Herbs and plants in immunomodulation (Review)

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Abstract. The present review article aimed to present a focused summary of the main immunomodulatory properties of some of the most frequently used herbaceous plants either in traditional medicine or as food supplements: andrographis (*Andrographis paniculata*), astragalus (*Astragalus propinquus/membranaceus*), black cumin (*Nigella sativa*), cardamom (*Elettaria cardamomum*), purple coneflower (*Echinacea*), ginger (*Zingiber officinale*), licorice (*Glycyrrhiza glabra*), shiitake (*Lentinula edodes*) and turmeric (*Curcuma longa*). These plants were selected based on their popularity, accessibility as a supplement, their known effects on the immune system, and the amount of scientific research performed on their extracts and active ingredients. The present review also discusses the anti-inflammatory, antioxidant and anti-cancer properties of these plants in relation to their immunomodulating mode of action. In this manner, the present review aims to provide a more targeted, manageable and useful data set, that may serve as the basis for diversification, and subsequent and more detailed research on these plants and their compounds.

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1. Introduction

Medicinal herbs and spices have been used throughout human history for their healing properties and their quality-of-life benefits. They have constituted the major therapeutics in ancient medicinal systems, such as traditional Chinese medicine (TCM) (1), Ayurveda (2), Kampo (Japan) and numerous others (3). The interest in medicinal plants and their extracts and multi-component drugs that include active substances of natural origin has increased exponentially over the past few decades. The rationale and main goal is the development of not only potent, but also safe therapeutic compounds that would not elicit the plethora of unwanted side-effects otherwise caused by synthetic allopathic medications. Therefore, the immunomodulating activity of numerous traditionally used herbs and spices has gained increasing attention in recent years.

The immune system is relatively complex; thus, any factors influencing the functions of the immune system may also influence other systems in the human body, such as the nervous system, endocrine system, metabolism etc. Consequently, research in this field is quite diverse, and the modulation of the immune system aims to prevent disease, as well as to identify novel targets that may serve as the basis for novel and more effective therapeutics. One of the main approaches in all traditional medicine systems for preserving health and wellbeing and at the same time preventing disease, is a healthy wholesome diet that includes a number of plant-based foods. This diet has a specific focus on herbs and spices, as these can support the healthy and balanced functioning of the immune system. In this respect, studies have indicated that diet influences the various intrinsic and extrinsic factors of the immune system (4,5).

Herbs and spices have been a staple in the natural diets of all cultures globally. They have been highly valued for their anti-inflammatory properties, particularly considering

that one of the major causes for the development of disease is low-grade chronic inflammation. Taken together, there are countless inflammation-lowering plants in different parts of the globe; some of these are widely known and can be found relatively easily around the globe, including thyme, oregano, rosemary, sage, basil, mint, dill, parsley, fenugreek, clove, nutmeg, cinnamon, turmeric, tulsi, lemon grass, ginger, chili pepper, pepper and numerous others (6). A vast variety of their constituents, such as flavonoids, polysaccharides, lactones, alkaloids, diterpenoids, glycosides etc. have been reported to be responsible for the immunomodulatory and anti-inflammatory properties of these plants. Notably, some of these compounds, such as curcumin, gingerol and capsaicin, appear to inhibit one or more of the steps linking pro-inflammatory stimuli to cyclooxygenase (COX) activation (7). In addition, the activation of NF-κB, a key regulator of the production of COX-2, is associated with a variety of inflammatory diseases, including cancer, atherosclerosis, myocardial infarction, diabetes, allergies, asthma, arthritis, Crohn's disease, multiple sclerosis, Alzheimer's disease, osteoporosis, psoriasis and septic shock (8,9); in this regard, the inhibition of COX should prevent the activation of the alternative NF-κB pathway and in this manner, may reduce inflammation and related symptoms (10).

Summarizing the nutraceutical properties of such an immense variety of herbs would be an extremely difficult, if not impossible, task, for any review article. Hence, the present review concentrated on a selection of promising, yet at the same time, quite popular and widely accessible plants, such as *Andrographis* (*Andrographis paniculata*), *Astragalus* (*Astragalus propinquus/membranaceus*), black cumin (*Nigella sativa*), cardamom (*Elettaria cardamomum*), purple coneflower (*Echinacea*), ginger (*Zingiber officinale*), licorice (*Glycyrrhiza glabra*), shiitake (*Lentinula edodes*) and turmeric (*Curcuma longa*). These plants are often promoted as natural immune boosters in the form of nutritional supplements. The key signal transduction pathways and activation methods for each herb are illustrated in Fig. 1.

