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Review

Cytokines, the Tumor Microenvironment, and Selected Plant-Derived Natural Products

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Abstract

Cytokines are produced by immune and other cells and work as cellular messengers to regulate an immune response and other biological processes. As the main components of the tumor microenvironment (TME), cytokines are involved in the major events of cancer development, including cancer and cancer stem cell proliferation, angiogenesis, invasion, and metastasis. They also modulate immune functions and inhibit tumor progression and resistance to conventional therapies and thus have been regarded as promising targets for cancer treatment. Recently, tumor reversibility has attracted wide interest, for which the TME plays a critical role. Many plant-derived products exhibit potential tumor-inhibitory and cytokine-modulatory activities, including andrographolide, artemisinin, berberine, camptothecin, capsaicin, curcumin, digoxin, morphine, paclitaxel, and vinblastine, indicating their possible use in cancer reversal. Thus, in the present review, correlations among cytokines, the TME, tumor immunity, and tumor reversibility have been discussed, and the potential effects of selected plant-derived natural products on these issues have been addressed.

Keywords: cellular messengers; cytokines; natural products; tumor microenvironment; cancer reversal

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1. Introduction

Cytokines are immunomodulating proteins, which include interferons (IFNs), interleukins (ILs), the tumor necrosis factor (TNF) superfamily, chemokines, and growth factors, and they affect almost all biological processes [1]. As cell–cell communication factors, cytokines are released by one cell and bind to the cytokine receptors on the surface of other cells to regulate their activities thus functioning as chemical messengers to elicit immune responses against various pathogens [2].

Cytokines are involved in regulating protumor and antitumor activities to control the major processes in the development of cancer, including immune activation and suppression, inflammation, cellular damage, angiogenesis, cancer stem cells, and cancer cell invasion and metastasis [3]. They also work as signaling proteins in the tumor microenvironment (TME) to promote tumor progression, angiogenesis, and immunosuppression (i.e., the innate inflammatory cytokines, including IL-1β, TNF-α, and IL-6) or to stimulate tumor immunity (immunity against tumor) (i.e., IFN-γ and IL-12) [4]. Thus, cytokines show antitumor potential by inhibiting cancer cell proliferation, inducing cancer cell apoptosis, and/or enhancing the antitumor immune response [5]. They have also been used as immunoregulating agents, e.g., IL-33, which supports tumor immunity by influencing host responses while it is also supportive of tumor development [6].

Cancer is characterized by abnormal, aggressive, and unrestrained cell growth and proliferation, in which cytokines work as messengers to allow cells to communicate with each other in the TME and thus play a crucial role. Some cytokines promote cancer cell proliferation and metastasis and induce malignancy, such as the innate inflammatory cytokines, IL-1β, IL-6, and NF-α, while certain other cytokines stimulate tumor immunity to suppress tumor growth, like IFN-γ and IL-12 [4]. In the TME, cytokines are signaling proteins and thus play a key role in tumor immunity [4,5].

Medicinal plants have long been used for the treatment of various human diseases, and their secondary metabolite constituents have played an important role in the discovery of new anticancer agents. These products have shown modulatory effects on the production and expression levels of various cytokines, including ILs, IFNs, and TNFs, including certain phenolic compounds, such as curcumin, emodin, eugenol, 6-gingerol, genistein and quercetin, in addition to the sulfur-containing compound allicin and the quinone drug thymoquinone, as well as the sesquiterpene lactone, parthenolide [7,8]. Of these, several compounds have potential use as adjuvants to ameliorate the cytokine storm for the treatment of the COVID-19 virus, due to their inhibitory effects on cytokines [9–11]. Moreover, natural products show regulatory effects on immune cells and cytokines through various mechanisms and thus potentially could benefit tumor immunity through remodeling the TME [12]. These agents act on both immune cells and malignant transformed cells and then change the dying malignant cells to activate an immune response, indicating that they could help counteract the known side effects of conventional treatments to support cancer immunotherapy [12,13].

2. Cytokines and Cancer

2.1. Major Cytokines and Cytokine Signaling Pathways in Cancer

There is a complex interplay between cytokines and their signaling pathways in cancer biology. Cytokines are synthesized from the cluster of differentiation 4+ ($CD4^+$) type 1 or type 2 helper T (Th) cells ($CD4^+$Th1s or $CD4^+$Th2s) and their activity is context dependent. Cytokines function as hormones of the immune system to enhance tumor immunity [e.g., IFN-α, IFN-γ, IL-2, IL-12, IL-15, granulocyte-macrophage (GM) colony-stimulating factor (CSF), and transforming growth factor-β (TGF-β, at early cancer stages)] or to promote tumor progression, angiogenesis, and metastasis [e.g., IL-1β, IL-6, TGF-β (at later cancer stages), and TNF-α] [1,2] (Figure 1).

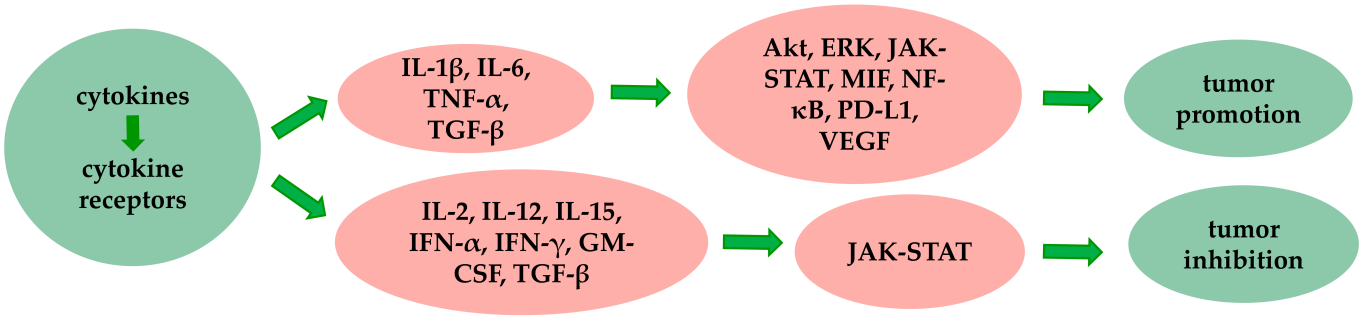

Figure 1. Major correlations among cytokines, cytokine signaling pathways, and tumor development.

Of these, IL-1 induces the gene expression and synthesis of cyclooxygenase-2 (COX-2), activates B cells, and acts as a co-factor for T cell proliferation in the presence of antigens or mitogens. A member of the IL-1 family, IL-33 functions as a context-dependent immune response regulator upon the local microenvironment to show effects on tumor immunity to suppress tumor growth or on a repair-like program to support tumor development. IL-2 activates B cells and augments T cell proliferation, while IL-12 induces IFN-γ production [1,2,4–6].

Many cytokines utilize heterodimeric receptors by binding to their cytokine ligand via Janus kinase (JAK)-signal transducers and activators of transcription (STAT) pathways. Of these, IL-6 and TNF-α have been characterized as pro-tumorigenic cytokines to affect all stages of tumor development, owing to their ability to activate the oncogenic transcription factors, nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), activator protein-1 (AP-1), and STAT3. Thus, they have been regarded as targets for the adjuvant treatment of cancer [14]. IL-6 binds to its receptor, IL-6R, and its signaling partner glycoprotein 130 (gp130), a ubiquitously expressed protein, to initiate the phosphorylation of STAT3 signaling, which subsequently activates two downstream pathways, the JAK-STAT3 pathway and the JAK-Src homology 2 (SH2) domain tyrosine phosphatase 2 (SHP2)-mitogen-activated protein (MAP) kinase pathway. JAK is bound constitutively to the cytoplasmic domain of gp130 and activates the phosphorylation of STAT3 when IL-6 binds to IL-6R [15]. In addition, IL-6 associates with IL-6R *trans*-presented by dendritic cells (DCs) to send a signal to gp130-expressing cells. Gp130 signals via STAT3, of which the downstream signaling pathway shows effects on promoting cancer cell growth and the survival of immune-suppressive myeloid cells [4].

The IL-6 family includes the canonical members IL-6, IL-11, IL-27 and the structurally related members IL-12, IL-23, and IL-31, which utilize shared receptors composed of gp130 to interact with the JAK-STAT pathway [16]. IL-12 communicates with T cells and NK cells to induce IFN-γ production that supports tumor immunity, while IL-27 can directly block the Th17 cell differentiation induced by IL-6 and IL-23 and induce IL-10 production. The majority of tumor-associated IL-10 produced by activated T regulatory cells (Tregs) decreases the activity of most immune cells but activates mast cells and B cells, which is required to restrain Th17-type inflammation in the TME. However, in some contexts, IL-10 promotes cytotoxic T cell activity and IFN-γ production to show anticancer potential [4,17]. In addition, programmed cell death protein 1 (PD-1) acts on its ligand (PD-L1) to suppress the activation of cytotoxic T cells, while IL-17 and TNF-α are co-expressed by Th17 cells in many tumors. These cytokines were found to induce PD-L1 expression in HCT116 human colon cancer cells through activation of the Akt, NF-κB, and extracellular signal-regulated kinases 1/2 (ERK1/2) signaling pathways [18]. As an important tumor promoter, the production of TNF-α by ovarian cancer cells was found to stimulate the secretion of cytokines, IL-6 and macrophage migration-inhibitory factor (MIF), angiogenic factor, vascular endothelial growth factor (VEGF), and the chemokines, chemokine (C-C motif) ligand 2 (CCL2) or monocyte chemoattractant protein-1 (MCP-1) and C-X-C motif chemokine ligand 12 (CXCL12) or stromal cell-derived factor-1 (SDF-1). These could act as an autocrine tumor-promoting network in the ovarian cancer microenvironment to support tumor growth and spread [19].

Macrophages are antigen-presenting cells for adaptive immunity to provide a defense mechanism against harmful microorganisms and cancer cells. They can be activated by lipopolysaccharide (LPS) or cytokines IFN-γ and GM-CSF to selectively lyse tumor cells. However, macrophages in the TME, the tumor-associated macrophages (TAMs), can also secrete substances to exhibit protumoral functions associated with tumor progression and metastasis and thus regulate tumor growth both positively and negatively. Of these, M1 and M2 macrophages that reveal specific gene expression patterns (pro-inflammatory M1 and anti-inflammatory M2) coexist. The M_1 macrophages participate in the immune response against tumor cells through IFN-γ and LPS, while the M2 macrophages promote cancer progression by targeting IL-4, IL-10, and IL-13 [20,21]. A macrophage-specific activation marker, cluster of differentiation 163 (CD163) encoded by the *CD163* gene is the hemoglobin (Hb) scavenger receptor for the uptake of Hb into the plasma and functions as a potential inflammation biomarker and therapeutic target [22]. As an important biomarker for the

modulation of immune responses in the TME, CD163 associates classically with the M2 phenotype of macrophages. Tumor-derived cytokines, including IL-6, IL-10, and GM-CSF, promote the differentiation of monocytes into $CD163^+$ macrophages, which contribute to immune suppression and tumor progression to enhance tumor growth, stemness, and therapy resistance and thus serve as a target for cancer therapy [23].

2.2. Cytokines, Infection, and Cancer

Cytokines act as molecular messengers to regulate the immune response and cellular proliferation and to control inflammation, which include pro-inflammatory (e.g., IL-1, IL-6, and TNF-α) and anti-inflammatory (e.g., IL-4, IL-10, IL-11, IL-13, and TGF-β) cytokines and affect a non-specific response to infection and a specific response to antigen [1]. While inflammation is involved in immune cell activation and is essential for host defense against pathogens, in which cytokines show effects on the interactions between inflammatory cells [3]. Also, cytokines are important in the immune response to infections, and they may be required for tumor-regulatory inflammatory responses. Tumors have been described as unhealed wounds, with a persistent damage–repair cycle. Within this cycle, IL-33 is released into the extracellular space upon tissue damage to initiate early inflammatory responses [6]. Thus, it has been demonstrated that many cancers are associated with chronic inflammation, while solid tumors have inflammatory infiltrates. Additionally, immune cells mediate their effects on cancer development through proinflammatory cytokines, of which TNF and IL-6 regulate tumor-associated inflammation and tumorigenesis [14,19] (Figure 2).

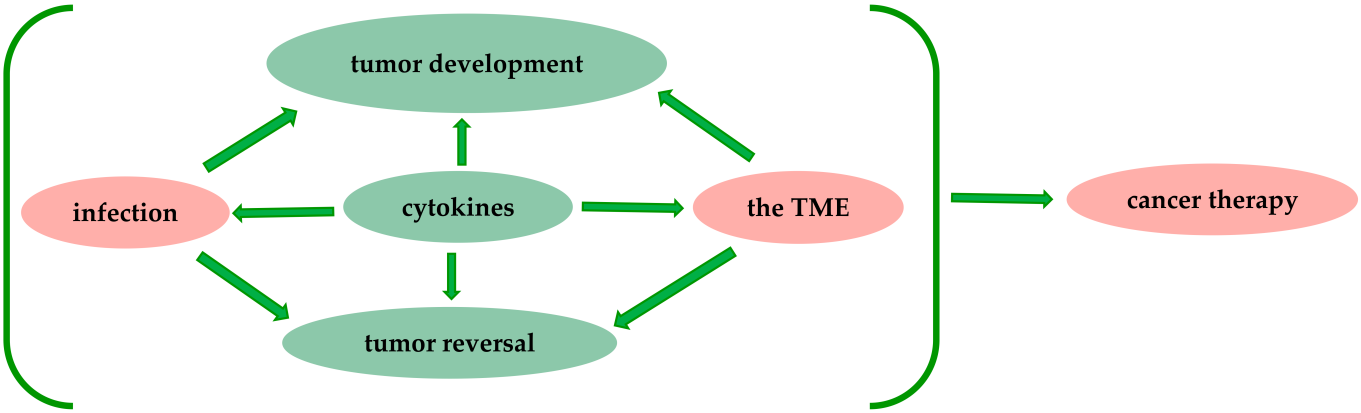

Figure 2. Major correlations among cytokines, the TME, infection, tumor development and reversal, and cancer therapy.

2.3. Cytokines and the Tumor Microenvironment

The TME is the surrounding environment of tumors, which includes discrete and interacting elements, such as extracellular matrix, stromal cells, molecular diffusible factors, and topologic geometry of the emerging tissue. The TME is composed of cancerous and non-cancerous cells and their produced and released molecules, where the constant interactions control tumor development. In addition, the TME regulates the transcription of genes associated with differentiating pathways and participates in shaping cell phenotypes that could trigger programmed cell death signals to induce cell apoptosis. The immune activation response induces cancer cells to secrete cytokines, of which the dynamic variation determines the differentiation of immune cells. As a result, the TME represents a morphogenetic support to drive epithelial cell differentiation and phenotype transformation to contribute to cancer development and thus has become a promising target for cancer therapy [24–26].

