

Review

Dendritic Cells (DCs)-Based Cancer Immunotherapy: A Review on the Prospects of Medicinal Plants and Their Phytochemicals as Potential Pharmacological Modulators

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Abstract: Dendritic cells (DCs) are specialized antigen-presenting cells in humans and animals that provide antigen-specific T-cell immunity in the body. It also establishes a linkage between innate and adaptive immune responses. Various studies have shown that malignancies or cancer may impair DCs and effector T-cell functions. DCs have now become a new molecular target for the treatment of cancer. Modified matured DCs could be novel biological modifiers to treat various diseases, including cancer. This review aims to provide an update on the impacts of various plant materials and their phytochemicals on DC-based cancer immunotherapy. Existing literature on DC-based cancer immunotherapy and plant-based pharmacological modulators has been explored over the last decade using various online databases such as Google Scholar, PubMed, Science Direct, and Scopus. Mounting evidence from preclinical and clinical findings suggests that various plants and their bioactive phytochemicals are effective in modulating the immune system and signaling pathways involved in anti-tumor immunity. Despite the prospective role of herbs in DC-based cancer immunotherapy, most of the studies are limited by either preclinical models or crude plant extracts. This review provides a useful perspective for developing potential plant-derived pharmacological modulators in DC-based cancer immunotherapy.

Keywords: dendritic cells; cancer immunotherapy; cytokines; T-cells; immunopharmacology; medicinal herbs

1. Introduction

Dendritic cells (DCs) are dominant antigen-presenting cells and play a vital role in processing and presenting antigens to T-cells that can be directed to humoral and cellular antigen-specific immune responses against specific benign and malignant tumors [1]. Mouse and human DCs seem to be similar or parallel. It has been reported that DC precursors existing in the bone marrow are categorized into two groups on the basis of their localization: lymphoid organ resident DCs and migratory tissue DCs [2,3]. The DCs, which reside in lymphoid organs, uptake antigens from blood and transfer them to the local T

cells. In contrast, DCs in migratory tissues transfer antigens from tissues to the lymph node and present antigens from tissues to T-cells. On the basis of the marker on the cell surface, the DCs are divided into two groups in mice: one is conventional DCs and the other is plasmacytoid DCs (pDCs). The pDCs release a huge amount of type 1 interferon due to viral infections [4].

Immature DCs have the capacity to uptake and process antigens, which are subsequently converted to matured DCs and migrate to the target lymphoid organs [5]. Matured DCs are characterized by a high level of major histocompatibility complex (MHC) as well as related co-stimulatory molecules such as CD80, CD83, and CD86 that stabilize the interaction between DCs and naive T lymphocytes [6]. The mature DCs produce proinflammatory cytokines such as interferon-gamma (IFN- γ) and interleukin 12 (IL-12), which activate Th1 cells and catalyze the activation of cytotoxic T lymphocytes. Activated cytotoxic T lymphocytes (CTL) migrate to the tumor microenvironment and induce apoptosis via the release of perforin and granzymes. Dendritic cells can also induce natural killer (NK) cells and B cells [7]. Pro-inflammatory cytokines such as IL-12, IL-6, and tumor necrosis factor- α (TNF- α), produced mainly by DCs, alter the tumor microenvironment as well as induce the cytotoxic activity of NK cells and clonal expansion of CD4⁺ and CD8⁺ T-cells [8]. Some proinflammatory cytokines (TNF- α , IL-1 α/β and IL-6) can induce an immune response in the tumor microenvironment. They also produce reactive oxygen species (ROS) and reactive nitrogen species (RNS) that infiltrate the tumor microenvironment and destroy tumor cells [9,10]. The malignant can inhibit or inactivate DCs or effector T-cells by secreting inhibitory molecules or immunosuppressive cytokines (IL-10 and TGF- β) [11]. The dendritic cells present extracellular antigens on MHC-II molecules to CD4⁺ T cells and, on the other hand, intracellular antigens on MHC-I molecules to CD8⁺ T cells.

The dendritic cells not only present extracellular antigens on MHC-II molecules to CD4⁺ T-cells but also present intracellular antigens on MHC-I molecules to CD8⁺ T-cells, which play a pivotal role in anticancer immunity [12]. The dendritic cells present antigens to helper T cells and produce distinct Th1, Th2, Th17, and follicular T cells. Based on cytokine expression, Th1 and Th2 cells produce IFN- γ and IL-4, IL-5, and IL-13, respectively. Th17 cells show a great degree of change and convert to Th1 cells. Anticancer immunity is provided by IFN- γ -producing T helper cells [13]. Over the last decade, ex vivo generated DCs and in vitro targeting DCs have been extensively studied as potential cancer vaccines [11]. Meanwhile, several DC-based cancer vaccine trials against specific antigens have been conducted, such as ovarian cancer, prostate cancer, metastatic melanoma cancer, glioblastoma, and pancreatic cancer [14]. However, it has been reported that DC-based cancer vaccines are not so effective in clinical trials due to low maturation, migration, and reduced IL-12 secretion [15,16]. For this reason, the ex vivo-generated DCs need to be stimulated by adjuvant to make fully matured DCs with increased IL-12 secretion from these cells [17]. Recently, the Food and Drug Administration of the USA approved a DC-based vaccine against human prostate cancer named Sipuleucel-T. It has been shown that early-stage of clinical trials of DC-based cancer vaccines increase the nonspecific immune responses in cancer patients with aggressive tumor progression and immune dysfunction that limit the effectiveness of the vaccines [11,18]. To overcome this problem, tumor cell lysate (TCL)-loaded DCs with phytomolecule adjuvant increased the effectiveness of vaccines in an in vivo animal model [18].

The medicine from plant extracts and its active components has immunomodulatory effects on the maturation of DCs [19,20]. Plant-derived polysaccharides (PDPs) can stimulate the maturation of DCs and present internalized antigens to naive T-cells. The naive T-cells activate T-cells and remove the tumor. The plant-derived polysaccharides (PDPs) can also be used as adjuvants in DC-based cancer vaccines or act as independent agents in intrinsic anti-tumor activities [21]. Mixed polysaccharide fractions from plant roots enhance the efficiency of the DC-based cancer vaccine against metastasis of 4T1 mammary carcinoma in mice [18]. Traditional herbal medicine can reduce the toxicity of chemotherapy and radiotherapy and enhance anti-tumor therapies with decreased cancer-derived

pains#. It also reduces postoperative complications and increases the survivability of cancer patients [22]. Another report showed that immunomodulatory activity on the human Monocyte-Derived Dendritic Cell (MDDCs) vaccine, which was pulsed with plant extract and human papillomavirus 16 (HPV16) tumor protein and was shown to be effective against HPV16 related tumors in an animal model [23]. Plant extract of Oregon grape (*Mahonia aquifolium*) stimulates peripheral blood mononuclear cells (PBMCs) and induces cytotoxicity and apoptosis of the tumor cells [24]. Kauroo et al. investigated Mauritius endemic plants (*Psidium lithospermifolia*, plants from the Asteraceae family) for anticancer activities in T-cell lymphoma and melanoma cells. They also found that plant extract components have potential anticancer activities in vitro studies [25]. Plant tuber extract (*Dioscorea alata* var. *purpurea*) acts as an adjuvant of bone-marrow-derived dendritic cell (DC) based vaccine for cancer immunotherapy [26]. The maturation of dendritic cells is important for initiating immune responses. The tumor microenvironment inhibits the maturation of DCs, and it is a great problem for DC-based tumor immunotherapy. PDPs induce phenotypic and functional maturation of DCs [27]. Alcoholic extracts of plants (*Tinospora cordifolia*) induce the differentiation of dendritic cells from macrophages in the presence of granulocyte-macrophage colony-stimulating factor (GM-CSF), TNF, and IL-4 [28]. It has been proven that most therapeutic plants can modulate DC activities and can be used as a therapeutic target to treat cancer [29]. For this reason, this review discusses the potential application of phytochemicals in dendritic cell (DC)-based cancer immunotherapy.