2. *Andrographis (Andrographis paniculata)*

Andrographis is a herbaceous plant of the Acanthaceae family, known in Europe as the 'King of Bitters'. Traditional applications in Ayurvedic medicine and TCM, among others, vary widely and include supporting liver and gallbladder function, detoxification, digestion, immune response (through the modulation of the levels of immune cells), maintaining normal body temperature, as well as use for its antiviral, cardio protective and hepatoprotective properties (11). According to previous phytochemical studies, the aerial parts of the plant possess most of the medicinal properties and are the source for the isolation of diterpenoid lactones, which are the major phytochemical and flavonoid constituents; the roots are the source of several different compounds, such as xanthones, some noriridoids and trace/macro elements (12-14). Other researchers, using a broad variety of formulations, extracts and pure compounds, have demonstrated anti-inflammatory, immunomodulating, antioxidant, cytotoxic, anti-microbial and anti-malarial properties (15).

Various extraction methods of *Andrographis paniculata* have been tested, based on determining free radical scavenging of extracts using the high-performance liquid chromatography-ultraviolet mass spectrometry method and the DPPH test (16). The main antioxidant compounds in plants are known as flavonoids and phenols (17). A previous study concluded that an aqueous extract has a higher concentration of total flavonoids compared to an ethanol extract, and a radical scavenging activity of 66.8 vs. 57.8% in ethanol; however, the ethanol extract appears to have more phenols compared to the aqueous extract, even though the potency of the aqueous extract is higher in antioxidant activities (16). Several phytochemicals, extracted from the leaves of *Andrographis* (namely andrographolide, neoandrographolide, isoandrographolide, andrograpanin, 7-*O*-methyl-wogonin, 14-deoxy-11,12-didehydroandro-grapholide and skullcapflavone) have been examined for their anti-inflammatory and anti-allergic effects *in vitro* (18,19). The majority of these compounds have been shown to induce a concentration-dependent inhibition of the release of inflammatory mediators from cultured macrophages, stimulated by lipopolysaccharides (LPS), such as nitric oxide (NO) and prostaglandin E2, interleukin (IL)-1β and IL-6. The compound with the broadest effect appeared to be andrographolide, whereas 7-*O*-methylwogonin was unique in its potent dose-dependent ability to inhibit A23187-induced (calcimycin-stimulated) histamine release in RBL-2H3 rat basophil leukemic cells (18). In a previous study, andrographolide, dehydroandrographolide and neo-andrographolide were shown to exhibit anti-inflammatory effects by interfering with both COX-1 and COX-2 enzyme activity (20). Dehydroandrographolide demonstrated the highest efficacy in modulating the level of LPS-induced TNF-α, IL-6, IL-1β and IL-10 secretion in human blood, in a concentration-dependent manner; its mechanism of action may be related to the downregulation of the expression of genes involved in the inflammatory cascade (20), as research using mice has demonstrated that dehydroandrographolide can inhibit NF-κB activation in mice (21). The diterpenes, andrographolide and neoandrographolide, have been shown to induce significant antibody responses in mice, delayed hypersensitivity response against sheep red blood cells, as well as non-specific immune responses (22). When ethanol extract was applied instead of purified diterpenes, an immune response was still observed, albeit considerably milder, suggesting that other constituents in the alcohol extract may provide an entourage immunostimulating effect (22).

Further studies investigating the mechanisms of action are expected to contribute towards an improved assessment and understanding of the complex pharmacological effects of this plant. In addition, safety should be evaluated through laboratory and clinical studies on the toxicity of the different extracts and certain pure phytochemical isolates.

3. *Astragalus (Astragalus propinquus/membranaseus)*

Astragalus is a leguminous plant and its main chemical composition includes astragaloside, Astragalus polysaccharide (APS), astragalus flavonoids, selenium and other trace elements (23). In TCM, where it is known as Huangqi, it is used both as a medicine and food; it is believed to stimulate