Extracellular vesicles (EVs) are the membrane-bound particles released by various types of cells, which contain a variety of biomolecules, such as lipids, proteins and nucleic acids. They can be transmitted between cancer and stromal cells to remodel the TME, and those derived from tumors stimulate the immune response to support tumor immunity, while cytokines exploit EVs to mediate their functions [27,28]. As chemical messengers, cytokines are powerful regulators of the TME and are crucial for the control of cancer, while Tregs and related cytokines are involved in tumor immune escape (TIE) [2,3]. These are involved in tumor initiation, promotion, invasion, and metastasis through directing cancer cells and remodeling the TME and hence have been regarded as promising cancer targets. Thus far, cytokine immunotherapy has shown promise in effective cancer treatment, which could well be improved by various feasible strategies, including the use of recombinant cytokines and cytokine engineering [5,29–31].

2.4. The Tumor Microenvironment and Cancer Reversal

Cancer is a complex biophysical and biochemical process, in which the cell–stroma interaction plays a pivotal role for both neoplastic transformation and metastasis. Traditionally, cancer has been regarded as an irreversible disease resulting from accumulated gene mutations and chromosomal abnormalities. However, deregulation of the interaction between cancer cells and the TME has been recently claimed. Differential from traditional cancer therapy, cancer reversal means normalization of cancer cells and the reversal of tumors to normal tissues, which may represent a new avenue for the treatment of cancer. It has been well evidenced that tumors can be induced to normal tissues under a correct signal conveyed by the TME, which regulates the transcription of genes and cell phenotypes and thus determines neoplastic transformation and invasion. This indicates that the TME could play a critical role in the reversion of malignancy [24]. In addition, the TME contributes actively to carcinogenesis through its effects on intracellular processes and tissue organization, and its change can lead frequently to the tissue fibrosis that is associated with cancer development. Thus, modification of the TME may induce cancer reprogramming in 3D in vitro or animal models [25]. Furthermore, as demonstrated recently, cancer-associated fibroblast (CAF)-derived cytokines can support the protumor TME and tumor growth, and thus both the TME and CAFs have become promising targets for the development of anticancer agents [26]. These indicate that normalization of the TME through regulation of its main component, the cytokines, could form the basis of a reasonable strategy for cancer treatment.

2.5. Cytokines and Tumor Immunity

Cytokines function as small messengers to activate or to suppress immune responses against pathogens, and thus they have shown pro- or antitumor activity, upon environmental conditions [1–3] (Figure 3). They mediate immune cell activities to modulate the immune response and hence reflect the immunologic phenomena, while those produced by cancer cells may act as tumor growth factors to support tumor evasion from immune surveillance [32]. In the TME, cytokines can promote immunosuppression to support tumor progression or stimulate tumor immunity to inhibit tumor growth, and so they have become a cancer therapeutic target [4]. Thus, cytokines show antitumor potential and have been used in cancer immunotherapy [5]. For example, IL-33 can improve features associated with the response of the checkpoint blockade, depending on the immune-inflamed TME, and it also shapes the tissue context to permit or restrict its effectiveness [6]. However, their potential is challenged by their complex activity, and therefore further efforts will be required for the potential use of cytokines in cancer immunotherapy [33].

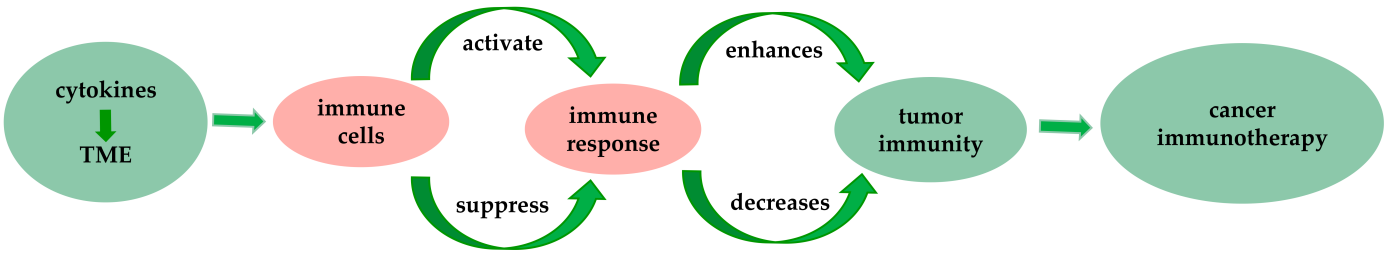

Figure 3. Major correlations among cytokines, tumor immunity, and cancer immunotherapy.

T lymphocytes are major effector cells in cellular immunity and produce cytokines to regulate other types of immune cells. Of these, $CD4^+$ T cells regulate immune and non-immune cells via the production of cytokines and are called helper T (Th) cells. Th cells regulate adaptive immunity to control extracellular pathogens [34]. In addition, the clinical success of cytokine therapy has been enhanced by several engineering strategies, including engineered albumin fusion, polymer conjugation, and peptide mimetics, which improve the pharmacodynamic and pharmacokinetic profiles of cytokines [35]. Moreover, cytokines allow immune cells to communicate with each other to respond to a target antigen, and they also directly stimulate immune effector cells and stromal cells in the TME to recognize and kill cancer cells. Thus, these messengers play a dual role in vaccination and adoptive cell strategies for cancer, and several cytokines have been evaluated for their potential in cancer immunotherapy. While IFN-α and IL-12 have been approved by FDA for the treatment of melanoma and renal cell carcinoma, and a further understanding of the cytokine signaling pathways would be supportive [36].

Thus far, cancer immunotherapy has been used successfully for the treatment of various types of cancer, with chimeric antigen receptor (CAR)-T and CAR-natural killer (NK) cell therapies having attracted wide interest. For example, several CAR-T cell products have been approved by the USA Food and Drug Administration (FDA) for the treatment of hematological malignancies. However, these immunotherapies have been challenged by their lower effectiveness for the treatment of certain solid tumors, due to the immunosuppressive TME, limited persistence, and metabolic constraints. Fortunately, this problem seems able to be potentially overcome by cytokine-enhanced CAR therapies, including the use of IL-2 superkines to enhance selective CAR-T expansion, IL-15-armed CAR constructs to sustain persistence, and IL-12 and IL-18 co-expression systems to remodel the TME. These engineered cytokines have improved the efficacy and safety of CAR cancer therapies [37], while several cytokines have been used in cancer gene therapy for the correction of cancer-related mutations. For example, gene-encoding IFN-α, an FDA-approved drug, has been inserted into viral vectors for the development of cancer gene therapies, indicating that the cytokine-based gene therapies may provide a valuable option for cancer immunotherapy [38]. However, this has been restricted by the toxic effects, short half-lives, and rapid renal clearance rates observed in the clinical use of cytokines. Thus, the use of antibody-fused cytokines (immunocytokines) could be promising, and several antibody formats have been engineered and fused to cytokines, including anti-PD-1-based immunocytokines that selectively deliver cytokines to intratumoral $CD8^+$ T cells to show potent antitumor activity [39]. Interestingly, IL-7 shows multiple beneficial immune effects and has been demonstrated for its potential use as an adjuvant for cancer immunotherapy [40].

3. Effects of Selected Plant-Derived Products on the Production and Release of Cytokines

3.1. Overview of Plant-Derived Products and Cytokines

Many medicinal plants and some of their secondary metabolites have shown modulatory effects on the expression levels of various cytokines [7,8], which support their possible use as adjuvants to ameliorate the cytokine storm and related conditions [9–11]. As a fundamental immune response to injury or infection, inflammation involves the activation of immune cells and the release of cytokines, with chronic inflammation contributing to the development of cancer. Many natural products exhibit anti-inflammatory activity through the regulation of cytokine production and release and thus may afford therapeutic interventions for inflammation-mediated cancer [41,42]. They regulate cytokines, which are the signaling proteins in the TME, indicating their effects on the TME and their possible modulatory activity on cancer immunotherapy [4,5,43].

In addition, certain natural products regulate cytokine production in the TME through various mechanisms and hence enhance the efficiency of cancer immunotherapy by remodeling the TME [12,13,44–46]. Thus, these agents could potentially be used in combination strategies to synergize with other immunotherapeutic agents to overcome immunosuppression and therapeutic resistance challenges [47]. In the following paragraphs, the effects of several medicinal plants and their secondary metabolite constituents on cytokine production have been summarized, with their potential activity against tumor immunity being addressed. These natural products have been selected based on their cytokine-regulatory properties discussed in both previous review articles and recent reports in the primary scientific literature. The compound types include phenolic derivatives, isoprenoids, and alkaloids and other nitrogen-containing substances.

3.2. Effects of Selected Extracts of Some Medicinal Plants on the Production of Cytokines

The effects on cytokine production and the cytokine-targeted immunoregulation of extracts of several medicinal plants have been recently summarized. The species considered include *Allium sativum* L. (garlic) (Amaryllidaceae), *Berberis vulgaris* L. (barberry) (Berberidaceae), *Crocus sativus* L. (saffron) (Iridaceae), and *Curcuma longa* L. (turmeric) (Zingiberaceae). As discussed previously, garlic (*A. sativum*) is a widely used herb showing various pharmacological properties, which stimulates the IFN-γ production by splenocytes and enhances the immune responses by increasing immune enzymes, cell activities, and antibodies. Barberry (*B. vulgaris*) increases the production of IFN-γ and IL-12 and decreases the level of IL-4 in mouse spherocytes, while it lowers the levels of TNF-α, IL-6 and IL-12 in mouse macrophages. Furthermore, saffron (*C. sativus*) decreases the levels of IL-10 and IFN-γ in phytohemagglutinin (PHA)-stimulated lymphocytes and increases the ratio of IFN-γ/IL-4 of peripheral blood mononuclear cells (PBMCs), while turmeric (*C. longa*) increases the levels of IL-2, IL-6, IL-10, IL-12, IFN-γ, and TNF-α in mouse splenocytes [45].

In addition, *Aloe vera* (L.) Burm.f. (syn. *Aloe barbadensis* Miller) (Asphodelaceae) has been reported for its effects on cytokine production. For example, *A. vera* nanovesicles (AVpNVs) decreased the secretion of the pro-inflammatory cytokines IL-1β, IL-6, and TNF-α in murine RAW264.7 and human THP-1 M0 macrophages induced by LPS and showed an anti-inflammatory effect in these cells, while a blended fibroin/aloe gel extract film promoted skin wound healing through activation of the mitogen-activated protein kinases (MAPK)/(ERK) signaling pathway [48,49].

Several berries have shown cytokine-regulatory effects, including Aronia berries, barberries (discussed immediately above), blueberries, Brazilian berries, and goji berries. The fruits of black chokeberry [*Aronia melanocarpa* (Michx.) Elliott] (Aronia berries) (Rosaceae) showed anti-infective, antitumor, and immunomodulatory activities. Consumption of

these berries reduced the levels of IL-6 and TNF-α and elevated the level of IL-10 in the plasma of the individuals involved [50,51]. Similarly, the fruits of *Vaccinium caesariense* Mack. (blueberries) (Ericaceae) reduced the production and mRNA expression of IL-6 and TNF-α in mouse macrophages induced by LPS or oxidized low-density lipoprotein (oxLDL) and the intake of these berries altered mouse serum cytokine levels and inhibited mouse breast tumor growth and metastasis [52,53]. Treatment with a photoactivated water extract of the fruit bark of *Myrciaria cauliflora* (Mart.) O. Berg (jaboticaba, Brazilian berries) (Myrtaceae) led to an increased level of TNF-α and a decreased level of IL-10 in draining the lymph nodes of mice stimulated by methicillin-resistant *Staphylococcus aureus* (MRSA), while treatment with an ethanol extract of jaboticaba peel resulted in a decreased level of TNF-α in human prostate cancer cells [54,55]. Furthermore, supplementation with 5% of the fruits of *Lycium barbarum* L. (goji berries or wolfberries) (Solanaceae) reduced the murine lung pathology caused by influenza infection. Although no statistical significance was observed, lowered levels of IL-1β, IL-6, and TNF-α were found in the lungs and spleens of infected mice, while decreased levels of these cytokines in the brain, spinal cord, and retina of mice, and of the gene expression of IL-1β and TNF-α in the epididymis of rabbits, were reported when the animals were treated with goji berries [56–58].

Various beverages made of the leaves of *Camellia sinensis* L. Kuntze (Theaceae), including green tea, are well known for their antioxidant, anti-inflammatory, and immune-potentiating properties [7]. The level of TNF-α but not IL-12 was reduced by the treatment of LPS-induced rat lung L2 cells with an ethanol extract of green tea [59], and such a treatment decreased the levels of IL-4, IL-5, and IL-13 in the bronchoalveolar lavage fluid (BALF) of ovalbumin (OVA)-induced mice [60]. However, in a trial study with obese women, no obvious changes were observed in their serum levels of IL-1β, IL-4, IL-6, IL-10, IL-17α, and TNF-α, when the subjects were supplemented daily with green tea capsules containing around 450 mg of epigallocatechin gallate (EGCG) for eight weeks [61].

Zingiber officinale Roscoe (ginger) (Zingiberaceae) has been used widely in various foods and beverages, and its cytokine-related anti-inflammatory and immunomodulatory properties have been well demonstrated [62]. A meta-analysis indicated that ginger intake significantly reduced the circulation level of TNF-α but not IL-6 [63]. In a trial study with well-trained male endurance runners, the plasma levels of IL-1β, IL-6 and TNF-α were reduced by supplementation with 500 mg (capsules) of ginger powder (three times each day for 6 weeks) [64]. Similarly, the serum levels of TNF-α and IL-1β declined when older patients with osteoarthritis were supplemented with 500 mg (capsules) of ginger powder (twice each day for three months) [65].

3.3. Effects of Selected Plant-Derived Phenolic Derivatives on the Production of Cytokines

Phenolic compounds are the most widely occurring natural products that show regulatory effects on the expression of various cytokines, including the anthracene and/or anthraquinone, coumarin, flavonoid, lignan, stilbenoid, and other compound types [7]. Presented in the following paragraphs are summaries of the cytokine-regulatory activities of 11 plant-derived aromatic compounds, including cardamonin (**1**), curcumin (**2**), emodin (**3**), eugenol (**4**), gallic acid (**5**), 6-gingerol (**6**), phyllanthusmin C (**7**), quercetin (**8**), resveratrol (**9**), silibinin (**10**), and xanthotoxol (**11**) (Figure 4). Flavonoids are a large group of naturally occurring phenolic compounds found widely in edible plants and they have attracted increasing interest for their potential therapeutic effects, including their induction of adaptive cellular responses by modulating signaling pathways and gene expression in metabolic regulation [66]. The activity of flavonoids against cytokines has been discussed in previous review articles [7–13], as represented by cardamonin (**1**) and quercetin (**8**). Cardamonin (**1**) is a chalcone derived especially from cardamom [*Elettaria cardamomum* (L.)