2. Effects of Plant Extracts on In Vitro Dendritic Cell Biology and Its Effects in Cancer Cells

2.1. Dendritic Cells Differentiation and Maturation

Although the immature DCs have high endocytic activity to capture antigens and the ability to initiate T-cell stimulation [30]. The maturation of DCs is necessary for antigen-specific T-cell immunity [31]. Different types of proinflammatory cytokines (IL-1, TNF- α , PGE2, etc.), lipopolysaccharide (LPS) from bacteria and natural products induce DC maturation. Mature DCs show surface expression of costimulatory molecules such as CD40, CD80, CD86, and MHC II, which are essential to produce an antigen-specific T cell immune response [4,29]. It has been reported that different types of plant extracts and their active components have been shown to enhance DC differentiation (Table 1). Pine cone extract, the traditional Japanese herbal plant kampo, and water-soluble extract of the fern *Polypodium leucotomos* induce DC differentiation both in vitro and in vivo [29].

Plant-derived polysaccharide (PDP) extracts induce DC maturation and provide anti-tumor immunity [21]. Plant polysaccharides obtained from the medicinal herb *Polyporus umbellatus* induce activation and maturation of murine BMDC through TLR [32]. Another study also showed that plant polysaccharide (PLP) from *Pueraria lobata* induces surface phenotype expression of CD40, CD86, and major histocompatibility complex I/II [27]. The *Dioscorea* plant extract (DsII polysaccharides) increased the maturation of DCs and also enhanced the TLR-loaded DC-mediated T-cell activation and proliferation, which induces strong immunity against melanoma in animals [26]. It has been found that a plant of *Nicotiana benthamiana* does not affect dendritic cell differentiation but induces maturation. The plant does not have any effect on antigen uptake capacity [23]. Neem leaf glycoprotein (NLGP) induces the maturation of DCs and also increases the expression of MHCs and co-stimulatory molecules CD83, CD80, CD86, and CD40 [33]. Dendritic cells pulsed with Astragalus polysaccharide showed increased DC maturation and induced allogeneic lymphocyte proliferation. It also increased the expression of CD11c and MHC class II molecules on DCs [34,35]. The immunomodulatory effect of aged garlic extract 14 kDa protein showed increased expression of CD40 surface phenotypes of DCs, but it had no effect on CD86 and MHC II expressions [36]. The seed extract of *Plantago asiatica* induces the maturation of DCs and also increases the expression of MHC II, CD80, and CD86 surface phenotypes on DCs [37]. Medicinal herbs, including *Thymus daenensis*, *Thymus vulgaris*, and *Zataria multiflora*, combinedly induce DC-mediated T-cell activation. The herbs also showed

increased CD40 surface phenotype expression on DCs [38]. Bordbar et al. showed that licorice roots containing 18- α and 18- β -glycyrrhetic acid stimulate DCs that enhance T-cell immunity against specific antigens [39]. Some plant components were found to initiate DC differentiation and maturation in vitro, such as lupine acetate of cortex periplocae, the aqueous and organic fractions from *Petiveria alliacea*, an acidic polysaccharide from ginseng (*Panax ginseng*), and *Lycium bararum* polysaccharide (LBP) [29]. In the same way, another traditional Chinese herb, *Achyranthes bidentata*, induces surface phenotypes and maturation of DCs and also boosts immune responses in mice [40]. The fermented mistletoe extract component matures DCs and is used as an adjuvant for the treatment of cancer patients [41].

Table 1. Plant extracts on dendritic cells (DCs) differentiation and maturation.

Plant Name/Extracts	Differentiation and Maturation of DCs	Phenotypic Marker	References
<i>Polypodium leucotomos</i>	Differentiation	-	[21,29]
<i>Polyporus umbellatus</i>	Maturation	-	[32]
<i>Pueraria lobata</i>	Maturation	CD40, CD80 and MHC I/II	[27]
<i>Dioscorea</i> spp.	Maturation	-	[26]
<i>Nicotiana benthamiana</i>	No differentiation, but induce maturation	-	[23]
Neem leaf glycoprotein	Maturation	CD83, CD80, CD86, CD40 and MHCs	[33]
Astragalus polysaccharide	Maturation	CD11c and MHCII	[34,35]
Aged garlic extract	—	Increase CD40, but no effect on CD86 and MHCII	[36]
Seed extract <i>Plantago asiatica</i>	Maturation	CD80, CD86 and MHCII	[37]
<i>Thymus vulgaris</i> , <i>Thymus daenensis</i> , <i>Zataria multiflora</i>	Maturation	CD40	[38]
Licorice roots containing 18- α and 18- β -glycyrrhetic acid	Maturation	-	[39]
Lupine acetate of cortex periplocae, the aqueous and organic fractions from <i>Petiveria alliacea</i> , acidic polysaccharide from Ginseng (<i>Panax ginseng</i>) and <i>Lycium bararum</i> polysaccharide (LBP)	Both maturation and differentiation	-	[29]
Chinese herb <i>Achyranthes bidentata</i>	Maturation	-	[40]
Fermented mistletoe extract	Maturation	-	[41]

2.2. Activation of T-Cells

It has been found that several plant components stimulate mature DCs to induce T-cell proliferation [42], which are given in Table 2. The plant-derived polysaccharide *Angelica gigas Nakai* (Angelin) activates DCs increases T-cell proliferation. It also increases Th1 cytokines such as IL-12 and IFN- γ [43,44]. *Capparis spinosa* polysaccharides induce DC maturation and increase the proliferation of CD8 and CD4 T-cells [45]. Another study showed that Safflower *Carthamus tinctorius* enhances DC-mediated T-cell polarization and increases the cytotoxic activity against tumors [46]. Water extract of *Glycyrrhiza uralensis* stimulated DC maturation, enhanced HPV16 specific CD8+ T-cell proliferation and reduced tumor size [47]. *Dioscorea* tuber phytoextracts confer immunomodulatory activities through DC-mediated activation of T-cell proliferation [18]. Immunomodulatory activity of plant extract (*Nicotiana benthamiana*) containing HPV16-E7 protein in human monocyte-derived dendritic cells induces HPV16-E7 specific cytotoxic activity [23]. Another report showed that plant-derived polysaccharides (PDPs) can induce DC maturation and

provide T cell immunity [21]. The butanol fraction of the stems and leaves of *Echinacea purpurea* significantly influences BMDC maturation and T-cell proliferation [29]. It has been observed that uncarinic acid C, uncarinic acid D, and triterpene esters isolated from *Uncaria rhynchophylla* plants were found to activate cytokine production of human DCs towards Th1 immune responses [48].

Table 2. Plant extract pulsed DCs on T-cell activation.

Plant Name/Extracts	DCs on T-Cell Activation	References
Polysaccharide <i>Angelica gigas Nakai</i> (Angelin)	Increase T-cell proliferation and Th1 cytokines	[43,44]
<i>Capparis spinosa</i> polysaccharides	Increase proliferation of CD4 and CD8 T-cells	[45]
Safflower <i>Carthamus tinctorius</i>	Enhances DCs mediated T-cell polarization	[46]
<i>Glycyrrhiza uralensis</i>	Increase tumor-specific CD8 T-cell proliferation	[47]
<i>Dioscorea</i> tuber phytoextracts	Increase T-cell proliferation	[18]
plant extract of <i>Nicotiana benthamiana</i>	Enhances cytotoxic activity of tumor-specific T-cell	[23]
Butanol fraction of stem and leaf extract of <i>Echinacea purpurea</i>	Increase T-cell proliferation	[21]
Uncarinic acid C, uncarinic acid D and Triterpene esters from <i>Uncaria rhynchophylla</i>	Increase T-cell proliferation and Th1 cytokines	[48]

