Hokkaido, Japan, strongly activated type 1 immunity and significantly inhibited the growth of tumor in a mouse model [65]. Green plant DNA is a natural source of CpG DNA, and may provide the ability to activate DCs and inhibit tumor growth in tumor-bearing mice by stimulating secretion of IL-12, and enhances expression of MHC and co-stimulatory molecules by BMDCs [66]. Moreover, grape seed proanthocyanidins might lower UV-induced immunosuppression throughout DNA-repair-dependent functional activation of DCs in mice [67]. Polysaccharide fractions obtained from the root of *Astragalus membranaceus* and *Codonopsis pilosulae* and *Ficus carica* polysaccharides displayed enhanced efficiency of DC-based cancer vaccine [68,69]. In a mouse model, CM-Glucan (carboxymethylated Beta-(1, 3) (1, 6) glucan); trade name Immunomax®; injections significantly prolonged total survival and cured 31% of mice, which was

associated with activation of DCs via TLR-4 and stimulation of natural killer cells [70].

2.4.2. Treatment of infectious diseases

Many plant materials enhance the ability of the immune system to fight infection. Although microbial agents have different effects in stimulating the immune system, the availability of plant or herbal extracts that enhance the immune response against infectious agents has increased dramatically. This may be crucial to introduce and provide an alternative and inexpensive medication.

2.4.2.1. Viral infections. Ginseng extract (CVT-E002) reduces symptoms of viral infection in clinical trials mediated by DC modulation and increased T-cell activation [71]. Moreover, *Astragalus* polysaccharides enhance the immune response and have been used as an adjuvant for hepatitis B virus DNA vaccine by stimulating DC maturation and reducing the amount of the regulatory T cells [72]. Additionally, the traditional Chinese medicines Bushen Jiedu Recipe and Jianpi Jiedu Recipe, were demonstrated to stimulate the recovery of DC function in patients with chronic hepatitis B virus infection [73]. A combination of herbal extracts comprising *Tanacetum vulgare* (tansy), *Rosa canina* and *Urtica dioica* (nettle) in addition to selenium, flavonoids, and carotenes known as Setarud, was found to inhibit maturation of myeloid DCs and significantly increase CD4 count, and therefore, used for the treatment of HIV infection [74]. Three Guatemalan plant extracts from *Justicia reptans*, *Neurolaena lobata*, and *Pouteria viridis* were found to inhibit HIV replication, by preventing transmission of virus from DCs to lymphocytes [75]. Total extract of Korean Red Ginseng and its constituents were found to affect influenza A virus infection by induction of TNF-α/inducible nitric oxide synthase-producing DCs in mouse lungs [76]. Additionally, treatment of human respiratory epithelial cells (16HBE) infected by influenza virus H1N1 with Patchouli alcohol extract induces antiviral effects by inhibition of cytokines released by immune cells including DCs *in vitro* [77].

2.4.2.2. Bacterial infections. Dietary rice bran was found to increase myeloid DCs in the lamina propria and mesenteric lymph nodes, suggesting promising influence on the modulation of mucosal immunity for protection against enteric infections [78]. *Astragalus* root and elderberry fruit extracts induced IFN-β production, slightly reduced the proinflammatory response to *Escherichia coli*, and improved endocytosis in immature DCs. Therefore, both extracts may be beneficial in microbial activity [79].

2.4.2.3. Parasitic infections. In leishmaniasis, the interactions between the parasites and DCs are complex and involve conflicting processes leading to control or progress of the infection. Alkaloid extract of *Evanta* or the purified alkaloid 2-phenilquinoline decreased DC secretion of IL-12p40 and levels of IFN-γ and IL-10 secreted by T cells co-cultured with these DCs, which may contribute to the regulatory effects toward inflammation [80]. *P. ginseng* was also found to affect cutaneous leishmaniasis caused by *Leishmania mexicana in vitro* by induction of Th1 cytokine IL-12 by DCs [81].