Maton] (Zingiberaceae) and shows multiple pharmacological properties mediated through various signaling pathways to benefit human health, including its potential antitumor, immunomodulatory, and anti-inflammatory activities [67,68]. Cardamonin inhibited the pro-inflammatory cytokines IL-1β, IL-6, and TNF-α, and showed anti-inflammation-related activities through the NF-κB and related signaling pathways [69–73].

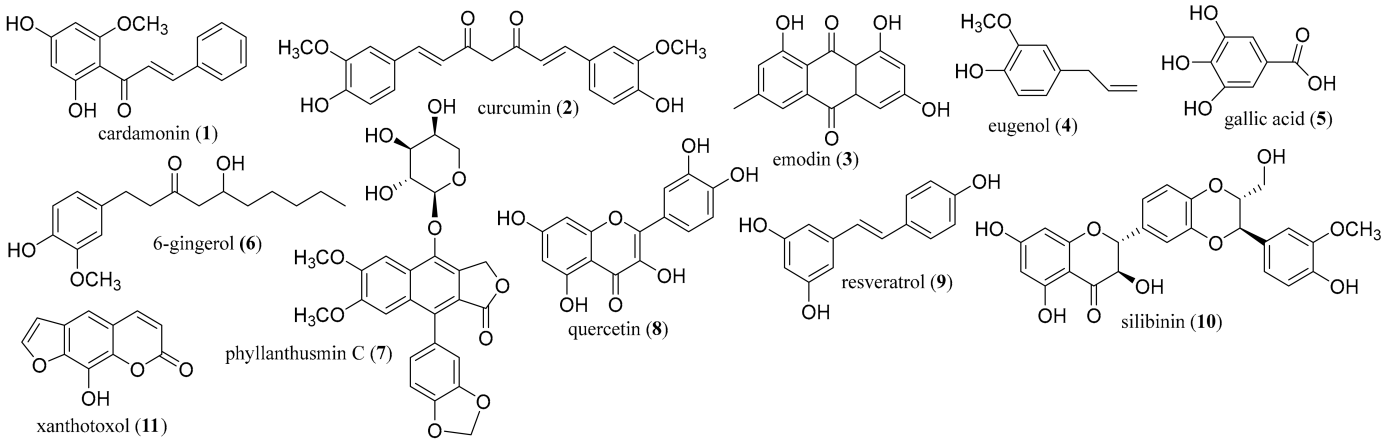

Figure 4. Structures of selected plant-derived phenolic derivatives (**1**–**11**) that show regulatory effects on the production of cytokines.

The expression of these cytokines (IL-1β, IL-6, and TNF-α) in alveolar macrophages of MH-S mice induced by phorbol 12-myristate 13-acetate (PMA) and their production from mouse primary peritoneal macrophages induced by LPS and IFN-γ/LPS-stimulated murine BV2 microglial cells were reduced by cardamonin [69,71,72]. Additionally, the levels of these cytokines in the serum of mice injected with λ-carrageenan and in the rat sciatic nerve were decreased, but those of the anti-inflammatory cytokines, IL-10 and TGF-β, were increased in the rat sciatic nerve, when the animals were treated with cardamonin [70,73]. The mRNA expression of IFN-γ, IL-6, IL-15, MCP-1, and TNF-α in LPS-stimulated RAW264.7 murine monocyte/macrophage-like cells, both the levels and the mRNA expression of IL-6 and TNF-α in the inflamed mouse colons induced by dextran sulfate sodium (DSS), and the levels of IL-6 and TNF-α in PBMCs from human subjects with primary Sjogren's syndrome were decreased with cardamonin treatment [74,75]. Interestingly, the mRNA expression of IL-6 in macrophages induced by THP-1 human leukemic cells was reduced substantially by cardamonin [76], and both the mRNA and protein expression of the chemokine CCL2 in MDA-MB-231 and MDA-MB-468 human triple-negative breast cancer cells induced by TNF-α were inhibited by this compound [77].

Quercetin (**8**) is a well-known bioactive flavonol found in abundance in many edible plants, and its effects on cytokine expression and production have been discussed in several previous review articles. These include its decrease of the gene expression of IL-1β, IL-6, IL-8 and TNF-α in human mast cells and the production of TNF-α, IL-6, G-CSF, GM-CSF, IFN-γ-induced protein 10 (IP-10 or CXCL10), and MCP-1 in mouse macrophages and its increase of the level of IL-27 in influenza A-treated MDCK cells. Additionally, quercetin stimulated Th cells to produce IFN-γ and downregulated Th2-derived IL-4 in PBMCs [8,9]. Treatment with quercetin was recently found to decrease the arsenic-induced elevation in gene expression of the pro-inflammatory cytokines, IL-1β, IL-6, and TNF-α, and the anti-inflammatory cytokines, IL-4, IL-10, and TGF-β, in rat colon tissues [78]. In serum from hepatoma-bearing mice, combination treatment with quercetin and anti-PD-1 decreased the levels of IL-4 and IL-6 but increased those of IL-10 and IFN-γ, while this treatment inhibited the macrophage-related genes of IL-1β, IL-6, IL-12a, and TNF-α but increased those of IL-10 and TGF-β [79]. Moreover, quercetin inhibited the proliferation of SW620

human colorectal cancer cells and induced cell apoptosis, and it increased the macrophage-associated production of IL-6 and IL-12 but decreased those of CXCL8 and IL-10 from SW620 cells co-cultured with M0 macrophages. These indicate that quercetin shows an antitumor potential by targeting CXCL8 to inhibit macrophage M2 polarization to reshape the TME [80].

As one of the major bioactive components of turmeric (*Curcuma longa* L.) (Zingiberaceae), the diarylheptanoid curcumin (**2**) shows modulatory effects on cytokines to mediate multiple pharmacological properties. As summarized previously, curcumin (**2**) regulates the secretion of anti-inflammatory cytokines like IL-4 and IL-13 in the nucleus and inhibits the production of pro-inflammatory cytokines, including CXCL8, IFN-γ, IL-1β, IL-2, IL-6, IL-12, TNF-α, IP10, MCP-1, and macrophage inflammatory protein 1α (MIP-1α) by targeting MAPK, PI3K, and NF-κB [7–9]. More recently, curcumin was found to suppress IL-18 production and to modulate IL-18-related signaling pathways, including the NF-κB pathway. IL-18 enhances the production of other pro-inflammatory cytokines, facilitates Th cell polarization, and amplifies the inflammatory cascade, and thus curcumin shows potential therapeutic effects on various inflammatory diseases [81]. Additionally, curcumin treatment reduced the serum levels of IL-4, IL-6, IL-21, and IgG, but increased that of IL-10, while it inhibited the secretion of IL-7 and IL-21 but enhanced those of IL-2, IL-4, and IL-10 in the colonic tissues of mice with DDS-induced ulcerative colitis and alleviated DSS-induced colitis [82,83]. Furthermore, curcumin reduced the production of IL-6 and IL-17A but increased that of IL-10 by the PBMCs from women with gestational diabetes mellitus [84], while it suppressed TAM-induced malignant behaviors. In the TAMs isolated from the ascites of ovarian cancer patients and co-cultured with SKOV3/OVCAR-3 ovarian cancer cells, the production of IL-10 was reduced, but that of IL-12 was enhanced by curcumin, which also decreased the mRNA expression of CCL23, CXCR2, and TGF-β but increased those of IL-1, IL-12, and TNF-α in the TAMs [85].

6-Gingerol (**6**), a major bioactive phenolic constituent of fresh ginger (*Zingiber officinale* Roscoe) (Zingiberaceae) and the rhizomes of several other *Zingiber* species, shows various bioactivities, including antimetastatic, anti-infective, and immunomodulatory properties. As summarized previously, 6-gingerol (**6**) inhibited the production of IL-1β, IL-12, and TNF-α in LPS-stimulated macrophages and the rat brain and reduced IL-1β-induced inflammation by decreasing the mRNA expression of IL-6 and CXCL8, COX2 over-expression, and NF-κB activity [9]. In high glucose-induced THP-1 human leukemia monocytes, 6-gingerol reduced the protein and mRNA expression of IL-1β, IL-6, and TNF-α [86].

Several small phenolic compounds (molecular weight < 300 Da), including emodin (**3**), eugenol (**4**), gallic acid (**5**), resveratrol (**9**), and xanthotoxol (**11**) (Figure 4) have been reported for their effects on cytokine production and expression. Of these, emodin (**3**) is a widely occurring plant-derived anthraquinone, which was found to inhibit the polarization of LPS-induced M1 RAW264.7 macrophages and the production of IL-6, IL-1β and TNF-α in RAW264.7 cells [87]. Additionally, emodin reduced the serum levels of these cytokines and IFN-γ in rats with acute severe craniocerebral injury [88]. The mRNA expression of IL-1β and TNF-α in oxLDL-primed DC2.4 mouse DCs was decreased but that of TGF-β was increased by emodin treatment. Moreover, emodin suppressed breast cancer cell stemness and migration and reduced macrophage infiltration, angiogenesis, and IL-17 expression in the breast tumor tissues from high-fat diet (HFD)-induced mice to suppress tumor growth [89], while it inhibited the IL-6-stimulated JAK2/STAT3 pathway and showed potential antitumor activity [8]. Surgery-triggered breast tumor growth and lung metastasis were suppressed by emodin through its inhibitory effects on inflammatory monocytes and macrophages. The mRNA expression of IFN-γ and TNF-α in the primary tumors was

increased, but those of IL-1β, IL-4, IL-6, and TGF-β in the primary tumors and lungs of mice were decreased by emodin treatment [90].

The phenylpropanoid eugenol (**4**) is the major bioactive volatile constituent of clove oil and may be isolated from the dried buds of *Eugenia caryophyllata* Thunb. (Myrtaceae). As summarized previously, eugenol (**4**) reduced the TNF-α level in bronchoalveolar lavage fluid (BALF) and the levels of IL-1 and IL-6 in a mouse lung homogenate, while it decreased those of IFN-γ, TGF-β, and TNF-α but increased the IL-10 level in the affected ankle joints of mice [8,9]. In addition, eugenol showed protective effects against dityrosine-induced hepatotoxicity in mice, while it resulted in lowered levels of IL-6, IL-8, and TNF-α and an increased level of IL-10 in dityrosine-induced mouse plasma and livers, and in HepG2 human hepatoma cells [91]. Treatment with eugenol nanoparticles reduced the bacterial burden in infected mouse lung tissues and also elevated the levels of IFN-γ, GM-CSF, MCP-1, and TNF-α in the lung tissues, serum, and BALF of *Pseudomonas*-infected mice [92].

Gallic acid (**5**) is a small phenolic acid antioxidant found abundantly in edible plants that shows antifungal, antimicrobial, anti-inflammatory, and cytotoxic properties. It suppressed the levels of IL-1, IL-6, IL-12, IL-17, IL-23, TGF-β, TNF-α, CCL2 and CCL7 in 2,4,6-trinitrobenzene sulfonic acid (TNBS)-induced ulcerative colitis and rheumatoid arthritis fibroblast-like synoviocytes (RA FLS). It selectively inhibited the Th2 cytokines, IL-4 and IL-5, but not the Th1 cytokine, IFN-γ, in anti-CD3-stimulated spleen cells [9]. More recently, gallic acid was found to lower the LPS-induced increase of the expression of IL-1β and IL-6 and the mRNA expression of IL-17A and to increase that of IL-10, while it restored the levels of all these cytokines in the lung tissues of rats with LPS-induced acute lung injury. Additionally, gallic acid reduced rat lung tissue damage through the IL-10-AKT1/GSK3β/NRF2 axis [93]. Consistently, it decreased the LPS-induced increase of the release of both IL-6 and TNF-α but increased those of IL-4 and IL-10, while it restored these cytokines in the LPS-treated macrophages [94]. Moreover, gallic acid showed a protective effect on ulcerative colitis. It decreased the concentrations of IFN-γ, IL-6, IL-17A, IL-23 and TNF-α, but increased those of IL-10, IL-22, and TGF-β in the serum of mice with DSS-induced ulcerative colitis [95]. In the PBMCs from psoriasis patients, gallic acid decreased the frequency of IL-17- and IFN-γ-producing cells within the $CD3^+$ (T) and $CD3^+CD4^+$ (Th) and within the $CD3^+$, $CD3^+CD4^+$ (Tc), $CD3^+CD4^-$ (Tc), and $CD3^-CD56^+$ (NK) compartments, respectively [96]. It potentiated tumor-infiltrating $CD8^+$ T cells from the tumor tissues of patients with gastric adenocarcinoma to increase gastric cancer cell apoptosis. This was found to be associated with the elevated secretion of IFN-γ, IL-2, and TNF-α and a decreased expression of IL-6 and IL-17A by tumor-infiltrating $CD8^+$ T cells [97].

Resveratrol (**9**) is a stilbenoid found in many edible plants and shows beneficial effects on human health. It decreased the production of IL-1β, IL-6, IL-8, IL-12 and TNF-α from LPS-stimulated human periodontal ligament cells and inhibited those of IL-2, IFN-γ, and TNF-α by splenic lymphocytes or peritoneal macrophages. It blocked the increased secretion of IL-6 and TNF-α in EV71-infected RD cells and the release of GM-CSF and CXCL8 by stimulated alveolar macrophages from patients with chronic obstructive pulmonary disease [9]. In addition, resveratrol attenuated the levels and/or mRNA expression of IL-1β, IL-6, and TNF-α in palmitate-exposed macrophages, in the hippocampal region of mice with surgery-induced neuroinflammation, and in bovine mammary epithelial cells and mouse mammary gland with non-esterified fatty acid-induced inflammation [98–100]. It also decreased the levels of these cytokines and increased the level of IL-10 in the plasma of patients to potentially support COVID-19 treatment [101]. Furthermore, resveratrol supplementation decreased the levels of IL-1β and IL-8 but increased that of IL-6 in low-volume lavage samples collected from mares with persistent breeding-induced endometritis [102],

while its treatment reduced the serum level of IL-12 but raised that of IL-10 in ischemic stroke rats [103]. Interestingly, in A549, NCI-H460, NCI-H226, and NCI-H1299 human lung cancer sphere-forming cells, resveratrol inhibited the level of IL-6, which could enhance the stemness of lung cancer stem-like cells, and thus it suppressed lung tumor growth by targeting the TME [104].