2.3. Cytokines Production

Many studies observed that plant extracts stimulated matured DCs to increase T-cell proliferation and production of immunostimulatory cytokines such as the T helper cytokines (Th1) IL-12 and IFN- γ [49], which are shown in Table 3. The extract of the Kurosengoku Japanese soybean initiates the production of IFN- γ and IL-12 from DCs [50]. Another group found that the active component galactomannan isolated from the *Caesalpinia spinosa* plant gives rise to the maturation of DCs and also increases mRNA levels of proinflammatory cytokines [51]. Water extract of *Glycyrrhiza uralensis* stimulates the maturation of DCs and expands the concentration of proinflammatory cytokines IL-12, TNF- α , IL-6, IL-6, and IL-1 β , and these changes initiate the Th1 immune response and provide cytotoxicity against tumors [47]. Plant-derived polysaccharides from *Ficus carica* facilitate the maturation of DCs and increase the mRNA expression of IFN- γ , IL-1, IL-6, and IL-23 [52]. Angelin from the medicinal plant *Angelica gigas Nakai* initiates dendritic cell maturation and increases the production of inflammatory cytokines IL-1 β , TNF- α , IL-12, IFN- α , and IFN- β [43]. The polysaccharides from *Astragalus mongholicus* stimulated DCs to induce the expression of IL-12p70 [35]. Polysaccharide (PLP) isolated from *Pueraria lobata* and *Mori fructus* acts on DCs and increases the production of interleukin IL-1 β , TNF- α , and IL-12 [27,53]. Seeds of *Plantago asiatica* induce DC maturation and production of increased TNF- α and IL-12p70, and decreased IL-10 [54]. Water extract of *Pleurotus ferulae* enhances the maturation of DCs through the Toll-like receptor4 (TLR4) signaling pathway and increases the production of IL-6, IL-12, and TNF- α in a dose-dependent manner [55]. A purified polysaccharide isolated from *Polyporus 7u* prompts the activation of bone marrow-derived DCs and the production of IL-12 cytokines [32]. Plant-derived polysaccharides from *Angelica gigas* and *Capparis spinosa* stimulated DCs to enhance the production of IL-1 β , TNF- α , IL-12, IFN- α , and IFN- β cytokines [44,45]. Ethanol extract of *Phyllanthus amarus*-generated tumor lysate pulsed monocyte-derived DCs induces the mRNA expression of IL-6 and IL-12 cytokines [14]. The polysaccharides from *Ficus carica* promote DC maturation and increase mRNA expression of IL-6, IL-12, IL-23, and IFN- γ [52].

Table 3. Plant extracts stimulated DCs on immunostimulatory cytokines production.

Plant Name/Extracts	DCs on Immunostimulatory Cytokines Production	References
Japanese soybean Kurosengoku extracts	Increase production of IFN- γ and IL-12	[50]
Galactomannan from <i>Caesalpinia spinosa</i>	Increase concentration of IL-1 β , IL-6, IL-12, and TNF- α	[47]
Polysaccharides-derived from <i>Ficus carica</i>	Increase mRNA expression of IL-1, IL-6, IFN- γ , and IL-23	[53]
Angelan from <i>Angelica gigas Nakai</i>	Increase TNF- α , IL-12, IFN- α , IFN- β , and IL-1 β	[43]
Polysaccharides from <i>Astragalus mongholicus</i>	Increase expression of IL-12p70	[35]
Polysaccharide (PLP) isolated from <i>Pueraria lobata</i> and <i>Mori fructus</i>	Increase production of interleukin IL-1 β , IL-12, and TNF- α	[27,53]
Seeds of <i>Plantago asiatica</i>	Increase production of TNF- α and IL-12p70, and decrease IL-10	[54]
Water extract of <i>Pleurotus ferulae</i>	Increase production of IL-6, IL-12, and TNF- α in dose-dependent manner	[55]
Polysaccharide from <i>Polyporus umbellatus</i>	Increase production of IL-12 cytokine	[32]
Plant-derived polysaccharides from <i>Angelica gigas</i> and <i>Capparis spinosa</i>	Increase production of IL-1 β , IL-12, IFN- α , IFN- β , and TNF- α cytokines	[44,45]
Ethanol extract of <i>Phyllanthus amarus</i>	Increase expression IL-6 and IL-12cytokines	[14]
Polysaccharides from <i>Ficus carica</i>	Increase mRNA expression of IL-6, IL-12, IFN- γ , and IL-23	[52]

2.4. Plant Extracts Pulsed DCs-Based Anti-Tumor Immunity through Various Signaling Pathways

The maturation of DCs is critical for initiating immune responses. In Table 4, plant extract polysaccharide (PLP) from *Pueraria lobata*-activated DCs enhances T-cell stimulation through the TLR4 signaling pathway. Here, extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK), p38 mitogen-activated protein kinase (MAPK) phosphorylation, and nuclear factor kappa-light-chain-enhancer of activated B cells p65 (NF- κ Bp65) subunit are the downstream molecules of Toll-like receptor 4 (TLR4) [27]. It has been reported that neem leaf glycoprotein (NLGP) is popular for its anti-tumor therapy. NLGP-pulsed DCs activate forkhead box P3+ (FoxP3+) Treg downregulation, T-bet upregulation, signal transducer and activator of transcription (STAT) 1 and STAT4 high phosphorylation, and STAT3 low phosphorylation, which ultimately induces Th1 immune response [4]. Huang et al. reported that polysaccharide from *Plantago Asiatica* induces DC maturation through the TLR4 pathway [54]. Water extract of *Glycyrrhiza uralensis* dose-dependently promotes DC maturation and cytokine production through the Toll-like receptor (TLR) 4 signaling pathway [47]. The polysaccharide-derived from *Mori fructus* and *Platycondon grandiflorum*-pulsed DCs mediated T-cell proliferation through mitogen-activated protein kinase MAPK (increased phosphorylation of JNK, ERK, c-Jun, p38 and MAPKs) and NF- κ B (increase nuclear translocation of NF- κ B p65 and iKB α / β degradation) signaling pathway where TLR4 is a membrane target molecule [53,56]. Angelan from *Angelica gigas Nakai* plant polysaccharide stimulated dendritic cells mediated tumor immunotherapy, where TLR4 is a membrane target and downstream signaling molecules are NF- κ B/Rel (increased translocation of NF- κ B p50/p65, RelB and c-Rel) and MAPK (increased phosphorylation of p38, JNK, and ERK) [43,44]. Another study found that *Lycium barbarum* polysaccharides induce TLR2 and TLR4-mediated functional activation of DCs via activation of NF- κ B [57]. Li et al. reported that maturation of dendritic cells is induced by *Radix Glycyrrhizae* polysaccharide through NF- κ B and MAPK (increased MAPK, p38, and JNK phosphorylation but no change in ERK) signaling pathways [58]. Fractioned Dioscorea phytoextract (DsII) enhances

the potency of DC-based cancer immunotherapy through pathogen-associated molecular pattern (PAMP) signaling, which is required for potent activation of naive T-cells [18].

Table 4. Plant extracts pulsed DCs on various signaling pathways in anti-tumor immunity.

Plant Name/Extracts	DCs on Signaling Pathways	References
Polysaccharide (PLP) from <i>Pueraria lobata</i>	DCs enhances T-cell stimulation through TLR4 signaling pathway	[27]
Neem leaf glycoprotein (NLGP)	DCs activates FoxP3+ Treg downregulation, T-bet upregulation, and STAT1 and STAT4 high phosphorylation, and low phosphorylation STAT3	[4]
Polysaccharide from <i>Plantago Asiatica</i>	DCs maturation through TLR4 pathway	[54]
Water extract of <i>Glycyrrhiza uralensis</i>	DCs maturation and cytokines production through TLR4 signaling pathway	[47]
Polysaccharide-derived from <i>Mori fructus</i> and <i>Platycondon grandiflorum</i>	DCs mediated T-cell proliferation through MAPK and NF- κ B signaling pathway	[53,56]
<i>Lycium barbarum</i> polysaccharides	TLR2 and TLR4 mediated functional activation of DCs via activation of NF- κ B	[57]
Angelan from <i>Angelica gigas Nakai</i> plant polysaccharide	DC mediated tumor immunotherapy through TLR where downstream target molecules are NF- κ B/Rel and MAPK	[43,44]
<i>Radix Glycyrrhizae</i> polysaccharide	Maturation of DCs through NF- κ B and MAPK	[58]
<i>Dioscorea</i> phytoextract (DsII)	DC-based cancer immunotherapy through PAMPs signaling pathway	[58]