2.4.3. Treatment of allergy

Allergy affects many people and is a major cause of hospitalization for anaphylactic reactions worldwide. DCs play an important role in the establishment of allergy leading to Th2-mediated responses. Plant and herbal extracts may play an essential role in modulating DC function and activation of T-cell responses. In a murine model of asthma, Shikonin exhibits dose-dependent inhibition of BMDC maturation *in vitro* and inhibits allergic inflammation and airway hyper-responsiveness [82]. It is reported that treatment of children with asthma with traditional Chinese medicine Wuhu Decoction suppresses several DC markers. This suggests an effective medication for children with asthma that may be related to its ability to regulate the co-stimulatory molecules of DCs [83]. Protein-free oat plantlet extract displays anti-inflammatory and immunoregulatory activities *in vitro*, which are demonstrated by their effect on the phenotype and function of DCs differentiated from monocytes. This extract decreased DC expression of MHC class II molecules and significantly weakened their stimulatory activity on autologous T cells. Protein-free extract may be useful to avoid developing sensitization to dietary proteins in atopic patients [84].

2.4.4. Treatment of inflammatory and autoimmune diseases

Several lines of research have demonstrated the ability of some plant/herb products or extracts to suppress DC response, maturation and cytokine secretions either *in vitro* or *in vivo*. Water extract of Malian medicinal plant *Biophytum petersianum* Klotzsch (Oxalidaceae) was found to induce activation of DCs, while there was slight response on T cells, B cells, and natural killer cells, suggesting the valuable use of the plant in the treatment of several types of immune diseases [85]. Additionally, water extract of *Zataria multiflora* and *Thymus vulgaris* (thyme) plants showed immunomodulatory effects on allogenic T-cell proliferation and activated DCs [86]. An active compound extracted from peony root has been used to treat rheumatoid arthritis by suppressing DC maturation, activation and differentiation of Th1 cells [87]. Similarly, MCS-18, a natural product obtained from *Helleborus purpurascens*, has been shown to inhibit the expression of important murine BMDC-specific molecules and lead to impaired T-cell stimulation and reduced B-cell proliferation and immunoglobulin production, which may suggest its use in inflammatory and autoimmune disorders [88]. Also, the extract of the stinging nettle leaf IDS 30 (*Hox alpha*) was shown to prevent DC maturation and cytokine secretion, whereas it increased endocytosis of DCs to dextran, without stimulating T cells, suggesting it as a possible treatment in rheumatoid arthritis [89]. Similarly, *Cymbopogon citratus* (lemongrass), either dried leaves or its fractions, significantly inhibited the LPS-induced NO production and inducible NO synthase expression by DCs, suggesting its beneficial role in the treatment of inflammatory diseases [90]. The effect of 18-β-glycyrrhetinic acid, the main bioactive component of licorice root extracts

showed anti-inflammatory effects mediated by DC on *Propionibacterium acnes*-induced acute inflammatory liver injury [91]. Treatment of experimental colitis rats *in vivo* with Qingchang Huashi Recipe showed significant suppression effects of DC infiltration and activation [92]. Also, total glucosides of peony extracted from the roots of *Paeonia lactiflora* inhibit DC maturation and function, which reduces immune-mediated inflammation *in vivo* [93]. Additionally, *Wedelia chinensis*, a medicinal herb commonly used in Asia, showed anti-colitis effects in mice by suppressing Th1, Th17, and DC responses in colon tissues [94]. Moreover, stem bark of *Kalopanax pictus* (Araliaceae) extract are beneficial in the treatment of various inflammatory diseases through their ability to suppress DC inflammatory cytokines such as IL-12 p40 and IL-6 [95]. Finally, *Panax quinquefolium* saponins (American ginseng), Danhong (extracted from Radix Salviae miltiorrhizae and Flos *Carthami tinctorii*), were found to suppress atherosclerotic effects mediated by DC maturation inhibition [96,97].

3. Conclusion

The immune response can be either stimulated or suppressed in favor of human health. DCs are crucial cells of the immune system that are adapted to perform these mechanisms. Plants and plant products and their purified components have become an area of research interest. Further studies are required to explore the benefit of these products to be used as tools for immunomodulation required for disease prevention and therapy with minimal side effects at lowest cost.

Conflict of interest

I wish to confirm that there are no known conflicts of interest associated with this publication.

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