The small furanocoumarin xanthotoxol (**11**) was isolated from the entire plant of *Saussurea obvallata* (DC.) Sch.Bip. (Asteraceae) and found to reduce the secretion and mRNA expression of IL-1β, IL-6, and TNF-α by LPS-induced macrophages [105]. Its treatment decreased the levels of IL-1β, IL-8, and TNF-α in the cortex of rats with ischemia/reperfusion injury [106].

Lignans are a large group of naturally occurring dimeric phenylpropanoids, of which many arylnaphthalene lignan lactones have been reported for their potent cytotoxicity toward human cancer cells and for their immunoregulatory propensity [107]. Of these, phyllanthusmin C (**7**), which is not a phenol per se, isolated from different parts of *Phyllanthus poilanei* Beille (Phyllanthaceae), was active when tested against HT-29 human colon cancer cells [108]. It was found further to induce IFN-γ production by human $CD56^{bright}$ and $CD56^{dim}$ NK cell subsets via upregulation of Toll-like receptor (TLR)-mediated NF-κB signaling. NK cells are effective in cancer treatment, indicating that phyllanthusmin C could show potential effects on tumor immunity [109].

Silibinin (**10**) is a flavonolignan derived from the seeds of *Silybum marianum* L. Gaertn. (Asteraceae) and shows various bioactivities. It reduced tumor sphere formation and suppressed PD-L1 expression in renal cells to inhibit renal tumor growth [43]. In IgE-primed rat basophilic leukemia (RBL)-2H3 cells, silibinin reduced the production of cytokine-induced neutrophil chemoattractant-1 and -2a (CINC-1 and -2a), IL-1α, IL-2, IL-4, IL-13, MIP-3α, IFN-γ, activin A, GM-CSF, intercellular adhesion mol.-1 (ICAM-1), Fas ligand (FasL), and TNF-α [110]. It inhibited the secretion of IL-6 and IL-8 by house dust mite (HDM)-stimulated BEAS-2B human bronchial epithelial cells and lowered the levels of IL-4, IL-5, IL-13, and IFN-γ in BALF of HDM-exposed mice [111]. Additionally, silibinin reversed the ischemia-reperfusion injury (IRI)-induced upregulation of IL-1β, IL-6, and TNF-α at the mRNA and protein levels in hypoxia/reoxygenation (H/R)-induced human renal proximal tubular [human kidney-2 (HK-2)] cells and in the serum of IRI mice [112]. Its treatment decreased the level of TNF-α but increased the levels of IL-1β, IL-4 and IL-10 in the diabetic wound tissues of mice [113]. Interestingly, silibinin reduced the synthesis of IL-1β, IL-6, IL-8, IL-12p70, IL-23, and TNF-α but increased those of IL-10 and TGF-β by monocytes to induce an M2-like phenotype polarization, and it decreased the secretion of IFN-γ, IL-6, IL-17, IL-22, IL-23, TNF-α but increased those of IL-10 and TGF-β by PBMCs from preeclamptic women [114,115]. Moreover, silibinin inhibited the LPS-induced production of IL-12, IL-23, and TNF-α in human PBMC-derived DCs and impaired the proliferation response of CD4 T lymphocytes evoked by LPS-matured DCs and their Th1/Th17 profile [116]. It also suppressed the mRNA expression of TGF-β2 in HCC1143 and HCC1806 human triple-negative breast cancer (TNBC) cells and inhibited cell motility [117].

3.4. Effects of Plant-Derived Isoprenoids on the Production of Cytokines

Isoprenoids are a large group of plant-derived components, including the monoterpene, sesquiterpene, diterpene, triterpene, and steroid subgroups. These products show various biological activities that are of benefit to human health, especially terpenoid lactones [118,119]. Some of these compounds regulate the production and/or release of cytokines to mediate their bioactivities, including andrographolide (**12**), artemisinin (**13**), betulin (**14**), betulinic acid (**15**), brevilin A (**16**), britanin (**17**), crocetin (**18**), cucurbitacin B

(**19**), digoxin (**20**), eburicoic acid (**21**), ginkgolide B (**22**), ginsenoside C-K (**23**), jolkinolide B (**24**), limonin (**25**), parthenolide (**26**), triptolide (**27**), ursolic acid (**28**), and withaferin A (**29**), as discussed in the following paragraphs. These cover the sesquiterpene lactones, **13**, **16**, **17,** and **26**, the linear diterpene, **18**, the diterpene lactones, **12**, **22**, **24**, and **27**, the tetracyclic triterpenoids, **19**, **21**, and **23**, the pentacyclic triterpenoids, **14**, **15**, and **28**, the triterpenoid lactone, **25**, and the steroidal lactones, **20** and **29** (Figure 5). The sesquiterpene lactone artemisinin (**13**) is a well-known antimalarial drug derived from *Artemisia annua* L. (sweet wormwood) (Asteraceae) and has demonstrated potential anticancer activity [118,119]. Its treatment decreased the levels of IL-1α, IL-1β, IL-6, and TNF-α in LPS-induced BV2 microglial cells and those of IL-6 and TNF-α in the serum and hippocampus of mice with sepsis induced by LPS [120]. It also reduced the levels of IL-1β, IL-13, IL-17, IL-23, and IL-33 in the serum of rats with ulcerative colitis induced by DSS to alleviate intestinal inflammation [121]. In addition, artemisinin has shown effects on cytokine-related tumor immunity. In HT-29 human colon cancer cells, artemisinin inhibited the LPS-induced IL-8 secretion and Th1 and Th17 cell differentiation [122], while it lowered the level of IL-1β but elevated that of IL-10 in tissues from mice with colon tumors induced by 1,2-*N*,*N*-dimethylhydrazine and also suppressed colon tumor formation [123]. The mRNA expression of IFN-γ and TNF-α in mouse breast tumor tissues was increased, but that of TGF-β was decreased by artemisinin treatment, with the antitumor immune response being enhanced [124]. Two pseudoguaianolide-type sesquiterpene lactones, brevilin A (**16**) and britanin (**17**), have been reported for their effects on cytokine production, of which brevilin A (**16**), derived from *Centipeda minima* (L.) A.Braun & Asch (Asteraceae), is a JAK-STAT and NF-κB inhibitor and shows potential antitumor and anti-inflammatory activities [125–127]. It decreased the levels of IL-6 and IL-8 in the IL-17A-induced human HaCaT keratinocytes and repressed the release of IL-1β, IL-6, and TNF-α in the serum collected from LPS-stimulated mice [126,127].

Britanin (**17**), identified from *Inula japonica* Thunb. (Asteraceae), regulates cytokines among its known biological properties [128–130]. For example, britanin increased the serum level of IL-2 but decreased that of IL-10 in mice with gastric cancer and inhibited tumor growth [129]. In LPS-stimulated RAW264.7 murine macrophage cells, britanin reduced the release and gene expression of IL-1β, IL-6, and TNF-α [128], and it also inhibited the secretion of IL-1β in LPS- and adenosine triphosphate (ATP)-induced bone marrow-derived macrophages [130].

Parthenolide (**26**) is an epoxylated germacranolide-type sesquiterpene lactone isolated from the feverfew plant, *Chrysanthemum parthenium* (L.) Bernh. [syn. *Tanacetum parthenium* (L.) Sch.Bip.] (Asteraceae). Its potential NF-κB-targeted antitumor activity has been summarized in previous review articles [8,18,19]. In addition, the production of IL-12 from LPS-stimulated mouse macrophages and the mRNA expression of IL-6, TNF-α, and MCP-1 in high glucose-induced HMrSV5 human peritoneal mesothelial cells, as well those of IL-17a, IL-22, and TNF-α in lymphocytes from the mouse central nervous system and of IFN-γ, IL-17a, IL-17f, and TNF-α in $CD4^+$ T cells from the mouse spleen, were inhibited by parthenolide, with the mRNA expression of IL-4 being enhanced in the lymphocytes and $CD4^+$ T cells [131–133]. Additionally, the peritoneal mRNA expression of IL-6 and MCP-1 in mice was suppressed by parthenolide [132]. The release of IL-1β, IL-6, and TNF-α from BV2 murine, HMC3 human microglia, and LPS-stimulated RAW264.7 mouse mononuclear macrophage cells were inhibited, and the levels of these cytokines in the serum of mice with cecal ligation and puncture-induced sepsis were decreased by treatment with parthenolide, with the release of IL-10 from the microglia cells being improved [134,135]. Importantly, parthenolide suppressed differentially the mRNA expression of IFN-γ, IL-2, and IL-4 in Jurkat T human leukemia cells activated by anti-CD3 antibodies and their

production by peripheral blood T cells collected from healthy adult donors and stimulated by anti-CD3/CD28 or phorbol 12-myristate 13-acetate (PMA)/ionomycin [136], while it induced the production of IFN-γ, IL-2, IL-4, IL-5, and IL-13 by PBMCs from subjects with contact allergy [137]. In HT-29 human colon cancer cells activated by TNF-α, parthenolide reduced the mRNA expression of IL-1β but increased that of IL-8, and it also inhibited proliferation and invasion of the cells [138].

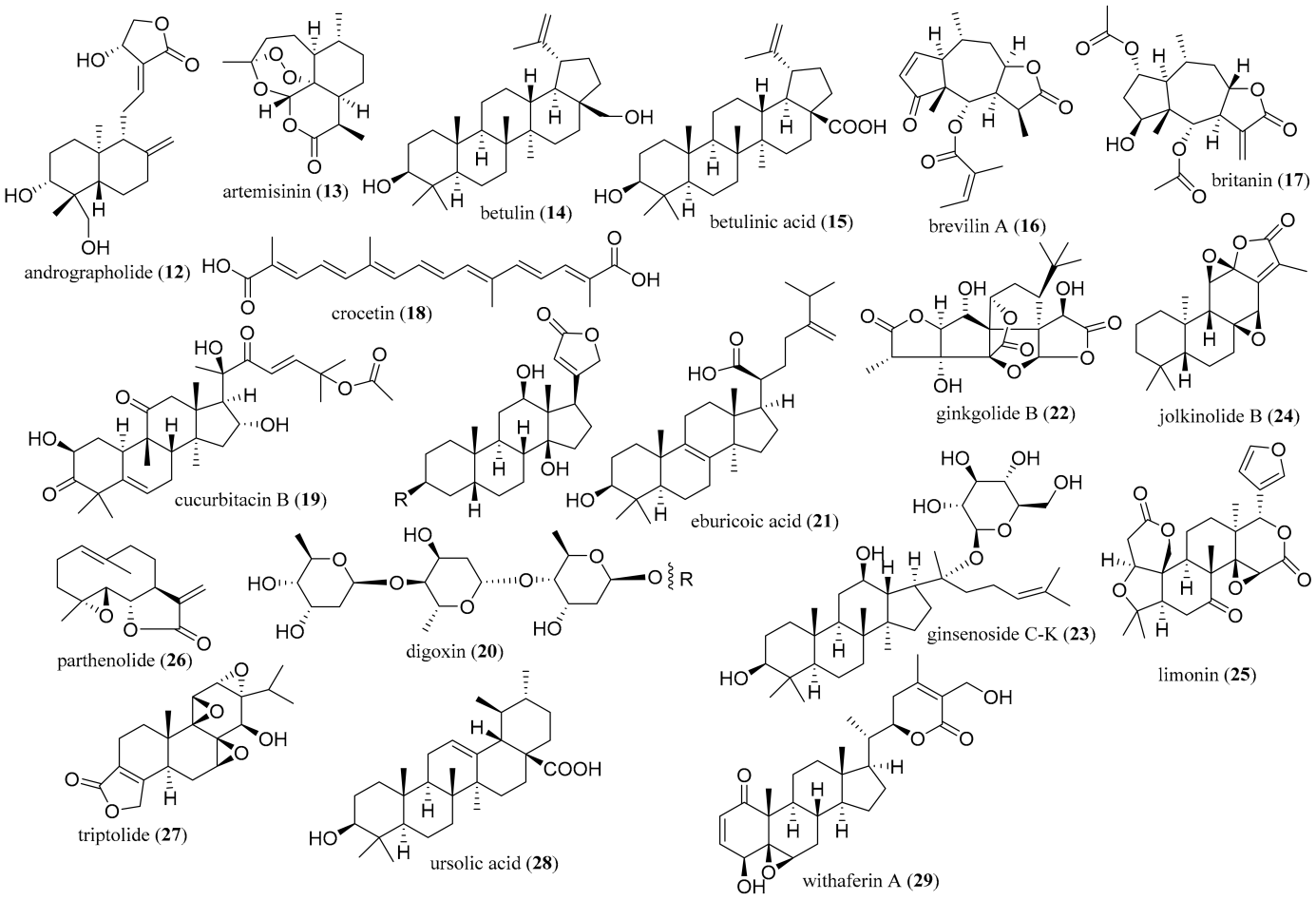

Figure 5. Structures of selected plant-derived isoprenoids (**12**–**29**) that show regulatory effects on the production of cytokines.

Crocetin (**18**) is an apocarotenoid dicarboxylic acid, a linear diterpene identified from saffron (the flowers of *Crocus sativus* L.) (Iridaceae), and shows effects on cytokine production [45]. Its treatment decreased the mRNA expression levels of IL-1β, IL-6, IL-10, and TNF-α in 1-methyl-4-phenylpyridinium (MPP)-treated mouse BV2 microglia cells and in the striatum from mice with Parkinson's disease induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) [139]. Such a treatment also lowered the cardiac mRNA expression of IL-1α, IL-1β, IL-6, IL-8, and TNF-α in rats with their hearts injured by ischemia/reperfusion [140], as well the levels of IL-6, IL-8, IL-10, and MCP-1 in the mucosal tissue of the trigone of the urinary bladder and the left pelvis of rats with urinary tract infection induced by urethane [141]. In human phytohaemagglutinin (PHA)-stimulated lymphocytes, crocetin lowered the expression of protein and mRNA of IL-4 and IL-17A but enhanced that of IL-10, while it also increased the mRNA expression of IFN-γ [142]. In addition, administration of crocetin decreased the serum levels of IL-1β and TNF-α in mice with cervical tumors induced by methylcholanthrene (MCA) [143].