3. Plant Extracts Pulsed DCs on In Vivo Cancer Immunotherapy

Various studies have been conducted on animal models to evaluate the effects of different plant extract components on DC-based cancer immunotherapy in vivo (Table 5). Polysaccharides from *Astragalus membranaceus* and *Astragalus mongholicus* injected in laboratory mice inhibit the growth of metastatic lung cancer [59]. Treatment of H22-bearing mice (Hepatoma) with plant extracts polysaccharide LBP (*Lycium barbarum*) stimulated DCs enhances the anti-tumor function [60]. Another study found that an extract of *Larix leptolepsis*, one of the renowned woods in Hokkaido, Japan, promotes type 1 immune response and inhibits tumor growth in mice [61]. Furthermore, grape seed proanthocyanidins decrease UV-induced immune function by repairing DNA on functional activation of DCs in mice [62]. *Tinospora cordifolia* is an alcoholic extract that boosts the dendritic cell differentiation of tumor-associated macrophages, enhancing tumor cytotoxicity and increasing the survivability of tumor-bearing mice [28]. The immunostimulatory plant DNA CpG activates DCs and inhibits the growth of tumors in mice by stimulating the secretion of surface phenotypes of co-stimulatory molecules, MHC and IL-12 cytokines from BMDCs [63]. In mice, CM-Glucan (carboxymethylated Beta-(1,3) (1,6) glucan); brand name Immunomax[®] injection) significantly inhibits tumor growth and increases the survivability of mice through activation of DCs via TLR4 and natural killer cells [64]. The fractions of polysaccharide derived from the root of *Ficus carica* enhance the efficacy of DC-based cancer immunotherapy [52]. Plant-derived polysaccharide from *Carthamus tinctorius* provides the anti-tumor activity of DC-derived vaccines via polarization of Th1 cytokines and promotes cytotoxic activity [46]. Reishi mushroom *Ganoderma lucidum*-derived plant polysaccharide has immunomodulatory, antiangiogenic, and cytotoxic activity against tumors in mice [65]. The polysaccharide from *Dioscorea alata* var. *Purpurea* stimulates DCs and enhances anti-tumor activity in mice [26].

Table 5. Plant extracts pulsed DCs on in vivo study against cancer.

Plant Name/Extracts	DCs on In Vivo Study against Cancer	References
Polysaccharide LBP (<i>Lycium barbarum</i>)	Increase the number of DCs with anti-tumor immune function in mice	[60]
<i>Larix leptolepsis</i>	Activates DCs to initiate type 1 immunity and inhibit tumor growth in mice	[61]
Grape seed proanthocyanidins	Lowering the UV-induced immunosuppression by repairing DNA through activation of DCs in mice	[62]
Alcoholic extract of <i>Tinospora cordifolia</i>	Enhancing the differentiation of tumor-associated macrophages to DCs and increases cytotoxicity in tumor bearing mice	[28]
Plant DNA CpG	Activates DCs and decreases tumor growth in mice	[63]
Plant-derived agonist CM-Glucan (carboxymethylated Beta- (1,3) (1,6) glucan); trade name Immunomax [®]	Inhibit tumor growth in mice through activation of DCs	[64]
Polysaccharide from root of <i>Ficus carica</i>	Enhancing the activity of DC-based cancer immunotherapy in mice	[52]
Polysaccharide from <i>Carthamus tinctorius</i>	Increase the efficiency of DC-based cancer vaccine through the cytotoxic activity of CD8 T-cells	[46]
Polysaccharide from <i>Dioscorea alata</i> var. <i>Purpurea</i>	Stimulates DCs and enhances anti-tumor activity in mice	[26]

4. Application of Phytoextract in DCs-Based Clinical Study of Cancer Therapy

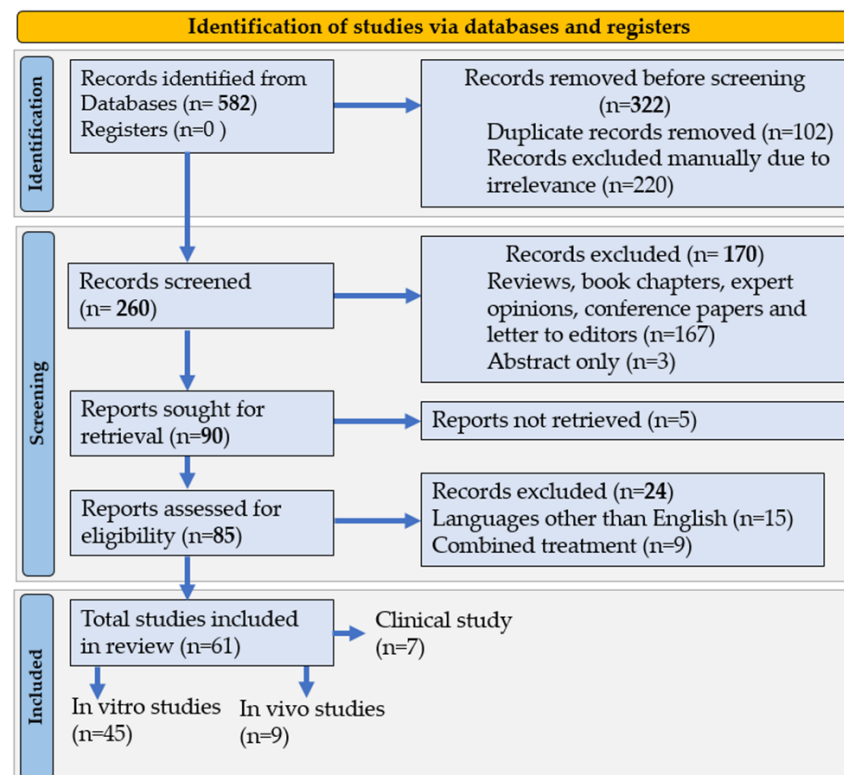
Dendritic cells play an important role in the initiation of immune responses for anticancer immunity. In cancer patients, dendritic cells are altered in the tumor microenvironment [1]. For this reason, modulation of DCs is suggested for cancer prevention and treatment. In the last couple of years, several studies have been performed to assess the role of plant extract in DC-based immunotherapy against cancer [66]. In Table 6, it has been reported that *Nicotiana benthamiana* NbPVX-E7 pulsed-MDDCs/PBMCs can prime human blood-derived lymphocytes from healthy individuals to induce human papillomavirus (HPV16 E7) specific cytotoxic activity [23]. Dendritic cell activation was observed in breast cancer patients who were given the Chinese herbal medicine Shenqi Fuzheng [67]. Another study showed that Lingdankang composite and DC cytokine-induced killer cells were effective against leukemia patients [68]. NLGP overcomes the indoleamine 2,3 dioxygenase mediated tolerance in dendritic cells by attenuating hyperactive regulatory T-cells in cervical cancer (stage IIIB) patients [69]. Furthermore, DCs exposed to Amomi Semen extract exhibited activated phenotypes of DCs and also secreted IL-12p70 cytokines, which inhibited the growth of tumor cells [70]. A traditional herb named Juzen-taiho-to is used in East Asia for the treatment of cancer patients. The glycolipid mixture containing B-glucosylceramides stimulates primary DCs that express intercellular adhesion molecule-1 (ICAM 1), triggering an immune response [50]. Lipid-soluble extract of *Pinellia pedatisecta* Schott stimulates intratumoral dendritic cell activation through suppressor of cytokine signaling 1 (SOCS1) in cervical cancer patients [71]. NLGP-pulsed DCs overcome the hyperactivity of regulatory cells in stage III cervical cancer patients [69].

Table 6. Plant extracts on DCs-based clinical study against cancer.