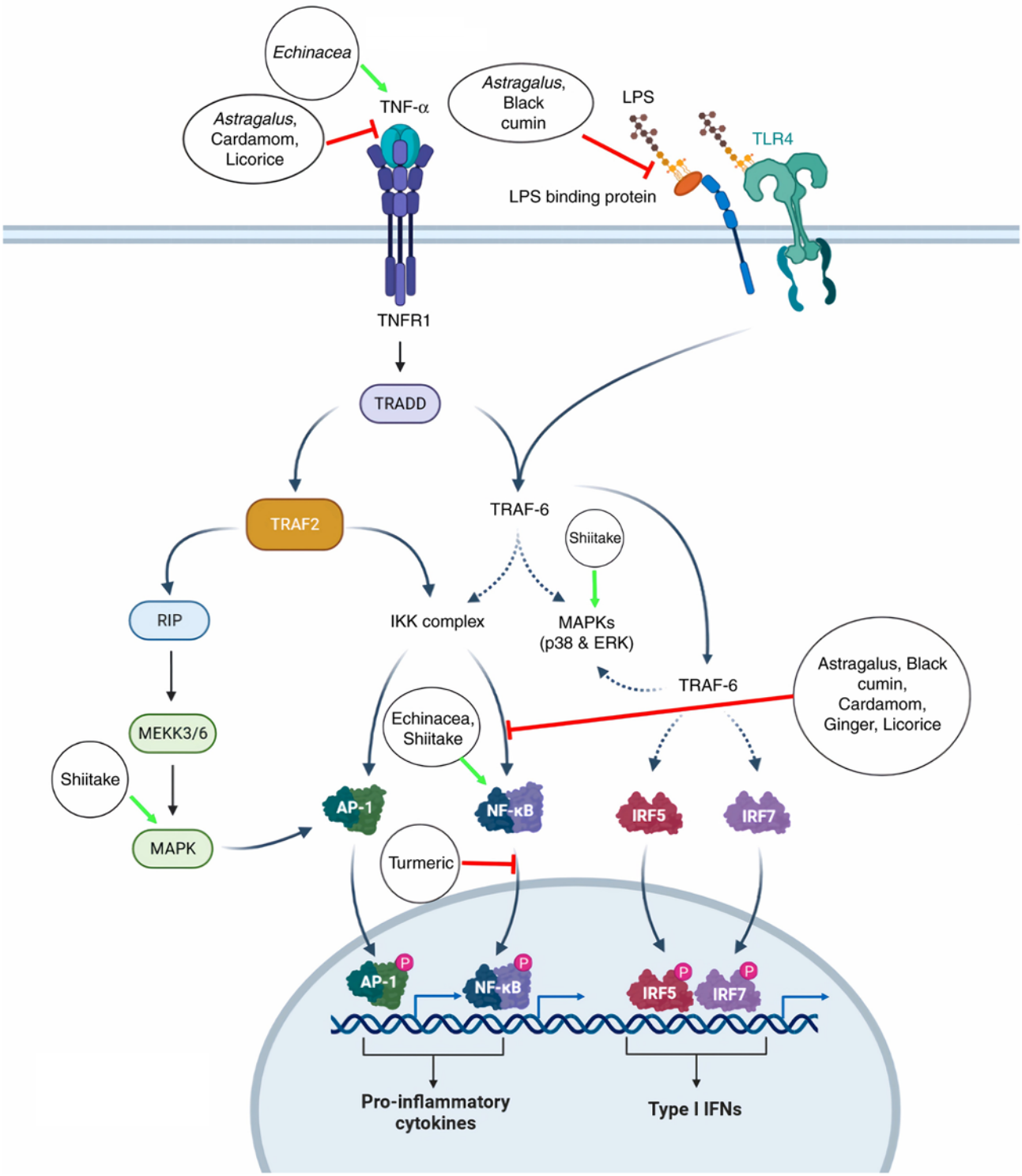

Figure 1. Schematic representation of the diverse actions of each herb and the transduction pathways that they are involved in. Their activation and inhibitory activities are marked by green and red arrows, respectively. LPS, lipopolysaccharide; TLR, Toll-like receptor; TRADD, TNFR1-associated death domain protein; TRAF, TNF receptor associated factor; IRF, interferon regulatory factor; AP-1, activator protein 1.