Four diterpene lactones, andrographolide (**12**), ginkgolide B (**22**), jolkinolide B (**24**), and triptolide (**27**), have been reported for their potential antitumor and other activities, of which the labdane andrographolide (**12**) is derived from *Andrographis paniculata* (Burm.f.) Nees (Acanthaceae) and shows selective activity against various human cancer cells [119]. This diterpene inhibited the production and the mRNA expression of IL-12 and TNF-α in LPS-activated murine peritoneal macrophages and those of IL-1β, IL-6, IL-8 in hypoxia-induced human keratinocytes, as well as the secretion of IL-1β, IL-6, IL-8, and TNF-α in LPS-induced canine mononuclear cells [144–146]. In addition, the levels of IL-6, IL-17A, and Il-17F in the serum and BALF of mice with ovalbumin (OVA)-stimulated asthma and those of IL-1β, IL-6, and TNF-α in the liver tissue of mice with high-fat diet (HFD)-induced hepatic inflammation were lowered by andrographolide [147,148]. Additionally, in U-87 MG human glioblastoma cells exposed to cadmium, the release of IL-6, IL-8, and CCL2 was suppressed by andrographolide [149].

Ginkgolide B (**22**) is a caged diterpene trilactone containing six five-membered rings, which was isolated from the leaves of ginkgo, *Ginkgo biloba* L. (Ginkgoaceae) and showed potential antitumor activity through inhibiting platelet-activating factor (PAF) [119]. Additionally, this trilactone was found to lower the levels and mRNA expression of IL-1β, IL-6, MCP-1, and TNF-α but to increase those of IL-10 in the serum of mice with collagen-induced arthritis (CIA) [150], while the levels of IL-1β, IL-6, and TNF-α in the cerebral tissues of mice with cerebral I/R injury were decreased by ginkgolide B treatment [151]. Moreover, this compound decreased the levels of IL-4, IL-5, and IL-13 but increased those of IL-12 and IFN-γ in the BALF of mice with house dust mite (HDM)-induced asthma [152]. Lower levels of IL-1α, IL-1β, IL-6, IL-12p70, and TNF-α and a higher level of IL-18 were observed in the lung tissue from mice with hyperoxia-induced lung injury from treatment with ginkgolide B [153].

Jolkinolide B (**24**) is an *ent*-abietane-type diterpene diepoxide lactone isolated originally from *Euphorbia jolkini* Boiss. (Euphorbiaceae) and has been discussed for its antitumor potential by targeting Akt/STAT3/mTOR [119]. It downregulated the mRNA expression of IL-6 and TNF-α in primary murine hepatocytes and Hep3B human hepatoma cells and in LPS-induced RAW264.7 murine macrophage cells and the ankle joints of CIA rats, and it inhibited the production of these cytokines by RAW264.7 cells [154,155]. In the brain tissue of middle cerebral artery occlusion/reperfusion (MCAO/R) rats, the levels of IFN-γ, IL-1α, IL-1β, IL-12, and TNF-α declined, while those of IL-4, IL-10, and TGF-β were elevated, when the rats were treated with jolkinolide B [156]. Additionally, lowered levels of IL-1β. IL-6, and TNF-α produced by the BALF of mice with LPS-induced mouse acute lung injury and those of IL-4, IL-5, IL-13, and TNF-α secreted by the BALF of mice with OVA-induced asthma were observed for jolkinolide B treatment [157,158].

Triptolide (**27**) is an 18(4→3)-*abeo*-abietane-type diterpene triepoxide lactone derived from *Tripterygium wilfordii* Hook.f. (Celastraceae), and the parent compound of Minnelide, a prodrug evaluated in clinical trials for the treatment of refractory pancreatic cancer [43,119]. The mRNA expression levels of IL-1β, IL-6, IL-8, IL-12, TNF-α, and INF-γ in LPS-induced chondrocytes and the serum levels of these cytokines in rats with osteoarthritis induced by monosodium iodoacetate (MIA) or by surgery were decreased, and the serum levels of IL-6, IL-17A, IL-22, IL-23, and TNF-α in imiquimod (IMQ)-induced psoriatic mice declined, as a result of triptolide treatment [159,160]. In the lung tissues, the mRNA expression of IL-5, IL-13, and CCL11, the levels of IL-1β, IL-6, IL-10, TNF-α, and INF-γ, and the levels of IL-1β, IL-6, IL-8 and TNF-α of mice with papain-induced acute type 2 lung inflammation, with LPS-induced lung injury, and with influenza A (H1N1) virus-induced pneumonia, respectively, were decreased, and mouse airway inflammation and lung injury were alleviated by triptolide treatment. Such a treatment also decreased the release of IL-1β,

IL-6, IL-8, and TNF-α from H1N1-infected human bronchial epithelial cells (HBEpiCs) and THP-1 human monocytic leukemia cells [161–163]. In AGS human gastric cancer cells induced by IL-1β, the expression of protein and mRNA of IL-8 was attenuated [164], and a downgrade of the serum levels and the mRNA expression of IL-10 and TGF-β in the spleen was observed in melanoma-bearing mice, with triptolide treatment [165].

Naturally occurring triterpenoids have been well demonstrated for their potential antitumor activity, including tetracyclic triterpenoids, such as the lanostane-type and dammarane-type triterpenoids [166]. Of these, a lanostane-type triterpenoid, eburicoic acid (**21**) derived from fungi and certain medicinal plants, including *Curculigo orchioides* Gaertn. (Hypoxidaceae), inhibited the release of IL-1β, IL-6, and IL-18 in oxidized low-density lipoprotein (ox-LDL)-induced human umbilical vascular endothelial cells (HUVECs) and those of IL-1β, IL-6, and TNF-α in LPS-induced RAW264.7 murine macrophage cells [167,168]. Additionally, the serum levels of IL-1β and TNF-α in mice with paw edema induced by λ-carrageenan were reduced by eburicoic acid [169].

As the main bioactive components of ginseng, the roots of *Panax ginseng* C.A.Mey. (Araliaceae), the ginsenosides mainly represent dammarane-type triterpene saponins and have attracted wide attention for their antitumor potential [166]. Of these, ginsenoside C-K (**23**) has been reported for its effects on cytokine production. For example, the secretion of IL-1β, IL-6, and IL-8 in TNF-α-induced human fibroblast-like synoviocytes and the expression of protein and mRNA of IL-1β and TNF-α in β-amyloid (Aβ) oligomer-induced BV2 murine microglial cells were found to be suppressed by ginsenoside C-K [170,171]. The renal protein expression of IL-1β, IL-6, and TNF-α in mice with diabetic kidney disease induced by imidazole propionate (IMP) and the serum levels of these cytokines in mice with MPTP-induced Parkinson' s disease were reduced [172,173], while their levels in the serum of lung-tumor-bearing mice were decreased, when mice were treated with ginsenoside C-K [174].

Cucurbitacins are highly oxygenated cucurbitane-type tetracyclic triterpenoids derived mainly from the plant family Cucurbitaceae, of which cucurbitacin B (**19**) has been demonstrated for its antitumor activity [166]. It down-regulated the expression of TNF receptor 1 (TNF-R1) in A549 human lung cancer cells and lowered the production of IL-1β, IL-6, and TNF-α by zinc finger protein 70 (ZNF70)-induced THP-1 human monocytic leukemia cells [175,176]. The levels of these cytokines in the colon tissues of mice with DSS-induced ulcerative colitis and those of IL-6, IL-17A, and TNF-α in the paw tissues of CIA-induced mice were decreased, with the level of IL-10 being increased, when mice were treated with cucurbitacin B [177,178].

Three pentacyclic triterpenoids, betulin (**14**), betulinic acid (**15**), and ursolic acid (**28**), distributed widely in higher plants, have shown promising antitumor activity, of which betulinic acid has been evaluated in phase I/II clinical trials for the potential treatment of dysplastic melanocytic nevi [166]. In turn, betulin (**14**) increased the mRNA expression level of IL-8 in human HT-29, RKO, and SW1116 colon cancer cells, as well in human normal CCD-841CoN colon cells [179]. It inhibited the production and mRNA expression of IL-1β and TNF-α in human osteoarthritis synovial fibroblasts and those of IL-1β, IL-6, and IL-8 in LPS-induced human gingival fibroblasts [180,181]. The levels of IL-6 and TNF-α declined but that of IL-10 was raised in the BALF of mice with LPS-induced pulmonary inflammation, while lowered levels of IL-1β, IL-6, and TNF-α were observed in the brain tissue of mice with microglia-mediated neuroinflammation, when these animals were treated with betulin [182,183]. Betulinic acid (**15**) reduced the levels and expression of IL-1β, IL-6, and TNF-α in the serum of CIA rats and in the spinal cord tissues of mice with chronic constriction injury, respectively [184,185]. It also suppressed the mRNA expression levels of IL-1β, IL-6, IL-10 and TNF-α in the duodenum, ileum, and colon of mice with

LPS-induced intestinal inflammation [186]. Ursolic acid (**28**) inhibited NF-κB activity and the growth of various human cancer cells to show potential antitumor activity [166,187]. In RAW264.7 mouse macrophage cells infected by *Leishmania donovani* parasites, ursolic acid enhanced the release of IL-12 and TNF-α but reduced those of IL-10 and TGF-β [188], while the renal levels of IL-1β, IL-6, and TNF-α of rats with cisplatin-induced oxidative stress and nephrotoxicity were lowered by treatment with ursolic acid [189]. This triterpene also inhibited the production of IL-1β, IL-6, TNF-α, and GM-CSF in murine B16F-10 melanoma cells and decreased the levels and the protein and mRNA expressions of IL-1β, IL-6, IL-18, and TNF-α in influenza A virus-triggered A549 human lung cancer cells [190,191]. Interestingly, the mRNA expressions of IL-1β, IL-6, TNF-α, and CCL-2 in both LPS-induced BGC-823 human gastric cancer cells and gastric tumors were reduced by ursolic acid treatment [192].

As a major bioactive component of the seeds of lemon [*Citrus limon* (L.) Osbek] (Rutaceae), limonin (**25**), the first member of the limonoids, a group of modified euphane-type tetracyclic furanotetranortriterpenoids, showed promising antitumor activity by targeting phosphoinositide 3-kinase (PI3K)/Akt, Wingless-related integration site (Wnt), and Yes-associated protein (YAP) [119]. It decreased the levels of the colonic inflammatory cytokines, IL-1β, IL-6, and TNF-α, in mice with DSS-induced chronic colitis and reduced the serum levels of IL-6 and TNF-α in rats with metabolic syndrome induced by a high-fat diet [193,194].

Steroids are widely occurring plant-derived natural products showing various bioactivities, of which the steroidal lactones have been reported for their potential antitumor activity, as represented by various cardiac glycosides and withanolides. Cardiac glycosides are well-known Na^+/K^+-ATPase (NKA) inhibitors, of which several compounds have long been used clinically for the treatment of cardiovascular disorders and have more recently been evaluated for their immunoregulatory and antitumor potential [195,196]. Of these, digoxin (**20**) targets NKA and other proteins or their signaling pathways to mediate its potential anticancer activity [197,198]. It also suppressed the mRNA expression levels of IFN-γ, IL-17A, IL-17F, and GM-CSF in murine cardiac allografts and those of IL-17A, IL-17F, IL-23R, IFN-γ in the colonic mucosa of mice with experimental colitis, with the level of IL-10 being increased [199,200]. Lowered serum levels of IL-1β, IL-17A, and TNF-α were observed after digoxin treatment in mice with diethylnitrosamine-induced acute liver injury [201]. In addition, the reduced production of IL-1β, IL-6, IL-17, and IL-23 in PBMCs of patients with rheumatoid arthritis was observed after digoxin treatment [202].

The withanolides, a group of C_{28} ergostanes derived from the Solanaceae plant family, comprise a six-membered δ- or a five-membered γ-lactone unit and exhibit multiple bioactivities, of which withaferin A (**29**), identified originally from *Withania somnifera* (L.) Dunal (Solanaceae), has been well demonstrated for its potential antitumor activity [203,204]. Withaferin A decreased the levels of IL-1β, IL-6, TNF-α in the joints of rats and murine brains, in addition to their mRNA expression levels in murine brains and angiotensin II-induced gastrocnemius muscles and in the kidneys of tumor-bearing mice [205–209]. Additionally, an increased level of IL-10 in rat joints and those of IL-10 and TGF-β in murine brains and lowered levels of IL-18 and MIP-2β in murine angiotensin II-induced gastrocnemius muscles were observed when the animals were treated with withaferin A [207–209].

3.5. Effects of Plant-Derived Alkaloids and Other Nitrogen-Containing Substances on the Production of Cytokines

Alkaloids and other naturally occurring nitrogen-containing compounds show potent bioactivities, of which many compounds target the TME to mediate promising antitumor activity. Of these, paclitaxel and vinblastine have been used clinically for the treatment of

various types of cancer, while camptothecin is the parent compound of the anticancer drugs topotecan, irinotecan, and exatecan [210]. Additionally, several of these agents regulate cytokine release, including berberine (**30**), camptothecin (**31**), capsaicin (**32**), colchicine (**33**), ellipticine (**34**), melatonin (**35**), morphine (**36**), nicotine (**37**), paclitaxel (**38**), piperine (**39**), tabersonine (**40**), tetrandrine (**41**), and vinblastine (**42**) (Figure 6).

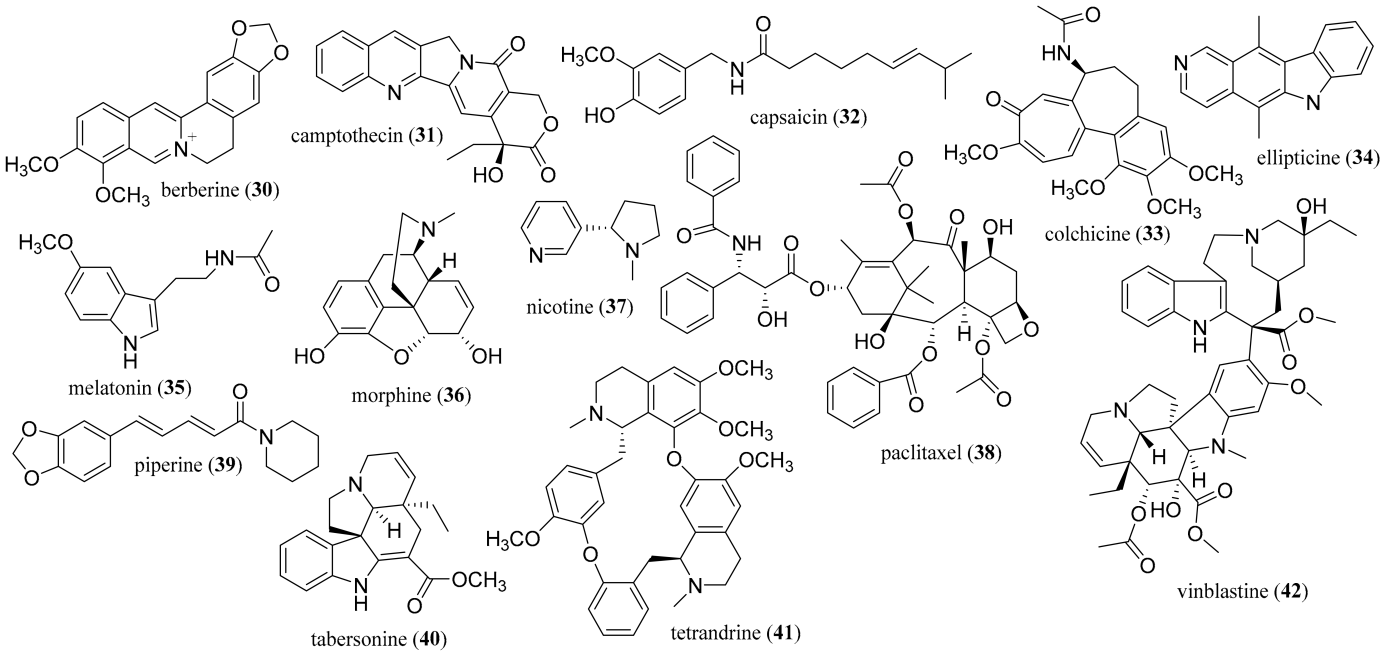

Figure 6. Structures of selected plant-derived alkaloids and other nitrogen-containing compounds (**30**–**42**) that show regulatory effects on the production of cytokines.