Plant Name/Extracts	DCs-Based Clinical Study against Cancer	References
<i>Nicotiana benthamiana</i> NbPVX-E7 pulsed-MDDCs/PBMC	Increase cytotoxic activity against HPV16 E7	[23]
Chinese herbal medicine Shenqi Fuzheng	DCs activation in breast cancer patients	[67]
Lingdankang composite combined DCs and cytokines	Effective against leukemia patients	[68]
Neef leaf glycoprotein (NLGP)	Dendritic cells attenuating hyperactive regulatory T-cells in cervical cancer (stage IIIB) patients	[69]
DCs exposed to Amomi Semen extract	Activation of phenotypes of DCs and inhibits the growth of tumor cells	[70]
Glycolipid mixture containing B-glucosylceramides from herb	DCs expressed ICAM 1 in cancer patients	[50]
Lipid-soluble extract of <i>Pinellia pedatisecta</i> Schott	Stimulates intratumoral dendritic cell activation in cervical cancer patients	[71]

5. Methodology and Search Strategy

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [72,73]. Online databases such as PubMed, Google Scholar and Scopus were accessed to retrieve published literature using the MeSH terms “dendritic cells” AND “cancer immunotherapy” AND “plants” AND “phytochemicals” AND “immunopharmacology”. Literature published in the last two decades was retrieved. For screening purposes, automatic search tools were used to remove some of the articles, on the other hand, others were screened manually. The articles which were published in languages other than English were removed during screening time. Reviews, book chapters, and conference papers were also excluded from this review. A total of 61 studies, including 45 in vitro studies, nine preclinical in vivo studies, and seven clinical trials, were retrieved and discussed in this study (Figure 1). The information obtained from research articles was systemized in the table.

**Figure 1.** PRISMA 2020 flow diagram for the systematic review of dendritic cell (DC)-based cancer immunotherapy with medicinal plants and their phytochemicals.

6. Conclusions and Future Aspects

Dendritic cells are a potential target for the development of anti-cancer immunotherapy. In recent years, various approaches for the maturation of DCs and the initiation of anticancer immune responses have been introduced. Nonetheless, DC-based immunotherapy did not lead to satisfactory outcomes in clinical cases. Occasionally, DCs generated in in vitro studies have been found to be defective and unable to migrate to lymph nodes. In some cases, low cellular infiltration increased the number of immunosuppressive cells and low cytotoxic activities were seen in DC-based tumor immunotherapy. For immunotherapy, several molecules with maturing DCs have been used for cancer treatment. Plants and plant-derived purified pulsed dendritic cell products show promise in cancer treatment (Figure 2). It is expected that DC-based immunotherapy will produce some promising results in the next 5 to 10 years. Although plant extracts have many beneficial properties, there are many limiting effects on the mechanism of action and molecular targets that prevent their development as therapeutics. More extensive studies need to be investigated for the benefits of herbal or herbal products in DC-based cancer treatment with low cost and minimal side effects.

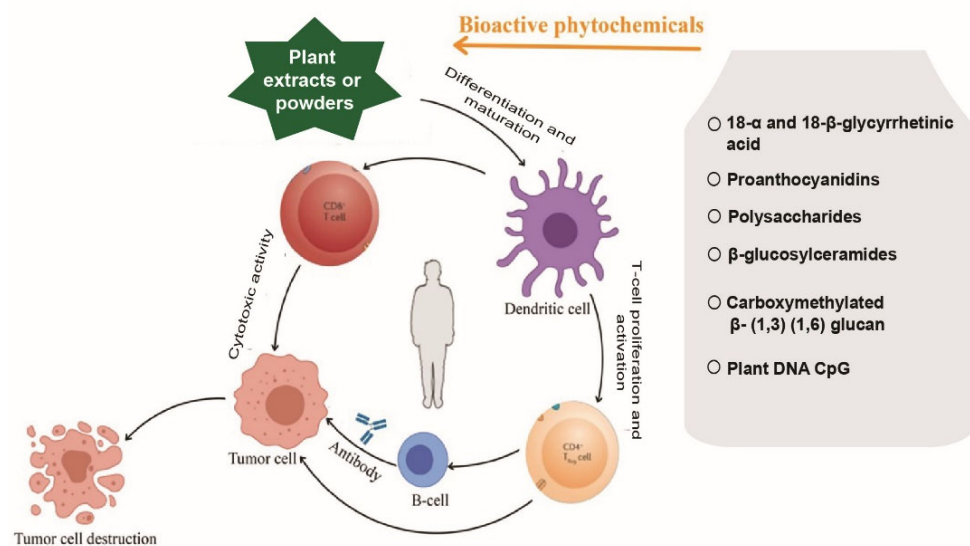


Figure 2. Schematic diagram of plants and their phytochemical-pulsed DC-based cancer immunotherapy. This illustration is modified from the previous literature [74–76]. Plant extracts or powders act on stem cells and differentiate into dendritic cells. It also acts on immature DCs and converts them to active, mature forms of DCs. Mature DCs bind with T-cells (CD4 and CD8) and initiate adaptive immune responses (humoral and cell-mediated immune responses) against tumor cells, which ultimately destroy tumor cells.

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Abbreviations

DCs: Dendritic cells; pDCs, plasmacytoid dendritic cells; MHC, major histocompatibility complex; CTL, cytotoxic T lymphocyte, NK, natural killer; TNF- α , tumor necrosis factor- α ; ROS, reactive oxygen species; RNS, reactive nitrogen species; IL, interleukin; TGF- β , Transforming growth factor- β ; Tregs, regulatory T cells; IFN- γ , interferon γ ; TCL, tumor cell lysate; PDPs, plant-derived polysaccharides; MDDCs, monocyte-derived dendritic cells; HPV16, human papilloma virus 16; PBMC, peripheral blood mononuclear cell; GM-CSF, granulocyte-macrophage colony stimulating factor; LPS, lipopolysaccharide; PLP, plant extract polysaccharide; NLGP, Neem leaf glycoprotein; LBP, *Lycium barbarum* polysaccharide; TLR4, Toll-like receptor 4; ERK, extracellular signal regulated kinase; JNK, c-Jun N-terminal kinase; MAPK, p38 mitogen-activated protein kinase; NF- κ Bp65, nuclear factor kappa-light-chain-enhancer of activated B cells p65; STAT, signal transducer and activator of transcription; PAMP, pathogen-associated molecular pattern; BMDC, bone marrow-derived dendritic cells; SOCS1, suppressor of cytokine signaling 1; ICAM 1, intracellular adhesion molecule 1; PGE2, prostaglandin E2.