the spleen and to replenish the vital energy that is considered to circulate the body in currents, also known as the qi (23). *Astragalus* is used to treat weakness, wounds, anemia, fever, multiple allergies, chronic fatigue, loss of appetite, uterine bleeding and prolapse (24). The main pharmacologically active ingredient is APS, a type of water-soluble heteropolysaccharide extracted from the stems or dried roots (25). APS exerts multiple bioactive effects, several of which have been thoroughly investigated, particularly for their activity in immune regulation and anti-aging. APS has further gained attention due to its ability to reduce blood sugar levels and lower blood lipid levels, as well as due to its antitumor, anti-fibrotic, antibacterial and antiviral effects, and its radiation shielding properties (23). As regards immunomodulation, APS has been shown to activate mouse macrophages and B-cells, rather than T-cells, leading to proliferation and

cytokine production via the activation of Toll-like receptor (TLR)4 (1). It has also been reported to inhibit the growth of the breast cancer cell line, MDA-MB-468 (26). Xu *et al* (27) demonstrated that APS strongly promoted the phagocytosis of *Mycobacterium tuberculosis* and the secretion of IL-1α, IL-6 and TNF-α by activated macrophages. Experimental data have also indicated that this particular polysaccharide can initiate splenocytes to secrete IL-2, IL-3, IL-4 and IL-6, and also induce interferon (IFN) production (23), with substantial evidence also pointing towards a concentration-dependent initiation of IL-10, IL-12 and IL-2 secretion (28). Furthermore, in carp models, APS has been shown to increase the levels of IL1-β, lysozyme C and TNF-α in the kidneys, gills and spleen, in a dose-dependent manner (29). Various experiments using H22 tumor-bearing mice have also demonstrated that the administration of APS increases the production of IL2, IL6 and TNF-α, which further highlights the effects of APS on the immune system and subsequently, its antitumor activity (30,31).

Several preclinical studies and clinical trials have demonstrated that *Astragalus* has more potent anticancer effects than immunomodulatory properties (32-34) and for this reason, it is recommended to cancer patients as a complementary and alternative therapy (35). Nonetheless, it has also exhibited immense potential in balancing Treg/Th17 cells, and is thus being investigated as a potential complementary treatment for patients with asthma (36) and perhaps for patients with diabetic nephropathy (37).

4. Black cumin (*Nigella sativa*)

Black cumin, also known as *Nigella sativa*, is a widely used medicinal plant of the Ranunculaceae family. Its popularity encompasses almost all traditional medicinal systems, such as Indian, Ayurveda and Siddha, Islamic Tibb-e-Nabawi and Western herbalism. In Bulgarian folklore, it is referred to as 'the herb that cures everything but death'. Black cumin has been broadly used as a (skin) tonic, a digestive, an anti-diarrheal, an appetite stimulant, an anti-bacterial, an antihypertensive, a diuretic and an analgesic. The majority of its therapeutic effects are considered to be due to thymoquinone (TQ), a major bioactive component of black cumin essential oil (38).

In vitro studies have demonstrated that the aqueous extract of black cumin exerts an anti-inflammatory and immunomodulatory effect, as it significantly enhances splenocyte proliferation in BLAB/c mice and C57/BL6 primary cells in a concentration-dependent manner (39). Specifically, the aqueous extract appears to favor the secretion of Th2, as opposed to Th1 cytokines by splenocytes; the secretion of key pro-inflammatory mediators, such as IL-6, TNF-α and NO by macrophages is significantly suppressed and the cytotoxic activity of natural killer (NK) cells against YAC-1 tumor cells is significantly enhanced (40). This suggests that black cumin bioactive compounds may be used as therapeutic agents for the regulation of several immune reactions in variety of conditions and diseases, such as cancer (40). In addition, the immunomodulatory activity of black cumin seed can be used for the prophylaxys of opportunistic infections and as adjuvant treatment in certain oncological patients (39). Other observations indicate that the seeds of *Nigella sativa* may represent a potential immunosuppressive cytotoxic agent (41). Preventative oral administration of N. sativa oil to rats daily has been shown to significantly reverse the reduction of hemolysin antibody titers related to the applied whole body gamma irradiation (42). This suggests that the oil may constitute a promising radioprotective agent against ionizing radiation, particularly against the immunosuppressive and oxidative effects of the latter (42).

Both the aqueous and alcoholic extracts of black cumin exhibit anti-inflammatory and analgesic properties, which are considered to be exerted by their TQ content. The concentration of the latter varies greatly throughout the different parts of the plant; it is 12-fold higher in the leaf callus than the seed extract. The anti-inflammatory effects of TQ on inflamed rat mix glial cells is evidenced by a significant reduction in NO production (43). In addition, oxidative stress and inflammation related to osteoporosis appear to be beneficially influenced by TQ via the inhibition of inflammatory cytokine production, such as IL-1 and IL-6, and the element of the NF-κB consensus site (44). It also appears to reduce the synthesis of monocyte chemoattractant protein (MCP)-1, TNF-α, IL-1β and COX-2 by pancreatic ductal adenocarcinoma cells in a concentration- and time-dependent manner. These results suggest that TQ may be a promising agent that combines the inhibition of proinflammatory pathways with a pro-apoptotic mode of action (45). Other researchers have also demonstrated the anti-inflammatory effects of TQ during an allergic response in the lungs, through the inhibition of prostaglandin D2 synthesis and Th2-driven immune responses (46).