Two small alkaloids, melatonin (**35**) and nicotine (**37**), have been reported for their effects on cytokines. Melatonin (**35**) is a tryptophan-derived indolamine identified from many edible plants, including Huangqin (*Scutellaria baicalensis* Georgi) (Lamiaceae), curcuma (*Curcuma aeruginosa* Roxb.) (Zingiberaceae), black pepper (*Piper nigrum* L.) (Piperaceae), corn (*Zea mays* L.) (Poaceae), and rice (*Oryza sativa* L.) (Poaceae). It regulates the production or release of various cytokines and shows multiple pharmaceutical properties [9], while, as an anti-inflammatory hormone, melatonin reshapes the TME to enhance tumor immunity [211]. For example, melatonin impaired the secretion of IL-12p70, IL-17 and TNF-α by LPS-induced DCs and decreased the levels of these cytokines and IL-10 in the BALF of mice with LPS-induced acute lung injury [212]. In U87-MG human glioblastoma cells, melatonin reduced the expression of TNF-α but increased those of IL-1β and IFN-β during Zika virus infection, while it suppressed the expression of all of these cytokines during dengue virus infection [213]. Dietary supplementation with melatonin down-regulated the mRNA expression of IL-1β, IL-10, and TNF-α but up-regulated that of TGF-β1 in the spleen, while it decreased the mRNA expression of IL-1β and IL-6 but increased those of IL-10 and TGF-β1 in the thymus of piglets with T-2 toxin-induced inflammation [214]. The serum levels and the mRNA expression of IL-1β, IL-6, and TNF-α in dilated cardiomyopathy mice induced by doxorubicin and the levels of these cytokines and MIP-2 in the serum and BALF of mice with sepsis-induced acute lung injury declined, when mice were treated with melatonin [215,216]. In addition, the serum levels of TNF-α and IFN-γ were raised in human subjects with non-atypical endometrial hyperplasia, while a higher level of TNF-α but lower levels of IL-6, IL-10, and IFN-γ were observed in the serum of AIDS patients, when they were treated with melatonin [217,218].

Nicotine (**37**), a pyridine–pyrrolidine alkaloid derived mainly from the tobacco plant, *Nicotiana tabacum* L. (Solanaceae), has been used as an immunomodulator of the peripheral nervous system for the treatment of ulcerative colitis, while it also showed regulatory effects on cytokines [9,219]. For example, nicotine stimulated the mRNA expression of IL-6 in EA.hy926 human endothelial cells and the production of IL-1β, IL-6, IL-17, and IL-21 by human periodontal ligament cells, with or without a co-culture with $CD4^+$ T cells [220,221]. The secretion of IL-2, IL-6, and TNF-α by 16HBE human bronchial epithelial cells and that of IL-8 by pancreatic cancer stroma cells were enhanced, but the secretion of IL-10 by 16HBE cells was inhibited, when cells were treated with nicotine [222,223]. Additionally, nicotine treatment inhibited the mRNA expression of IL-1β, MCP-1, and TNF-α in the placentas of mice with LPS-induced inflammation [224].

A nitrogen-containing compound [capsaicin (**32**)] and an alkaloid [piperine (**39**)] with a sidechain substituent both show activity on cytokines. Of these, capsaicin (**32**) is a vanillylamine derivative and the main active component of chili peppers, the fruits of the genus *Capsicum* (Solanaceae), and exhibits multiple cytokine-related bioactivities [225]. Capsaicin treatment led to the lowered secretion of IL-4, IL-6, IL-8, and TNF-α in HepG2 human hepatoma cells in combination with oleic acid [226]. It also decreased the production of IL-1β, IL-6, and TNF-α in LPS-induced THP-1 human leukemia cells [227], and those of IL-1β, IL-1Ra, IL-6, IL-10, IFN-γ, and TNF-α in HT-29 human colon cancer cell-induced PBMCs [228]. The mRNA expression of IL-1β, IL-6, and TNF-α in the gastric mucosa of healthy and aspirin-induced gastritis rats and the serum levels of IL-1β, IL-18, and TNF-α in rats with acute kidney injury induced by cecal ligation and puncture were lowered by capsaicin [229,230], while capsaicin decreased the serum levels of IL-1β, IL-17, IFN-γ, and TNF-α but increased that of IL-10 in mice with ankylosing spondylitis induced by cartilage proteoglycans [231].

The piperidine alkaloid, piperine (**39**), derived mainly from *Piper nigrum* L. (Piperaceae), functions as an immunomodulator to regulate several cytokines and shows various pharmacological properties [9]. Piperine inhibited IL-1β-induced IL-6 expression in TMK-1 human gastric cancer cells and the secretion of IL-1β and IL-8 by HeLa and IL-1β and MCP-1 by SiHa human cervical cancer cells to reduce tumorigenesis [232,233]. It suppressed the production of IL-1β, IL-6, and TNF-α by LPS-induced murine BV2 microglia cells and both the production and expression of IL-1β, TNF-α, and IFN-γ in LPS-stimulated J774.1 murine macrophage cells [234,235]. The release and mRNA expression of IL-1β and TNF-α in the mammary glands of mice with LPS-induced mastitis were inhibited by piperine [236]. While the reduced levels or the gene expression of these cytokines, along with the increased gene expression of IL-10 and the decreased level of IL-8, were observed in the lumbar spinal cord of rats with experimental autoimmune encephalomyelitis (EAE) and in the BALF of smoke-exposed mice, respectively, following piperine treatment [237,238]. In addition, piperine administration lowered the serum levels of IL-6, IFN-γ, and TNF-α in mice with DSS-induced colitis [239].

Two pentacyclic alkaloids [berberine (**30**) and camptothecin (**31**)] and a tetracyclic alkaloid [ellipticine (**34**)] have been investigated for their effects on cytokines. Of these, berberine (**30**) is a major active isoquinoline (benzodioxoloquinolizine) alkaloid derived from the rhizomes of *Coptis chinensis* Franch. (Ranunculaceae), which regulates cytokines and shows antitumor and anti-infective activities [10,240]. The production of IL-2, IL-4, IL-6, IL-10, IL-17A, TNF, and IFN-γ by SK-MEL-28 human melanoma cells was found to be improved, but the mRNA expression of IL-1β, IL-6, and TNF-α in SW982 human synovial fibroblast cells induced by LPS were suppressed by berberine [241,242]. Treatment with berberine decreased the production of IL-17, IFN-γ, and TNF-α but increased those of IL-4, IL-10, IL-27, IL-33, IL-35, and TGF-β by splenocytes and lymph nodes from EAE

mice [243]. It lowered the secretion and mRNA expression of IL-1β, IL-6, and MCP-1 in KGN human ovarian granulosa-like tumor cells and the production of IL-1β, IL-6, and TNF-α by THLE-2 and THLE-3 human hepatocytes and the serum levels of these cytokines in rats with gefitinib-induced liver injury [244,245]. In addition, the serum levels of IL-1β, IL-6, IL-8, IL-12, IFN-γ, and TNF-α in weaned piglets infected by enterotoxigenic *Escherichia coli* declined with berberine treatment [246]. Lowered levels of IL-1β and TNF-α in the serum and placental tissue of mice with LPS-induced pre-eclampsia-like symptoms and those of IL-17A and IFN-γ in the serum of mice with *S. flexneri*-induced dysentery were observed, with the levels of IL-10 and TGF-β being elevated in both mouse serum and placental tissue, when the animals were treated with berberine [247,248].

Camptothecin (**31**) is a potent cytotoxic topoisomerase I inhibitor identified from the bark of *Camptotheca acuminata* Decne. (Nyssaceae), and the semi-synthetic derivatives, topotecan and irinotecan, are used clinically for the treatment of ovarian and lung and colorectal cancers, respectively [249]. Camptothecin upregulated the expression of more than 20 cytokines in SW620 human colon cancer cells, including secreted phosphoprotein 1 (SPP1), IL-12B, CCL22, CXCL10, TNF, lymphotoxin-α (LTA), IL-17F, CCL17, CCL5, IL-22, IL-16, and CCL21 [250], and it reduced the production of MCP-1 and CXCL10 from primary human renal glomerular endothelial cells stimulated by IFN-α or IFN-γ [251]. TNF-α- and IFN-γ-secreted T cells and NK cells were increased in the peripheral blood and spleen of mice treated with nanoparticles formed by the self-assembly of camptothecin-conjugated cyclodextrin-based polymers [252]. Additionally, camptothecin lowered the mRNA expression of IL-6 and TNF-α in the midbrain of mice with Parkinson's disease induced by LPS and the levels of these cytokines and IL-1β in the colon tissue of mice with DSS-induced ulcerative colitis [253,254].

Ellipticine (**34**), a pyridocarbazole alkaloid isolated originally from the leaves of *Ochrosia elliptica* Labill. (Apocynaceae), exhibits potential antitumor activity by targeting p53 and topoisomerase II [255]. It inhibited the production and mRNA expression of IL-6 and TNF-α by LPS-stimulated murine RAW 264.7 immortalized macrophage cells and by PBMCs from a healthy volunteer and those of IL-6 and CXCL-1 by IL-17A- or TNF-α-induced BEAS-2B human immortalized bronchial epithelial cells [256,257].

Two nitrogen-containing compounds, with a sidechain connected to a tricyclic [colchicine (**33**)] or a tetracyclic [paclitaxel (**38**)] central ring system, have been investigated for their effects on cytokines. Of these, colchicine (**33**), a secondary metabolite isolated from *Colchicum autumnale* L. and *Gloriosa superba* L. (Colchicaceae), exhibits anti-inflammatory, antitumor, and immunomodulatory properties and is involved in the secretion of cytokines. Colchicine has long been used in the clinic for the treatment of Mediterranean fever, gout, pericarditis, and other inflammatory conditions through binding to α and β tubulin dimers of microtubules to inhibit their assembly [9,258]. It increased the expression of IL-10 in 3T3 immortalized mouse embryonic fibroblasts induced by $CoCl_2$ [259], and it inhibited the IL-1β-induced mRNA expression of IL-6 in rat cardiac fibroblasts [260]. Treatment with colchicine reduced the mRNA expression of IL-6, TGF-β, and TNF-α in the atria of rats with sterile pericarditis induced by epicardial application of sterile talcum powder [260]. Such a treatment also lowered the expression levels of IL-1β, IL-6, and TNF-α in murine gastric tissues, of IL-6 in the plasma, and of IL-3, IL-10, GM-CSF, and IFN-γ in the skin-conditioned media from mice with sickle cell diseases [261,262]. A five-day administration of colchicine led to a higher level of IL-10 in sera from PBMC culturing of patients with late acute myocardial infarction [259]. After a two-week treatment with colchicine, decreased serum levels of IL-6 and IL-8 were observed in patients with heart failure [263].

Paclitaxel (**38**), an established nitrogen-containing tetracyclic diterpene anticancer drug derived from the bark and needles of *Taxus brevifolia* Nutt. or the bark of *Taxus baccata* L.

(Taxaceae), has been used for the treatment of various cancers for over 30 years. It interacts with the immune system by regulating the release of cytokines, including IL-1, IL-6, IL-8, IL-12, Il-18, TNF, and TGF, and triggers pro-inflammatory responses to treat cancer [11,43,264], thus showing potential for additional use in cancer immunotherapy [265]. In murine bone marrow—derived macrophages (BMDMs), paclitaxel induced an increased release of IL-12p40 and TNF-α and produced more IL-1β and CCL3/MIP-1α, and reprogrammed tumor-associated macrophages to an M1-profile [266]. It also stimulated the production of IL-1α, IL-6, and IL-8 by normal human epidermal keratinocytes [267]. In addition, paclitaxel elevated the level and mRNA expression of IL-10 but decreased those of TGF-β1 in the hepatic tissues of rats with liver fibrosis induced by bile duct ligation. It decreased the levels of IL-1β, IL-6, IL-10, and TNF-α in the serum and BALF of mice with septic acute lung injury induced by cecal ligation and puncture [268,269]. Furthermore, paclitaxel treatment induced an increase in the plasma levels of IL-6, IL-8, and IL-10 in patients with breast cancer [270].

Morphine (**36**) is a morphinan alkaloid analgesic derived from the unripe seed pods of the opium poppy (*Papaver somniferum* L.) (Papaveraceae) and is used widely for the treatment of acute and chronic pain, including cancer-associated pain. Morphine binds to opioid receptors in the central nervous system to mediate analgesic activity but also shows certain side effects, such as addiction, dependence, and respiratory depression, while it has a complex relationship with cytokines, either increasing cytokine release or acting as an immunosuppressant to decrease certain cytokines [9,271]. As the first line treatment of cancer-related pain, morphine shows contradictory effects on cancer, either promoting or inhibiting tumor growth through the regulation of proliferation and migration of cancer cells by targeting various signaling pathways, while it regulates cytokine production to suppress the immune system [272]. For example, morphine inhibited the TNF-α production from the peritoneal cavity of Swiss–Webster and C57BL/6 mice to show suppressive effects on the early innate immunity response to an LPS challenge [273]. It increased the synthesis and release of IL-1β from rat microglial cells, the mRNA expression of IL-18 in the murine ileum myenteric plexus neurons, and the protein expression of both cytokines in rat myocardium tissues and cardiomyocytes [274–276]. It also reduced the LPS-induced increase in the release of IL-1β, IL-6, and TNF-α from BV-2 murine microglia cells [277], while elevated levels of these cytokines and lowered levels of IL-4, IL-5, and IL-10 in the injured sciatic nerve of mice induced by prenatal alcohol exposure were observed in mice treated with morphine [278].