References

1. Vulink, A.; Radford, K.J.; Melief, C.; Hart, D.N. Dendritic cells in cancer immunotherapy. *Adv. Cancer Res.* **2008**, *99*, 363–407. [[PubMed](#)]
2. Segura, E.; Amigorena, S. Inflammatory dendritic cells in mice and humans. *Trends Immunol.* **2013**, *34*, 440–445. [[CrossRef](#)] [[PubMed](#)]
3. Boltjes, A.; Van Wijk, F. Human dendritic cell functional specialization in steady-state and inflammation. *Front. Immunol.* **2014**, *5*, 131. [[CrossRef](#)] [[PubMed](#)]
4. Ebadi, P.; Karimi, M.H.; Amirghofran, Z. Plant components for immune modulation targeting dendritic cells: Implication for therapy. *Immunotherapy* **2014**, *6*, 1037–1053. [[CrossRef](#)]
5. Banchereau, J.; Steinman, R.M. Dendritic cells and the control of immunity. *Nature* **1998**, *392*, 245–252. [[CrossRef](#)]
6. Stockwin, L.H.; McGONAGLE, D.; Martin, I.G.; Blair, G.E. Dendritic cells: Immunological sentinels with a central role in health and disease. *Immunol. Cell Biol.* **2000**, *78*, 91–102. [[CrossRef](#)]
7. Martínez-Lostao, L.; Anel, A.; Pardo, J. How do cytotoxic lymphocytes kill cancer cells? *Clin. Cancer Res.* **2015**, *21*, 5047–5056. [[CrossRef](#)]
8. Ma, Y.; Shurin, G.V.; Peiyuan, Z.; Shurin, M.R. Dendritic cells in the cancer microenvironment. *J. Cancer* **2013**, *4*, 36. [[CrossRef](#)]
9. Balkwill, F. Tumour necrosis factor and cancer. *Nat. Rev. Cancer* **2009**, *9*, 361–371. [[CrossRef](#)]
10. Grivennikov, S.I.; Karin, M. Inflammatory cytokines in cancer: Tumour necrosis factor and interleukin 6 take the stage. *Ann. Rheum. Dis.* **2011**, *70* (Suppl. 1), i104–i108. [[CrossRef](#)]
11. Ahmed, M.S.; Bae, Y.-S. Dendritic cell-based therapeutic cancer vaccines: Past, present and future. *Clin. Exp. Vaccine Res.* **2014**, *3*, 113–116. [[CrossRef](#)] [[PubMed](#)]
12. Sprooten, J.; Ceusters, J.; Coosemans, A.; Agostinis, P.; De Vleeschouwer, S.; Zitvogel, L.; Kroemer, G.; Galluzzi, L.; Garg, A.D. Trial watch: Dendritic cell vaccination for cancer immunotherapy. *Oncoimmunology* **2019**, *8*, 1638212. [[CrossRef](#)] [[PubMed](#)]
13. Zhu, J.; Zhang, Y.; Shen, Y.; Zhou, H.; Yu, X. *Lycium barbarum* polysaccharides induce Toll-like receptor 2-and 4-mediated phenotypic and functional maturation of murine dendritic cells via activation of NF- κ B. *Mol. Med. Rep.* **2013**, *8*, 1216–1220. [[CrossRef](#)] [[PubMed](#)]
14. Mohamed, S.I.A.; Jantan, I.; Nafiah, M.A.; Seyed, M.A.; Chan, K.M. Dendritic cells pulsed with generated tumor cell lysate from *Phyllanthus amarus* Schum. & Thonn. induces anti-tumor immune response. *BMC Complementary Altern. Med.* **2018**, *18*, 232.
15. Sabado, R.L.; Bhardwaj, N. Directing dendritic cell immunotherapy towards successful cancer treatment. *Immunotherapy* **2010**, *2*, 37–56. [[CrossRef](#)] [[PubMed](#)]
16. Verdijk, P.; Aarntzen, E.H.; Punt, C.J.; de Vries, I.J.M.; Figdor, C.G. Maximizing dendritic cell migration in cancer immunotherapy. *Expert Opin. Biol. Ther.* **2008**, *8*, 865–874. [[CrossRef](#)]
17. Vacchelli, E.; Vitale, I.; Eggermont, A.; Fridman, W.H.; Fučíková, J.; Cremer, I.; Galon, J.; Tartour, E.; Zitvogel, L.; Kroemer, G. Trial watch: Dendritic cell-based interventions for cancer therapy. *Oncoimmunology* **2013**, *2*, e25771. [[CrossRef](#)]
18. Chang, W.T.; Lai, T.H.; Chyan, Y.J.; Yin, S.Y.; Chen, Y.H.; Wei, W.C.; Yang, N.-S. Specific medicinal plant polysaccharides effectively enhance the potency of a DC-based vaccine against mouse mammary tumor metastasis. *PLoS ONE* **2015**, *10*, e0122374. [[CrossRef](#)]

19. Chen, X.; Yang, L.; Howard, O.; Oppenheim, J.J. Dendritic cells as a pharmacological target of traditional Chinese medicine. *Cell Mol. Immunol.* **2006**, *3*, 401–410.
20. Li, J.; Li, J.; Zhang, F. The immunoregulatory effects of Chinese herbal medicine on the maturation and function of dendritic cells. *J. Ethnopharmacol.* **2015**, *171*, 184–195. [[CrossRef](#)]
21. Kikete, S.; Luo, L.; Jia, B.; Wang, L.; Ondieki, G.; Bian, Y. Plant-derived polysaccharides activate dendritic cell-based anti-cancer immunity. *Cytotechnology* **2018**, *70*, 1097–1110. [[CrossRef](#)] [[PubMed](#)]
22. Guo, Q.; Li, J.; Lin, H. Effect and molecular mechanisms of traditional Chinese medicine on regulating tumor immunosuppressive microenvironment. *BioMed Res. Int.* **2015**, *2015*, 261620. [[CrossRef](#)] [[PubMed](#)]
23. Di Bonito, P.; Grasso, F.; Mangino, G.; Massa, S.; Illiano, E.; Franconi, R.; Fanales-Belasio, E.; Falchi, M.; Affabris, E.; Giorgi, C. Immunomodulatory activity of a plant extract containing human papillomavirus 16-E7 protein in human monocyte-derived dendritic cells. *Int. J. Immunopathol. Pharmacol.* **2009**, *22*, 967–978. [[CrossRef](#)] [[PubMed](#)]
24. Andreicuț, A.D.; Fischer-Fodor, E.; Pârvu, A.E.; Țigu, A.B.; Cenariu, M.; Pârvu, M.; Cătoi, F.A.; Irimie, A. Antitumoral and immunomodulatory effect of *Mahonia aquifolium* extracts. *Oxidative Med. Cell. Longev.* **2019**, *2019*, 6439021. [[CrossRef](#)]
25. Kauroo, S.; Govinden-Soulangé, J.; Ranghoo-Sanmukhiya, V.M.; Miranda, K.; Cotham, W.E.; Walla, M.D.; Nagarkatti, M.; Nagarkatti, P. Extracts of select endemic plants from the Republic of Mauritius exhibiting anti-cancer and immunomodulatory properties. *Sci. Rep.* **2021**, *11*, 4272. [[CrossRef](#)]
26. Chang, W.-T.; Chen, H.-M.; Yin, S.-Y.; Chen, Y.-H.; Wen, C.-C.; Wei, W.-C.; Lai, P.; Wang, C.-H.; Yang, N.-S. Specific *Dioscorea* phytoextracts enhance potency of TCL-loaded DC-based cancer vaccines. *Evid.-Based Complementary Altern. Med.* **2013**, *2013*, 932040. [[CrossRef](#)]
27. Kim, H.S.; Shin, B.R.; Lee, H.K.; Kim, Y.J.; Park, M.J.; Kim, S.Y.; Lee, M.K.; Hong, J.T.; Kim, Y.; Han, S.-B. A polysaccharide isolated from *Pueraria lobata* enhances maturation of murine dendritic cells. *Int. J. Biol. Macromol.* **2013**, *52*, 184–191. [[CrossRef](#)]
28. Singh, N.; Singh, S.M.; Shrivastava, P. Effect of *Tinospora cordifolia* on the antitumor activity of tumor-associated macrophages-derived dendritic cells. *Immunopharmacol. Immunotoxicol.* **2005**, *27*, 1–14. [[CrossRef](#)]
29. Aldahlawi, A.M. Modulation of dendritic cell immune functions by plant components. *J. Microsc. Ultrastruct.* **2016**, *4*, 55–62. [[CrossRef](#)]
30. Fu, R.-H.; Wang, Y.-C.; Liu, S.-P.; Chu, C.-L.; Tsai, R.-T.; Ho, Y.-C.; Chang, W.-L.; Chiu, S.-C.; Harn, H.-J.; Shyu, W.-C. Acetylcorynoline impairs the maturation of mouse bone marrow-derived dendritic cells via suppression of I κ B kinase and mitogen-activated protein kinase activities. *PLoS ONE* **2013**, *8*, e58398. [[CrossRef](#)]
31. Nakahara, T.; Moroi, Y.; Uchi, H.; Furue, M. Differential role of MAPK signaling in human dendritic cell maturation and Th1/Th2 engagement. *J. Dermatol. Sci.* **2006**, *42*, 1–11. [[CrossRef](#)] [[PubMed](#)]
32. Li, X.; Xu, W.; Chen, J. Polysaccharide purified from *Polyporus umbellatus* (Per) Fr induces the activation and maturation of murine bone-derived dendritic cells via toll-like receptor 4. *Cell. Immunol.* **2010**, *265*, 50–56. [[CrossRef](#)] [[PubMed](#)]
33. Goswami, S.; Bose, A.; Sarkar, K.; Roy, S.; Chakraborty, T.; Sanyal, U.; Baral, R. Neem leaf glycoprotein matures myeloid derived dendritic cells and optimizes anti-tumor T cell functions. *Vaccine* **2010**, *28*, 1241–1252. [[CrossRef](#)] [[PubMed](#)]
34. Dong, J.; Gu, H.; Ma, C.; Zhang, F.; Chen, Z.; Zhang, Y. Effects of large dose of *Astragalus membranaceus* on the dendritic cell induction of peripheral mononuclear cell and antigen presenting ability of dendritic cells in children with acute leukemia. *Zhongguo Zhong Xi Yi Jie He Za Zhi Zhongguo Zhongxiyi Jiehe Zazhi = Chin. J. Integr. Tradit. West. Med.* **2005**, *25*, 872–875.
35. Shao, P.; Zhao, L.-H.; Pan, J.-P. Regulation on maturation and function of dendritic cells by *Astragalus mongholicus* polysaccharides. *Int. Immunopharmacol.* **2006**, *6*, 1161–1166. [[CrossRef](#)]
36. Ahmadabad, H.N.; Hassan, Z.M.; Safari, E.; Bozorgmehr, M.; Ghazanfari, T.; Moazzeni, S.M. Evaluation of the immunomodulatory effect of the 14 kDa protein isolated from aged garlic extract on dendritic cells. *Cell. Immunol.* **2011**, *269*, 90–95. [[CrossRef](#)] [[PubMed](#)]
37. Huang, D.-F.; Xie, M.-Y.; Yin, J.-Y.; Nie, S.-P.; Tang, Y.-F.; Xie, X.-M.; Zhou, C. Immunomodulatory activity of the seeds of *Plantago asiatica* L. *J. Ethnopharmacol.* **2009**, *124*, 493–498. [[CrossRef](#)]
38. Amirghofran, Z.; Ahmadi, H.; Karimi, M.H. Immunomodulatory activity of the water extract of *Thymus vulgaris*, *Thymus daenensis*, and *Zataria multiflora* on dendritic cells and T cells responses. *J. Immunoass. Immunochem.* **2012**, *33*, 388–402. [[CrossRef](#)]
39. Bordbar, N.; Karimi, M.H.; Amirghofran, Z. Phenotypic and functional maturation of murine dendritic cells induced by 18 alpha-and beta-glycyrrhetic acid. *Immunopharmacol. Immunotoxicol.* **2014**, *36*, 52–60. [[CrossRef](#)]
40. Zou, Y.; Meng, J.; Chen, W.; Liu, J.; Li, X.; Li, W.; Lu, C.; Shan, F. Modulation of phenotypic and functional maturation of murine dendritic cells (DCs) by purified *Achyranthes bidentata* polysaccharide (ABP). *Int. Immunopharmacol.* **2011**, *11*, 1103–1108. [[CrossRef](#)]
41. Dennerstein, L.; Lehert, P.; Guthrie, J. The effects of the menopausal transition and biopsychosocial factors on well-being. *Arch. Womens Ment. Health* **2002**, *5*, 15–22. [[CrossRef](#)] [[PubMed](#)]
42. Shainheit, M.G.; Smith, P.M.; Bazzone, L.E.; Wang, A.C.; Rutitzky, L.I.; Stadecker, M.J. Dendritic cell IL-23 and IL-1 production in response to schistosome eggs induces Th17 cells in a mouse strain prone to severe immunopathology. *J. Immunol.* **2008**, *181*, 8559–8567. [[CrossRef](#)] [[PubMed](#)]
43. Kim, J.Y.; Yoon, Y.D.; Ahn, J.M.; Kang, J.S.; Park, S.-K.; Lee, K.; Song, K.B.; Kim, H.M.; Han, S.-B. Angelan isolated from *Angelica gigas* Nakai induces dendritic cell maturation through toll-like receptor 4. *Int. Immunopharmacol.* **2007**, *7*, 78–87. [[CrossRef](#)] [[PubMed](#)]