Last but not least, a clinical trial was conducted as a prospective and double-blind study with descriptive analysis to investigate the anti-inflammatory effects of *Nigella sativa* in patients with allergic rhinitis (47). The results revealed that *Nigella sativa* reduced the congestion of the nasal mucosa, itching, mucosal pallor, runny nose and sneezing attacks, thereby suggesting that it may be beneficial as a treatment option when other anti-allergic drugs must be avoided for various reasons (47).

5. Cardamom (*Elettaria cardamomum*)

Cardamom is a traditional aromatic plant from the family of Zingiberaceae. The chemical composition of cardamom varies, depending on its origin and maturity stage. The seed contains 2 to 5% of the volatile compounds that contribute to the sweet and spicy flavor. The essential oil contains a considerable number of bioactive compounds, such as α-pinene, α-phellandrene, β-pinene, myrcene, limonene, sabinene, 1,8-cineole, linalool, terpinolene, γ-terpinene, linalyl acetate, α-terpineol, terpinen 4-ol, α-terpinyl acetate, geraniol, citronellol, trans-nerolidol and methyl eugenol (48). The particular flavor of cardamom is mainly owned by α-terpinyl acetate and 1,8-cineole (19). Over the years, cardamom has been used in the treatment of disorders, such as asthma, indigestion and congestive jaundice (49).

It has been demonstrated that cardamom possesses various pharmacological properties, such as antioxidant, anti-inflammatory, anticancer and antimicrobial properties (48). The

aqueous extract exerts immunomodulatory effects as well, which have been validated *in vivo*. In particular, it has been shown to significantly enhance splenocyte proliferation in a synergistic and concentration-dependent manner; based on an enzyme-linked immunosorbent assay, cardamom was shown to significantly inhibit the release of Th1-cytokines from splenocytes and to enhance Th2-cytokine release (50). Previous research has indicated that cardamom extract exerts anti-inflammatory effects in BALB/c mice, as it significantly enhances the cytotoxic activity of NK cells, thereby indicating an anticancer potential (50). Additional research has demonstrated that cardamom modulates the status of proliferation, and the modification of COX-2 and inducible nitric oxide synthase (iNOS) expression in apoptotic processes, suggesting that it may confer a protective effect in experimentally-induced colon carcinogenesis (51).

6. *Echinacea*

Echinacea belongs to a genus of herbaceous flowering plants, commonly known as coneflowers, with *Echinacea purpurea* being the herb most commonly used either to treat or prevent the common cold, despite the existence of contradictory data regarding its efficacy. For example, a 2014 systematic review claimed that *Echinacea* was ineffective against the common cold (51), whereas a subsequent meta-analysis found some evidence that it reduces the risk of repetitive respiratory infections (52,53).

Three species of *Echinacea* are widely used medicinally: *E. purpurea*, *E. angustifolia*, and *E. pallida* (54). Preparations of the root and aerial parts of the three species are all currently being promoted as immune stimulants (55). The immune-boosting effects of *Echinacea* are considered to result primarily through the targeting of non-specific immune mechanisms, including phagocytic activity, macrophage activation and NK cell activity. These effects have been demonstrated *in vitro*, where both the juice from the aerial part of *E. purpurea* and alcohol extracts from roots of *E. purpurea*, *E. angustifolia* and *E. pallida* have been used (56,57). In macrophages, phagocytosis and cytokine production (evidenced as increased levels of TNF-α, IL-1 and IFN-β) appear to be enhanced following treatment with *Echinacea* extracts (58). Increased leukocyte mobility and the activation of NK cells has also been reasonably demonstrated in animals and humans (58-61). Notably, *E. purpurea* polysaccharide-enriched extracts can promote the phenotypic and functional maturation of dendritic cells via the modulation of the JNK, p38 MAPK and NF-κB pathways (62). In addition, Fu *et al* (63) demonstrated that *Echinacea* extract was a potent activator of murine bone marrow-derived macrophages by increasing the expression of CD80, CD86 and MHCII molecules, and by upregulating the levels of markers of classically activated macrophages (M1), including CCR7, and the production of IL-1β, IL-6, IL-12p70, TNF-α and NO.