Tabersonine (**40**), a monoterpene indole alkaloid derived from the Madagascar periwinkle, *Catharanthus roseus* (L.) G.Don (Apocynaceae), shows multiple biological properties and has been reported for its effects on cytokines [11]. Tabersonine exhibits cytotoxicity against different types of human cancer cells [279], while it prevented an increase in the secretion of IL-6 and IL-8 by M-HeLa human cervical cancer cells infected by the bacterium, *Serratia proteamaculans* [280]. Additionally, tabersonine suppressed the production and/or synthesis of IL-1β, IL-6, and TNF-α by murine RAW 264.7 macrophage and BV-2 microglia cells induced by LPS, by LPS plus ATP, or by oxygen–glucose deprivation/reoxygenation-treated SK-N-SH human neuroblastoma cells [281–283]. Lowered levels of these cytokines were observed in the BALF, lung tissues, and serum from mice with LPS-induced inflammation and in the serum from rats after ischemia/reperfusion (I/R) treatment when the animals were administered with tabersonine [281–284].

An important dimeric indole alkaloid, vinblastine (**42**), derived from *Catharanthus roseus* (L.) G.Don (Apocynaceae), shows anticancer activity and has been developed as a cancer chemotherapeutic agent [285,286]. It also interacts with the cytokine network to regulate the immune response. For example, an increasing tendency in the release of IL-6

and TNF-α from K562 human myelogenous leukemia cells was observed for vinblastine treatment, even though no statistical differences were determined [287]. In a colon tumor animal model developed from the inoculation of MC38 murine colon cancer cells, vinblastine promoted the mRNA expression of IL-6, IL-12, and TNF-α in macrophages isolated from tumors and elevated the levels of IL-12 and IFN-γ in tumor tissues [288].

Tetrandrine (**41**), a bis-benzylisoquinoline alkaloid isolated originally from the roots of *Stephania tetrandra* S. Moore [syn., *Botryodiscia tetrandra* (S. Moore) L. Lian & Wei Wang] (Menispermaceae), has been used clinically for the treatment of several infections and cardiovascular diseases [289]. As a calcium channel blocker, tetrandrine has been demonstrated recently for its potential antitumor activity by acting at multiple molecular targets [289,290], while it regulates cytokines to show anti-inflammatory effects [291]. Tetrandrine suppressed the production of IL-1β, IL-6, and TNF-α from LPS-induced rat astrocytes and the mRNA expression of MIP-1a in these cells [292]. It also suppressed the production and mRNA expression of IL-6, IL-8, and TNF-α from HMC-1 human mast cells induced by phorbol 12-myristate 13-acetate (PMA) and A23187 (calcymycin) [293], and the production of IL-6, IL-8, IL-20, CCL20, and TNF-α from HaCaT human epidermal keratinocytes induced by IL-22 [294]. Moreover, tetrandrine reduced the secretion of IL-1β and IL-6 from mTHP-1 human macrophage-like monocytic leukemia cells stimulated by the supernatants from chimeric antigen receptor T (CAR-T) and Raji cell co-cultures and those of IL-2, IL-8, GM-CSF, IFN-γ, and TNF-α from co-cultured CAR-T and Raji cells [295]. It was found to inhibit the secretion of IL-1β and TNF-α from BV-2 murine microglial cells induced by amyloid beta 1-42 (Aβ1-42) [296]. In in vivo studies, tetrandrine treatment decreased the serum levels of mouse IL-6 and human IFN-γ in mice injected with Raji-LUC cells followed by CAR-T cells and the mRNA expression of IL-1β, MCP-1, and TNF-α in the lung tissues of mice with pulmonary inflammation and fibrosis induced by silicon dioxide [295,297]. It lowered the levels of IL-1β, IL-6, and TNF-α in the serum and hippocampal tissues of rats with subarachnoid hemorrhage established by the endovascular perforation method and downregulated the gene expression of these cytokines in the brain tissues of mice with Alzheimer's disease [296,298]. In a clinical trial study with colon cancer patients, tetrandrine was found to reduce the release of IL-1β, IL-6, and IL-15 by PBMCs cultured with a patient colon tumor tissue culture supernatant and to inhibit HCT116 colon cancer cell proliferation. The levels of IL-1β and IL-15 in the blood samples and of CCL5, CXCL2, and CXCL10 in a tumor tissue culture supernatant were decreased, while both the protein and mRNA expression levels of TNF-α in tumor tissues and blood samples declined when patients were treated with tetrandrine [299].

4. Discussion

Cytokines are involved in cancer cell proliferation and metastasis, of which several have been utilized clinically for the treatment of cancer. Cytokine immunotherapy reshapes tumor immune phenotypes, enhances cancer immunotherapeutic efficacy, and shows therapeutic promise when used in conjunction with other treatments, including small-molecule chemotherapeutic agents [30,36]. In addition, cytokines play an important role in mediating the immune response to infections, of which inflammation can enhance tumor initiation, progression and metastasis, and it can also be triggered by cancer therapy that could cause tissue injury and necrosis [29,300]. The inflammatory cytokine TNF-α is produced by malignant and non-malignant cells, and treatment of ovarian cancer cells with exogenous TNF-α was found to enhance production of other cytokines by the cells and to convert ascitic ovarian xenograft tumors to peritoneal masses [19]. Thus, cytokines may play a role in providing a balance between tumor-promoting and tumor-inhibiting inflammatory responses.

Cancer treatment has been challenged by cancer immune escape, the mechanism of which involves many factors, including PD-1 and PD-L1. PD-1 has been regarded as an immune checkpoint to inhibit the activation of T cells, while PD-L1 promotes the apoptosis of cytotoxic T cells. As an immunomodulatory effector, certain cytokines can up-regulate PD-L1 expression in human cancer cells, including IL-17 and TNF-α, while some other cytokines, such as IL-10 and TGF-β, contribute to tumor immune evasion through their role in cancer initiation and progression [18,29]. Thus, the regulation of cytokines could contribute to the control of cancer immune escape.

Tumors are highly heterogeneous depending on a mutator phenotype. They accumulate multiple mutations due to the skewed DNA damage repair and unstable genome of cancer cells and thus are traditionally regarded as being irreversible [301]. However, the revised tumor clones over the course of the tumor's evolution would incorporate the host's immunologic defenses so as to eliminate mutant cells, while continuously growing cancer cells could remove detrimental mutations [302], indicating a controversial status for heterogeneous tumors. There is increasing evidence of tumor reversion. For example, the neoplastic phenotype can be normalized by the regulatory effects of normal cells through intimate cellular contact, and it was found to be reversed when cancer cells were introduced into developing embryos. These indicate that tumors could be reversible, during which the cell–cell contacts and the embryo microenvironment would each play an essential role, while cell behavior can be modified by morphogens [301,303].

The TME regulates the transcription of the differentiation-associated genes and shapes cell phenotypes, thus becoming important in the normalization of tumor tissues [24–26]. Thus, the malignant phenotype was found to be reversed when human breast cancer cells were treated with inhibitory β1-integrin antibody or its Fab fragments in a 3-dimensional culture [304]. Moreover, the tissue microenvironment has been assumed to be critical in the regulation of normal and neoplastic cell development, and hence its correction could revert the malignant phenotype [305]. Following this, cancer could be reversed by modifying the TME, and engineering biomimetic materials to mimic the embryonic microenvironment would be supportive of such a cancer reversal [306].

Current cancer therapy focuses mainly on killing cancer cells, which, however, secrete various cytokines to support their survival, and cancer genomic instability provides an evolutionary advantage for this. In addition, the cytokines produced can help cancer cells escape from the host immune response and cancer treatments, which could lead to limited therapeutic effectiveness. This indicates that cytokines are important in the regulation of tumor survival and development and contribute to tumor immunity, and their engineering has been proposed as an innovative cancer immunotherapy [34,37]. Accordingly, it could be a promising strategy to decrease the aggressive growth of cancer cells and to normalize them to a non-malignant phenotype through the regulation of cytokines.

Many plant-derived natural products show regulatory activity against cytokines and tumor immunity to mediate their antitumor potential (Table 1). For example, digoxin (**20**) suppressed the mRNA expression levels of several cytokines, prolonged cardiac allograft survival, and attenuated murine colitis by downregulating Th17-related cytokines. It also targeted NKA and the related signaling pathways to mediate its potential anticancer activity [197–200]. Gallic acid (**5**) recalibrated the immune response through the regulation of cytokines but did not impair the host defense system. It potentiated tumor-infiltrating $CD8^+$ T cells to increase cancer cell apoptosis and has thus attracted wide interest as a possible adjunct therapy [93,97]. Quercetin (**8**) diminished the abundance of M2 macrophages and targeted CXCL8 to impede malignant activity and hence has some potential for use as an immunomodulatory agent to treat cancer [80]. Furthermore, vinblastine (**42**) was found to reset tumor-associated macrophages and to promote antitumor immune response [288].

These observations exemplify that natural products of plant origin may revert the malignant phenotype through regulation of the production of cytokines by cancer cells, so that cancer may lose its unrestrained growth and possibly could become a decreased problem for human health.

Table 1. Effects of plant-derived natural products on cytokine production.

No.	Compound	Host Plant	Target Cytokine	References
1	Cardamonin	*Elettaria cardamomum*	IL-1β, IL-6, and TNF-α; IL-10 and TGF-β; IFN-γ, IL-6, IL-15, MCP-1, and TNF-α	[69–77]
2	Curcumin	*Curcuma longa*	IL-1, IL-12, and TNF-α; CXCL8, IFN-γ, IL-1β, IL-2, IL-6, IL-12, TNF-α, IP10, MCP-1, and MIP-1α; IL-4 and IL-13; IL-10; L-18; IL-4, IL-6, IL-21; IL-7 and IL-21; IL-2, IL-4, and IL-10; IL-6 and IL-17A; CCL23, CXCR2, and TGF-β	[81–85]
3	Emodin	Widely occurring in plants	IL-1β, IL-6, and TNF-α; IL-1β, IL-4, IL-6, and TGF-β; IL-1β, TNF-α, and TGF-β; IL-17; IFN-γ and TNF-α	[87–90]
4	Eugenol	*Eugenia caryophyllata*	IL-1, IL-6, and TNF-α; IL-10, IFN-γ, TGF-β, and TNF-α; IL-6, IL-8, and TNF-α; IFN-γ, GM-CSF, MCP-1, and TNF-α	[91,92]
5	Gallic acid	Many edible plants	IL-1, IL-6, IL-12, IL-17, IL-23, TGF-β, TNF-α, CCL2 and CCL7; IL-4, IL-5, and IFN-γ; IL-1β, IL-6, IL-10, and IL-17A; IL-4, IL-6, IL-10, and TNF-α; IFN-γ, IL-6, IL-17A, IL-23 and TNF-α; IL-10, IL-22, and TGF-β; IFN-γ, IL-2, and TNF-α; IL-6 and IL-17A	[93–97]
6	6-gingerol	*Zingiber officinale*	IL-1β, IL-6, and TNF-α; IL-1β, IL-12, and TNF-α; IL-6 and CXCL8	[86]
7	Phyllanthusmin C	*Phyllanthus poilanei*	IFN-γ	[108,109]
8	Quercetin	Many edible plants	IL-1β, IL-6, and TNF-α; IL-1β, IL-6, IL-12a, and TNF-α; IL-1β, IL-6, IL-8 and TNF-α; IL-4, IL-10, and TGF-β; IL-6, G-CSF, GM-CSF, IP-10 or CXCL10, MCP-1, and TNF-α	[78–80]
9	Resveratrol	Many edible plants	IL-1β, IL-6, and TNF-α; IL-1β, IL-6, IL-8, IL-10, and IL-12; IL-1β, IL-6, IL-8, IL-12 and TNF-α; IL-6; IL-10; IL-2, IFN-γ, and TNF-α; IL-6 and TNF-α; GM-CSF and CXCL8	[98–104]
10	Silibinin	*Silybum marianum*	IL-1β, IL-6, and TNF-α; IL-1β, IL-4, IL-10, and TNF-α; IL-1β, IL-6, IL-8, IL-12p70, IL-23, and TNF-α; IL-12, IL-23, and TNF-α; IFN-γ, IL-6, IL-17, IL-22, IL-23, and TNF-α; IL-10 and TGF-β; CINC-1/2a, IL-1α, IL-2, IL-4, IL-13, MIP-3α, IFN-γ, activin A, GM-CSF, FasL, and TNF-α; IL-6 and IL-8; IL-4, IL-5, IL-13, and IFN-γ; TGF-β2	[110–117]
11	Xanthotoxol	*Saussurea obvallata*	IL-1β, IL-6, and TNF-α; IL-1β, IL-8, and TNF-α	[105,106]
12	Andrographolide	*Andrographis paniculata*	IL-1β, IL-6, and TNF-α; IL-1β, IL-6, IL-8; IL-1β, IL-6, IL-8, and TNF-α; IL-6, IL-8, and CCL2; IL-6 and IL-17A/F; IL-12 and TNF-α	[144–149]