44. Kim, J.Y.; Kim, Y.J.; Kim, J.S.; Ryu, H.S.; Lee, H.K.; Kang, J.S.; Kim, H.M.; Hong, J.T.; Kim, Y.; Han, S.-B. Adjuvant effect of a natural TLR4 ligand on dendritic cell-based cancer immunotherapy. *Cancer Lett.* **2011**, *313*, 226–234. [[CrossRef](#)] [[PubMed](#)]
45. Hamuti, A.; Li, J.; Zhou, F.; Aipire, A.; Ma, J.; Yang, J.; Li, J. *Capparis spinosa* fruit ethanol extracts exert different effects on the maturation of dendritic cells. *Molecules* **2017**, *22*, 97. [[CrossRef](#)]
46. Chang, J.-M.; Hung, L.-M.; Chyan, Y.-J.; Cheng, C.-M.; Wu, R.-Y. *Carthamus tinctorius* enhances the antitumor activity of dendritic cell vaccines via polarization toward Th1 cytokines and increase of cytotoxic T lymphocytes. *Evid.-Based Complementary Altern. Med.* **2011**, *2011*, 274858. [[CrossRef](#)]
47. Aipire, A.; Li, J.; Yuan, P.; He, J.; Hu, Y.; Liu, L.; Feng, X.; Li, Y.; Zhang, F.; Yang, J. *Glycyrrhiza uralensis* water extract enhances dendritic cell maturation and antitumor efficacy of HPV dendritic cell-based vaccine. *Sci. Rep.* **2017**, *7*, 43796. [[CrossRef](#)]
48. Umeyama, A.; Yahisa, Y.; Okada, M.; Okayama, E.; Uda, A.; Shoji, N.; Lee, J.-J.; Takei, M.; Hashimoto, T. Triterpene esters from *Uncaria rhynchophylla* drive potent IL-12-dependent Th1 polarization. *J. Nat. Med.* **2010**, *64*, 506–509. [[CrossRef](#)]
49. Sheu, S.-C.; Lai, M.-H. Composition analysis and immuno-modulatory effect of okra (*Abelmoschus esculentus* L.) extract. *Food Chem.* **2012**, *134*, 1906–1911. [[CrossRef](#)]
50. Takaoka, A.; Iacovidou, M.; Hasson, T.H.; Montenegro, D.; Li, X.; Tsuji, M.; Kawamura, A. Biomarker-guided screening of Juzen-taiho-to, an oriental herbal formulation for immunostimulation. *Planta Med.* **2014**, *80*, 283–289. [[CrossRef](#)]
51. Santander, S.; Aoki, M.; Hernandez, J.; Pombo, M.; Moins-Teisserenc, H.; Mooney, N.; Fiorentino, S. Galactomannan from *Caesalpinia spinosa* induces phenotypic and functional maturation of human dendritic cells. *Int. Immunopharmacol.* **2011**, *11*, 652–660. [[CrossRef](#)]
52. Tian, J.; Zhang, Y.; Yang, X.; Rui, K.; Tang, X.; Ma, J.; Chen, J.; Xu, H.; Lu, L.; Wang, S. *Ficus carica* polysaccharides promote the maturation and function of dendritic cells. *Int. J. Mol. Sci.* **2014**, *15*, 12469–12479. [[CrossRef](#)]
53. Shin, B.R.; Kim, H.S.; Yun, M.J.; Lee, H.K.; Kim, Y.J.; Kim, S.Y.; Lee, M.K.; Hong, J.T.; Kim, Y.; Han, S.-B. Promoting effect of polysaccharide isolated from *Mori fructus* on dendritic cell maturation. *Food Chem. Toxicol.* **2013**, *51*, 411–418. [[CrossRef](#)] [[PubMed](#)]
54. Huang, D.; Nie, S.; Jiang, L.; Xie, M. A novel polysaccharide from the seeds of *Plantago asiatica* L. induces dendritic cells maturation through toll-like receptor 4. *Int. Immunopharmacol.* **2014**, *18*, 236–243. [[CrossRef](#)] [[PubMed](#)]
55. Li, J.; Wang, X.; Wang, W.; Luo, J.; Aipire, A.; Li, J.; Zhang, F. *Pleurotus ferulae* water extract enhances the maturation and function of murine bone marrow-derived dendritic cells through TLR4 signaling pathway. *Vaccine* **2015**, *33*, 1923–1933. [[CrossRef](#)] [[PubMed](#)]
56. Park, M.J.; Ryu, H.S.; Kim, J.S.; Lee, H.K.; Kang, J.S.; Yun, J.; Kim, S.Y.; Lee, M.K.; Hong, J.T.; Kim, Y. *Platycodon grandiflorum* polysaccharide induces dendritic cell maturation via TLR4 signaling. *Food Chem. Toxicol.* **2014**, *72*, 212–220. [[CrossRef](#)] [[PubMed](#)]
57. Zhu, J.; Yamane, H.; Paul, W.E. Differentiation of effector CD4 T cell populations. *Annu. Rev. Immunol.* **2009**, *28*, 445–489. [[CrossRef](#)]
58. Li, X.; He, X.; Liu, B.; Xu, L.; Lu, C.; Zhao, H.; Niu, X.; Chen, S.; Lu, A. Maturation of murine bone marrow-derived dendritic cells induced by *Radix Glycyrrhizae* polysaccharide. *Molecules* **2012**, *17*, 6557–6568. [[CrossRef](#)]
59. Jing, X.-N.; Qiu, B.; Wang, J.-F.; Wu, Y.-G.; Wu, J.-B.; Chen, D.-D. In vitro anti-tumor effect of human dendritic cells vaccine induced by astragalus polysaccharin: An experimental study. *Zhongguo Zhong Xi Yi Jie He Za Zhi Zhongguo Zhongxiyi Jiehe Zazhi = Chin. J. Integr. Tradit. West. Med.* **2014**, *34*, 1103–1107.
60. He, Y.-L.; Ying, Y.; Xu, Y.-L.; Su, J.-F.; Luo, H.; Wang, H.-F. Effects of *Lycium barbarum* polysaccharide on tumor microenvironment T-lymphocyte subsets and dendritic cells in H22-bearing mice. *Zhong Xi Yi Jie He Xue Bao = J. Chin. Integr. Med.* **2005**, *3*, 374–377. [[CrossRef](#)]
61. Koizumi, S.-i.; Masuko, K.; Wakita, D.; Tanaka, S.; Mitamura, R.; Kato, Y.; Tabata, H.; Nakahara, M.; Kitamura, H.; Nishimura, T. Extracts of *Larix leptolepis* effectively augments the generation of tumor antigen-specific cytotoxic T lymphocytes via activation of dendritic cells in TLR-2 and TLR-4-dependent manner. *Cell. Immunol.* **2012**, *276*, 153–161. [[CrossRef](#)] [[PubMed](#)]
62. Vaid, M.; Singh, T.; Prasad, R.; Elmetts, C.A.; Xu, H.; Katiyar, S.K. Bioactive grape proanthocyanidins enhance immune reactivity in UV-irradiated skin through functional activation of dendritic cells in mice. *Cancer Prev. Res.* **2013**, *6*, 242–252. [[CrossRef](#)] [[PubMed](#)]
63. Wang, Y.; Wang, W.; Li, N.; Yu, Y.; Cao, X. Activation of antigen-presenting cells by immunostimulatory plant DNA: A natural resource for potential adjuvant. *Vaccine* **2002**, *20*, 2764–2771. [[CrossRef](#)]
64. Ghochikyan, A.; Pichugin, A.; Bagaev, A.; Davtyan, A.; Hovakimyan, A.; Tikhvatulin, A.; Davtyan, H.; Shcheblyakov, D.; Logunov, D.; Chulkina, M. Targeting TLR-4 with a novel pharmaceutical grade plant derived agonist, *Immunomax*[®], as a therapeutic strategy for metastatic breast cancer. *J. Transl. Med.* **2014**, *12*, 322. [[CrossRef](#)] [[PubMed](#)]
65. Xu, Z.; Chen, X.; Zhong, Z.; Chen, L.; Wang, Y. *Ganoderma lucidum* polysaccharides: Immunomodulation and potential anti-tumor activities. *Am. J. Chin. Med.* **2011**, *39*, 15–27. [[CrossRef](#)] [[PubMed](#)]
66. Okamoto, M.; Oh-e, G.; Oshikawa, T.; Furuichi, S.; Tano, T.; Ahmed, S.U.; Akashi, S.; Miyake, K.; Takeuchi, O.; Akira, S. Toll-like receptor 4 mediates the antitumor host response induced by a 55-kilodalton protein isolated from *Aeginetia indica* L., a parasitic plant. *Clin. Vaccine Immunol.* **2004**, *11*, 483–495. [[CrossRef](#)] [[PubMed](#)]
67. Li, H.-S.; Yang, B.; Su, X.-C. Effect of shenqi fuzheng injection on repairing the immune function in patients with breast cancer. *Zhongguo Zhong Xi Yi Jie He Za Zhi Zhongguo Zhongxiyi Jiehe Zazhi = Chin. J. Integr. Tradit. West. Med.* **2009**, *29*, 537–539.
68. Liu, Q.-C.; Wu, W.-H.; Li, G.-R. Effect of lingdankang composite combined dendritic cell-cytokine induced killer cells in treating leukemia. *Zhongguo Zhong Xi Yi Jie He Za Zhi Zhongguo Zhongxiyi Jiehe Zazhi = Chin. J. Integr. Tradit. West. Med.* **2009**, *29*, 347–350.