There are still open questions related to the long-term use of *Echinacea*. Although primarily considered for therapeutic purposes, some authors suggest the use of *Echinacea* as a prophylactic during winter (64). The long-term effects of *Echinacea* (in years) are unknown.

7. Ginger (*Zingiber officinale*)

Ginger (*Zingiber officinale* Rosc.) belongs to the family of Zingiberaceae. It has long been cultivated as a flavoring spice to Indian food (65) and is generally widely used in South East Asia. The constituents of ginger are numerous and vary, depending on the place of origin and form of rhizomes, e.g., fresh or dry. The ginger rhizome contains multiple compounds of interest, such as carbohydrates, minerals, phytochemicals, phenolic compounds, terpenes, polysaccharides, lipids, organic acids, and raw fibers (66). It also contains appreciable amounts of vitamins and minerals and some enzymes, among which the potent proteolytic enzyme, zingibain, appears to be of particular interest (67). Ginger contains >40 antioxidant compounds, which can be used to treat various inflammatory conditions (68).

Ginger, being both a traditional spice and medicine in TCM and Ayurveda, is also consumed in various forms in order to boost immunity, reduce nausea and to ease digestion, as evidenced by several clinical trials, while the dietary supplementation of the powdered rhizome (vertical root) daily may increase testosterone levels (69,70). As regards immune function, ginger has been shown to successfully lower TNF-α and IL-1β levels compared to placebo in patients knee osteoarthritis, where pain is caused by joint inflammation due to the overproduction of synovial cytokines; this demonstrates its ability to modulate inflammatory cytokine production in chronic disease (71). The structurally related substances, gingerol and shogaol in ginger inhibit prostaglandins by preventing the biosynthesis of prostaglandin synthase, and may also be effective against arachidonate 5-lipoxygenase, which is part of the leukotriene biosynthesis (2). Overall, ginger is believed to inhibit the synthesis of IL-1, TNF-α and IL-8, acting in a pro-inflammatory cytokine manner, through a mechanism that includes influencing of coding genes (72,73). In another study, [6]-shogaol was shown to downregulate inflammatory iNOS levels by inhibiting the expression of the COX-2 gene in macrophages, and the activation of NF-κB by disrupting the activation PI3K/Akt/IκB-kinases IKK and MAPK (74).

8. Liquorice (*Glycyrrhiza glabra*)

Liquorice (or licorice) is a plant of the family Fabaceae (*Glycyrrhiza glabra* L.). The use of licorice is well described and already has a history of several thousands of years. The plant has been implemented in TCM and medieval medicine as a tonic, to promote vitality, and to treat ulcers, gastritis, a variety of infections and other inflammatory conditions. The most significant compounds in terms of pharmacological activity include flavonoids, triterpenes and saponins, where the main bioactive compound is glycyrrhizin (5-24%) (75). The composition varies greatly depending on the species, geographical location and environmental conditions, with the species growing in Iran, China and Russia having the highest glycyrrhizin contents (76).

Licorice polysaccharides have demonstrated a potential immunomodulatory and anticancer effect in mice, by inducing and upregulating the expression of IL-7, an antitumor cytokine, as well as by affecting T-lymphocytes (77). Glycyrrhizin,

glabridin and isoliquiritigenin have exhibited apoptotic and anti-proliferative activity on cancer cells *in vitro* (78,79). Similarly, 18β-glycyrrhetinic acid, has exhibited immunomodulatory activity by enhancing T-cell proliferation, thereby increasing leukocyte concentration in murine models (80). The polyphenols of licorice induce apoptosis by upregulating the expression of Bax and Bid proteins and via the downregulation of Bcl-2, thus affecting the caspase pathway (81).

In 4T1 murine mammary cancer cells, licorice has been observed to inhibit and attenuate the progression of angiogenesis and metastasis of cancer cells, by reducing inflammation and tumor growth (82,83). The introduction of licorice compounds as adjuvant treatment in chemotherapy has demonstrated increased anticancer activity and hepatoprotection in murine models (84,85). Furthermore, licorice appears to downregulate the levels of the inflammatory cytokines, IL-6, IL-1 and TNFα *in vitro* (86). Such observations highlight the promising activity of licorice compounds *in vitro*, and undoubtedly warrant their testing in clinical trials to determine their safety and efficacy in various clinical settings.