Table 1. *Cont.*

No.	Compound	Host Plant	Target Cytokine	References
13	Artemisinin	*Artemisia annua*	IL-1α, IL-1β, IL-6, and TNF-α; IL-1β, IL-13, IL-17, IL-23, and IL-33; IL-1β and IL-10; IL-8; IFN-γ, TNF-α, and TGF-β	[118–124]
14	Betulin	Widely occurring in plants	IL-1β, IL-6, and TNF-α; IL-1β and TNF-α; IL-1β, IL-6 and IL-8; IL-6, IL-10, and TNF-α; IL-8	[179–183]
15	Betulinic acid	Widely occurring in plants	IL-1β, IL-6, and TNF-α; IL-1β, IL-6, IL-10 and TNF-α	[184–186]
16	Brevilin A	*Centipeda minima*	IL-1β, IL-6, and TNFα; IL-6 and IL-8	[125–127]
17	Britanin	*Inula japonica*	IL-1β, IL-6, and TNF-α; IL-1β; IL-2 and IL-10	[128–130]
18	Crocetin	*Crocus sativus*	IL-1β, IL-6, IL-10, and TNF-α; IL-1α, IL-1β, IL-6, IL-8, and TNF-α; IL-6, IL-8, IL-10, and MCP-1; IFN-γ and IL-10; IL-1β and TNF-α	[139–143]
19	Cucurbitacin B	Plants in the family Cucurbitaceae	IL-1β, IL-6, and TNF-α; IL-6, IL-10, IL-17A, and TNF-α	[175–178]
20	Digoxin	Plants of the genus *Digitalis*	IL-1β, IL-17A, and TNF-α; IL-1β, IL-6, IL-17, and IL-23; IFN-γ, IL-17A/F, and GM-CSF; IL-17A, IL-17F, IL-23R, and IFN-γ; IL-10	[195–202]
21	Eburicoic acid	*Curculigo orchioides*	IL-1β, IL-6, and TNF-α; IL-1β, IL-6, and IL-18; IL-1β and TNF-α	[166–169]
22	Ginkgolide B	*Ginkgo biloba*	IL-1β, IL-6, and TNF-α; IL-1α, IL-1β, IL-6, IL-12, IL-12p70, IL-18, and TNF-α; IL-1β, IL-6, IL-10, MCP-1, and TNF-α; IL-4, IL-5, IL-12, IL-13, and IFN-γ	[150–153]
23	Ginsenoside C-K	*Panax ginseng*	IL-1β. IL-6, and TNF-α; IL-1β and TNF-α; IL-1β, IL-6, and IL-8	[166,170–174]
24	Jolkinolide B	*Euphorbia jolkini*	IL-1β. IL-6, and TNF-α; IL-4, IL-5, IL-13, and TNF-α; IL-6 and TNF-α; IFN-γ, IL-1α, IL-1β, IL-12, and TNF-α; IL-4, IL-10, and TGF-β	[154–158]
25	Limonin	*Citrus limon*	IL-1β, IL-6, and TNF-α; IL-6 and TNF-α	[119,193,194]
26	Parthenolide	*Chrysanthemum parthenium*	IL-1β, IL-6, and TNF-α; IL-1β and IL-8; IL-4; IL-6; IL-10; IL-12; IL-6, MCP-1, and TNF-α; IFN-γ, IL-17a/f, IL-22, and TNF-α; IFN-γ, IL-2, and IL-4; IFN-γ, IL-2, IL-4, IL-5, and IL-13	[131–138]
27	Triptolide	*Tripterygium wilfordii*	IL-1β, IL-6, IL-8, IL-10, IL-12, TNF-α, and INF-γ; IL-1β, IL-6, IL-8, IL-5, IL-13, and CCL11; IL-1β and IL-8; IL-6, IL-17A, IL-22, IL-23, and TNF-α; IL-10 and TGF-β	[43,119,159–165]
28	Ursolic acid	Widely occurring in plants	IL-1β, IL-6, and TNF-α; IL-1β, IL-6, IL-18, and TNF-α; IL-1β, IL-6, TNF-α, and CCL-2; IL-1β, IL-6, TNF-α, and GM-CSF; IL-12 and TNF-α; IL-10 and TGF-β	[166,187–192]
29	Withaferin A	*Withania somnifera*	IL-1β, IL-6, TNF-α; IL-10 and TGF-β; IL-18 and MIP-2β; IL-10	[203–209]

Table 1. *Cont.*

No.	Compound	Host Plant	Target Cytokine	References
30	Berberine	*Coptis chinensis*	IL-1β, IL-6, and TNF-α; IL-1β, IL-6, and MCP-1; IL-1β, IL-6, IL-8, IL-12, IFN-γ, and TNF-α; IL-1β and TNF-α; IL-2, IL-4, IL-6, IL-10, IL-17A, TNF, and IFN-γ; IL-4, IL-10, IL-27, IL-33, IL-35, and TGF-β; IL-10 and TGF-β; IL-17, IFN-γ, and TNF-α; IL-17A and IFN-γ	[240–248]
31	Camptothecin	*Camptotheca acuminata*	IL-1β, IL-6, and TNF-α; IL-12B, IL-16, IL-22, IL-17F, CCL5, CCL17, CCL21, CCL22, CXCL10, LTA, TNF, SPP1; MCP-1 and CXCL10; IFN-α and -γ	[249–254]
32	Capsaicin	Chili peppers (*Capsicum* species)	IL-1β, IL-6, and TNF-α; IL-1β, IL-18, and TNF-α; IL-1β, IL-1Ra, IL-6, IL-10, IFN-γ, and TNF-α; IL-1β, IL-10, IL-17, IFN-γ, and TNF-α; IL-4, IL-6, IL-8, and TNF-α	[225–231]
33	Colchicine	*Colchicum autumnale*	IL-1β, IL-6, and TNF-α; IL-3, IL-10, GM-CSF, and IFN-γ; IL-6, TGF-β, and TNF-α; IL-6; IL-6 and IL-8; IL-10	[9,258–263]
34	Ellipticine	*Ochrosia elliptica*	IL-6 and TNF-α; IL-6 and CXCL-1	[255–257]
35	Melatonin	Many edible plants	IL-1β, IL-6, and TNF-α; IL-1β, IL-6, IL-10, and TGF-β1; IL-1β, IL-10, TNF-α, and TGF-β1; IL-10, IL-12p70, IL-17 and TNF-α; IFN-β, IL-1β, and TNF-α; TNF-α and IFN-γ; IL-6, IL-10, IFN-γ, and TNF-α	[211–218]
36	Morphine	*Papaver somniferum*	IL-1β, IL-6, and TNF-α; IL-1β and IL-18; IL-4, IL-5, and IL-10; TNF-α	[9,271–278]
37	Nicotine	*Nicotiana tabacum*	IL-1β, IL-6, IL-17, and IL-21; IL-2, IL-6, IL-8, IL-10, and TNF-α; IL-1β, MCP-1, and TNF-α	[219–224]
38	Paclitaxel	*Taxus brevifolia*	IL-1β, IL-6, IL-10, and TNF-α; IL-6, IL-8, and IL-10; IL-1α, IL-6, and IL-8; IL-1, IL-6, IL-8, IL-12, Il-18, TNF, and TGF; IL-12p40 and TNF-α; IL-1β and CCL3 or MIP-1α; IL-10 and TGF-β1	[11,43,264–270]
39	Piperine	*Piper nigrum*	IL-1β, IL-6, and TNF-α; IL-1β, TNF-α, and IFN-γ; IL-1β and TNF-α; IL-6, IFN-γ, and TNF-α; IL-6; IL-1β, IL-8, and MCP-1; IL-8 and IL-10	[9,232–239]
40	Tabersonine	*Catharanthus roseus*	IL-1β, IL-6, and TNF-α; IL-6 and IL-8;	[11,279–284]
41	Tetrandrine	*Stephania tetrandra*	IL-1β, IL-6, and TNF-α; IL-1β, IL-6, and IL-15; IL-1β and IL-6; IL-1β and IL-15; IL-1β and TNF-α; IL-1β, MCP-1, and TNF-α; IL-2, IL-8, GM-CSF, IFN-γ, and TNF-α; IL-6, IL-8, IL-20, CCL20, and TNF-α; IL-6 and IFN-γ; CCL5, CXCL2 and CXCL10	[289–299]
42	Vinblastine	*Catharanthus roseus*	IL-6, IL-12, and TNF-α; IL-6 and TNF-α; IL-12 and IFN-γ	[285–288]

Moreover, the pro-tumorigenic cytokines IL-1β, IL-6, and TNF-α affect all stages of tumor development [14], against which many natural products and their producing organisms show inhibitory activity (Table 1). These products have been used as therapeutic agents for the treatment of various human diseases, of which a number of agents have been

proved to regulate the release and protein and gene expression of cytokines in cancer and immune and other non-malignant cells. These include several edible plants, such as various berries, garlic, ginger, saffron, and turmeric and some of their purified constituents. Such products frequently inhibit the release and expression of the tumor-promoting cytokines, such as IL-1β, IL-6, and TNF-α, but increase those of the tumor-inhibiting cytokines, like IL-10, IFN-a, and IFN-γ (Figure 7), and they thus could show potential antitumor activity.

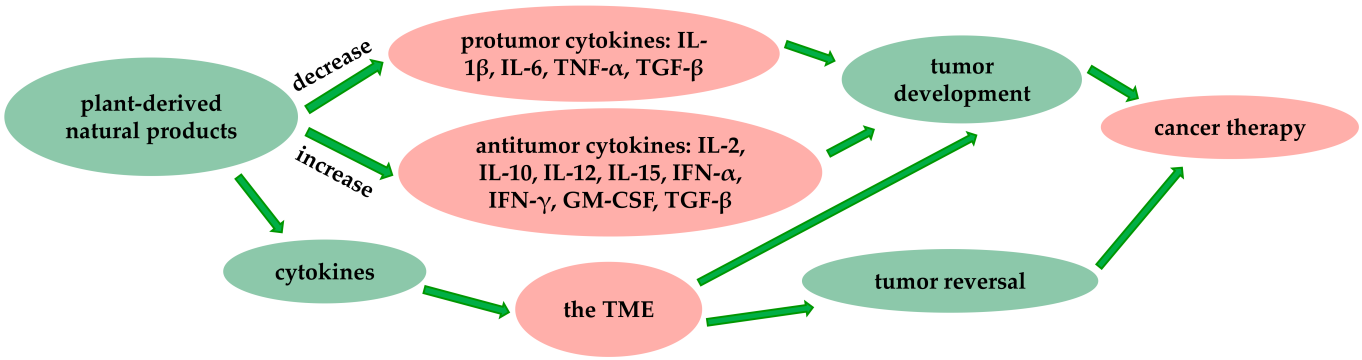

Figure 7. Major correlations among plant-derived natural products, cytokines, tumor development and reversal, and cancer therapy.

As summarized in Table 1, the major compounds presented in the present contribution showed inhibitory activity against the pro-inflammatory/protumor cytokines (e.g., IL-1, IL-6, and TNF-α) and/or activatory property toward the anti-inflammatory/antitumor cytokines (e.g., IL-4, IL-10, IL-11, IL-13, and TGF-β) in the cancer or infection models used. As a key host defense against pathogens, inflammation is closely correlated with cancer, for which cytokines are critical. There are many different inflammatory cells and mediators in the TME, while chronic inflammation can increase cancer occurrence risk. Thus, tumor-associated inflammation could offer a target for the treatment of malignancies [300,307,308]. Natural products have been well demonstrated for their anticancer and anti-infection activities through regulation of cytokine production and the TME via various mechanisms, indicating that these compounds could be promising lead compounds by targeting cytokines and the TME [12,13]. Several cytokines have been used as immunotherapeutic agents in clinical oncology, including IFNs and ILs, and their efficacy has been improved by advanced biomaterial delivery platforms [309]. Thus, natural products could also show some potential for adjuvant use in cancer cytokine immunotherapy.

Importantly, the TME also plays a critical role in cancer reversal. Many natural products show regulatory effects on the TME, and their properties may vary on the cells or tissues evaluated, especially normal and cancer cells or tissues, indicating their possible effects on tumor reversion [24]. In the TME, cytokines mediate their functions through the regulation of communication between cancer and stromal cells. In three-dimensional (3D) cell culture, cells are cultured in a three-dimensional environment to allow them to interact with other surrounding cells, which bridges the 2D cell culture and animal experiments to mimic the TME to evaluate more accurately the antitumor potential of lead compounds [310,311]. Thus, additional utilization of 3D cell culture models can be expected in future evaluation of the potential effects of natural products on tumor reversion. However, the general poor translational properties of natural products, including low solubility and bioavailability, tend to limit their development as pharmaceutical agents. Thus, advanced biotechnology, including synthetic modification and nanodrug delivery systems, could be employed to offer an advantage in this regard [11,119].

5. Conclusions

Cytokines are the main components of the TME and also contribute to tumor immunity. It has been amply demonstrated that cancer can be reversible, the mechanism for which the TME plays a key role. The present review addresses these issues, with the potential effects of selected plant-derived natural products on cytokine production, secretion, and expression, and cancer reversal having been discussed. The natural products presented include alkaloids and other nitrogen-containing compounds, such as berberine, camptothecin, capsaicin, colchicine, ellipticine, melatonin, morphine, and paclitaxel, in addition to isoprenoids, like andrographolide, artemisinin, and betulin, as well as phenolic compounds, including cardamonin, curcumin, and emodin. These substances all show effects on cytokines, indicating their possible use in normalizing cancer cells and tumors.

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Abbreviations

The following abbreviations are used in this manuscript:

Akt (PKB)	Protein kinase B
AP-1	Activator protein-1
BALF	Bronchoalveolar lavage fluid
CAR-T	Chimeric antigen receptor T
CCL2	Chemokine (C-C motif) ligand 2
CD163	Cluster of differentiation 163
CIA	Collagen-induced arthritis
CINC-1	Cytokine-induced neutrophil chemoattractant-1
COX-2	Cyclooxygenase-2
CSF	Colony-stimulating factor
CXCL12	C-X-C motif chemokine ligand 12
DC	Dendritic cell
DSS	Dextran sulfate sodium
EAE	Experimental autoimmune encephalomyelitis
ERK1/2	Extracellular signal-regulated kinases 1/2
EV	Extracellular vesicle
GM	Granulocyte-macrophage
gp130	Glycoprotein 130
HFD	High-fat diet
HUVEC	Human umbilical vascular endothelial cell
IFN	Interferon
IL	Interleukin

IMP	Imidazole propionate
IMQ	Imiquimod
IP-10	Interferon γ-induced protein 10 (CXCL10)
JAK	Janus kinase
LPS	Lipopolysaccharide
LTA	Lymphotoxin-α
MAP	Mitogen-activated protein
MAPK	Mitogen-activated protein kinase
MCP-1	Monocyte chemoattractant protein-1
MIA	Monosodium iodoacetate
MIF	Macrophage migration-inhibitory factor
MIP	Macrophage inflammatory protein
MMP	Matrix metalloproteinase
MPP	1-Methyl-4-phenylpyridinium
MPTP	1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine
mTOR	Mammalian target of rapamycin
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NK	Natural killer
NKA	Na^+/K^+-ATPase
OVA	Ovalbumin
Ox-LDL	Oxidized low-density lipoprotein
PBMC	Peripheral blood mononuclear cell
PD-1	Programmed cell death protein 1
PD-L1	Programmed cell death protein 1 ligand
PHA	Phytohaemagglutinin
PI3K	Phosphoinositide 3-kinase
SDF-1	Stromal cell-derived factor-1 (CXCL12)
SH2	Src homology 2
SPP1	Secreted phosphoprotein 1
STAT	Signal transducers and activators of transcription
TAM	Tumor-associated macrophage
Th	Helper T
TIE	Tumor immune escape
TGF-β	Transforming growth factor-β
TME	Tumor microenvironment
TNBC	Triple-negative breast cancer
TNF	Tumor necrosis factor
Tregs	T regulatory cells
VEGF	Vascular endothelial growth factor
Wnt	Wingless-related integration site
YAP	Yes-associated protein

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