69. Roy, S.; Barik, S.; Banerjee, S.; Bhuniya, A.; Pal, S.; Basu, P.; Biswas, J.; Goswami, S.; Chakraborty, T.; Bose, A. Neem leaf glycoprotein overcomes indoleamine 2, 3 dioxygenase mediated tolerance in dendritic cells by attenuating hyperactive regulatory T cells in cervical cancer stage IIIB patients. *Hum. Immunol.* **2013**, *74*, 1015–1023. [[CrossRef](#)]
70. Fukui, H.; Mitsui, S.; Harima, N.; Nose, M.; Tsujimura, K.; Mizukami, H.; Morita, A. Novel functions of herbal medicines in dendritic cells: Role of Amomi Semen in tumor immunity. *Microbiol. Immunol.* **2007**, *51*, 1121–1133. [[CrossRef](#)]
71. Wang, Y.; Lu, C.; Huang, H.; Yao, S.; Xu, C.; Ye, Y.; Gui, S.; Li, G. A lipid-soluble extract of *Pinellia pedatisecta* Schott orchestrates intratumoral dendritic cell-driven immune activation through SOCS1 signaling in cervical cancer. *J. Ethnopharmacol.* **2021**, *267*, 112837. [[CrossRef](#)] [[PubMed](#)]
72. Mohibbullah, M.; Haque, M.N.; Sohag, A.A.M.; Hossain, M.T.; Zahan, M.S.; Uddin, M.J.; Hannan, M.A.; Moon, I.S.; Choi, J.-S. A Systematic Review on Marine Algae-Derived Fucoxanthin: An Update of Pharmacological Insights. *Mar. Drugs* **2022**, *20*, 279. [[CrossRef](#)] [[PubMed](#)]
73. Akter, T.; Rahman, M.A.; Moni, A.; Apu, M.A.I.; Fariha, A.; Hannan, M.A.; Uddin, M.J. Prospects for Protective Potential of *Moringa oleifera* against Kidney Diseases. *Plants* **2021**, *10*, 2818. [[CrossRef](#)] [[PubMed](#)]
74. Laidlaw, B.J.; Craft, J.E.; Kaech, S.M. The multifaceted role of CD4+ T cells in CD8+ T cell memory. *Nat. Rev. Immunol.* **2016**, *16*, 102–111. [[CrossRef](#)]
75. Basu, A.; Ramamoorthi, G.; Albert, G.; Gallen, C.; Beyer, A.; Snyder, C.; Koski, G.; Disis, M.L.; Czerniecki, B.J.; Kodumudi, K. Differentiation and regulation of TH cells: A balancing act for cancer immunotherapy. *Front. Immunol.* **2021**, *12*, 669474. [[CrossRef](#)]
76. Fang, X.; Guo, Z.; Liang, J.; Wen, J.; Liu, Y.; Guan, X.; Li, H. Neoantigens and their potential applications in tumor immunotherapy. *Oncol. Lett.* **2022**, *23*, 88. [[CrossRef](#)]