9. Shiitake (*Lentinula edodes*)

Shiitake is a type of mushroom that grows on the Shii tree [*Castanopsis cuspidata* (Thunb.) Schottky]. It is well known as a dense, nutrient-rich food, and as a medicine for thousands of years (3,87). The mushroom has been proven to exert anticarcinogenic, antitumor, hepatoprotective, cardiovascular and immunomodulating effects. It also has antibacterial and antiviral properties and has been found to be a potent antioxidant (88). The chemical composition of the Shiitake mushroom consists of ~58-60% carbohydrates, 20-23% protein (with 80-87% digestibility), 9-10% fiber and 3-4% lipids (89). It is also an excellent source of vitamins, including D2 and B 1, 2, 5 and 12. In addition, Shiitake contains a plethora of minerals, namely zinc, copper, phosphorus, manganese, iron, potassium, calcium, magnesium and cadmium (87).

The antitumor polysaccharide, lentinan (LNT), a β-d-glucan, is regarded to be the most significant of the medicinal properties of the Shiitake mushroom; LNT forms a worm-like triple helix, that is heat-stable, water-soluble and alkali labile (90). However, due to limitations in 3D structure identification technology and crystal structure absence, there is still no detailed structure information of lentinan (91). Studies have suggested that LNT can cause the regression of solid type tumors of sarcoma 180 almost completely, as well as several other tumors, including methylcholanthrene-induced fibrosarcoma (92,93). It was later shown that the antitumor activity also affects synergic and autochthonous tumors and prevents viral and chemical oncogenesis (94). Overall, it has been demonstrated that β-glucans can serve as pathogen-associated molecular patterns, initiating immune responses through the binding of pattern recognition receptors, such as dectin-1, TLR2/4/6 and CR3 (95). Among, these, dectin-1 appears to be of the highest significance, as it constitutes a cell-like-receptor type II membrane protein, expressed in variety of cells, but mainly in neutrophils, dendritic cells and macrophages (96). The binding of LNT to these receptors leads to the activation of MAPK/NF-κB and spleen tyrosine kinase (Syk)/protein kinase C signaling (97). Following this, T-lymphocytes upregulate the expression of TNF-α, TLR4 and TLR9, whereas B-lymphocytes secrete IgG and enhance macrophage activity in mice (98). Additional activities of LNT include NK cell activation and an increased production of IFN-γ and IL-12 (99). These findings strongly suggest that lentinan and similar polysaccharides have key immunomodulatory properties and can be used to supplement ongoing treatment in a variety of cancerous diseases and tumors.

10. Turmeric (*Curcuma longa*)

Curcumin is a yellow polyphenolic pigment from the *Curcuma longa* L. (turmeric) rhizome, a flowering plant of the ginger family. It has been used throughout history for culinary and medicinal purposes, specifically in Ayurvedic and Chinese medicine. The use of the spice dates ~5,000 years back in history (100). Apart from its use as a culinary seasoning, turmeric has been historically used as an antimicrobial agent, an insect repellent and a natural coloring agent (101). Curcumin, demethoxycurcumin and bisdemethoxycurcumin are bioactive polyphenolic compounds, identified in turmeric, which have been collectively referred to as curcuminoids (CCMs) (4). It can be safely ingested in very high doses, as confirmed by several clinical studies (102).

The chemical composition of turmeric consists of ~70% carbohydrates, 6% proteins, 6% essential oils (phellandrene, sabinene, cineol, borneol, zingiberene and sesquiterpenes), 5% fat, 3% minerals (potassium, calcium, phosphorus, iron and sodium), 3-5% curcuminoids, and trace amounts of vitamins (B1, B2, C and niacin) (103,104). One of extensively researched effects of curcumin on inflammation is the inhibition of the TNF-α-induced activation and nuclear translocation of NF-κB (105). It also appears to exert inhibitory effects on several inflammatory cytokines, such as IL-1β, IL-2, IL-5, IL-6, IL-8, IL-12 and IL18 (106). Other activities include the downregulation of monocytes via MCP-1, and macrophage recruitment via macrophage inflammatory protein-1 α (107). Curcumin can also suppress the activity of protein kinases, including protein kinase A, phosphorylase kinase, mTOR and MAPKs, which play essential roles in various cellular responses, including the regulation of cell growth, proliferation, division, survival and death (103). Although curcumin lacks analgesic and antipyretic properties (106), the suppression of inflammation is a vital therapeutic effect.

Overall, curcumin is well-tolerated and has multiple beneficial effects; however, it has a low bioavailability which is a main obstacle to its application as a therapeutic agent (109). Nonetheless, adding piperine, an alkaloid present in black pepper (*Piper nigrum*), to the curcumin compound appears to increase its bioavailability by 2,000%, which allows for a highly improved therapeutic effect (110).

11. Conclusions and future perspectives

The present general overview of the few selected, very broadly promoted and highly popular immunomodulatory herbs (Fig. 2 and Table I), clearly demonstrates that all plants have very promising profiles as preventative tools in a general naturopathic setting, and most likely, in the therapy setting as well.

Table I. Summary of the names, active ingredients and chemical formulas of the included herbs and plants.

Plant name	Main active ingredient	Chemical formula	(Refs.)
Andrographis (*Andrographis paniculata*)	Andrographolide	$C_{20}H_{30}O_5$	(15,16)
Astragalus (*Astragalus propinquus/membranaseus*)	Astragaloside, Astragalus polysaccharide	$C_{28}H_{32}O_{17}$	(22)
Black cumin (*Nigella sativa*)	Thymoquinone	$C_{10}H_{12}O_2$	(38)
Cardamom (*Elettaria cardamomum*)	Terpinyl acetate, 1,8-cineole	$C_{12}H_{20}O_2$, $C_{10}H_{18}O$	(48)
Echinacea	Alkamides, caffeic acid derivatives	$C_9H_8O_4$	(54)
Ginger (*Zingiber officinale*)	Gingerol, shogaol	$C_{17}H_{26}O_4$, $C_{17}H_{24}O_3$	(67)
Liquorice (*Glycyrrhiza glabra*)	Glycyrrhizin, other polysaccharides	$C_{42}H_{62}O_{16}$	(76)
Shiitake (*Lentinula edodes*)	Lentinan, other β-glucans	$C_{42}H_{72}O_{36}$	(87)
Turmeric (*Curcuma longa)*	Turmeric	$C_{21}H_{20}O_6$	(104)

Figure 2. Images of the herbs discussed in the present review. (A) *Andrographis* (*Andrographis paniculata*), (B) *Astragalus* (*Astragalus propinquus/membranaseus*), (C) black cumin (*Nigella sativa*), (D) cardamom (*Elettaria cardamomum*), (E) *Echinacea*, (F) ginger (*Zingiber officinale*), (G) liquorice (*Glycyrrhiza glabra*), (H) shiitake (*Lentinula edodes*), (I) turmeric (*Curcuma longa*).

It is evident however, that there is still a long way to go before consistent data can be collected, that is easily applicable and reliable. At present, the available information in the scientific literature is relatively scattered and inconsistent. A broad variety of approaches have been applied to study each one of the different herbs and for this reason, the data cannot be easily summarized and processed. For some herbs, the main focus is on phytochemical constituent research, combined with some *in vitro* data regarding the application of various extracts on a broad spectrum of models, such as cell cultures, research animals, etc. (111). For other herbs, there is a comparison between the effects of single-isolated and purified compounds and some water-based or alcohol-based extracts (112). It is not very clear, however, what will occur when whole extracts are applied, or which of the pharmacologically active constituents play the major role in the observed effect. Presumably, the

entourage effect is much more significant in terms of conferring a therapeutic benefit rather than the effect of purified single compounds. Furthermore, whole extracts may have a much safer profile. As such, a considerable amount of research is required to provide ample evidence.

In addition, the available data on safety (the majority of data have been obtained via hepatocyte culture models) are not sufficient (5,113-115). Human clinical data are even more limited. There is partial information from some prospective observational trials; however, double-blinded, randomized, placebo-controlled trials (which are the golden standard) are lacking. Adequate research on all of these promising plants, even the few that were selected for discussion in the present review, would require a very consistent and structured approach, numerous resources invested in terms of time and funding, and more importantly, a good collaboration between research teams. However, despite all these visible hurdles, it can be considered that plant-based therapeutics represent a very promising area of pharmacological research and development, which may prove to be effective, both in terms of patient well-being and therapeutics, and in terms of industry profits.

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IT, KD and AZ performed the initial collection and curation of the data to be included in the review. AZ, NS, RH and TK reviewed the collected data and extracted relevant information. IT, KD, TK, AZ and NS summarized the data for each presented example. DAS, RH, MA and VZ reviewed and edited the manuscript. All authors have read and approved the final version of the manuscript. Data authentication is not applicable.

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Competing interests

DAS is the Honorary Editor of the journal, but had no personal involvement in the reviewing process, or any influence in terms of adjudicating on the final decision, for this article. The other authors declare that they have competing interests.

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