applied sciences

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Review

Pharmacological Properties and Safe Use of 12 Medicinal Plant Species and Their Bioactive Compounds Affecting the Immune System

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Abstract: This paper presents raw plant materials and their characteristic compounds which may affect the immune system. Plant-derived agents in specific doses affect the body's non-specific, antigen-independent defense system. They have immunostimulatory effects on the entire immune regulatory system. They can enhance the immune response through various factors such as macrophages, leukocytes, and granulocytes, as well as through mediators released by the cellular immune system. This paper was inspired by the threats caused by the COVID-19 pandemic. The proper functioning of the immune system is important in limiting the effects of viral infection and restoring the normal functioning of the body. This paper also emphasizes the importance of the skillful use of plant immunostimulants by potential patients, but also by those who prescribe drugs. It is important not only to choose the right plant drug but above all to choose the correct dose and duration of treatment.

Keywords: plant immunomodulators; sources; principles of use; effectiveness; alkamide complex; cichoric acid; echinacoside

Citation: Geszke-Moritz, M.; Nowak, G.; Moritz, M. Pharmacological Properties and Safe Use of 12 Medicinal Plant Species and Their Bioactive Compounds Affecting the Immune System. *Appl. Sci.* **2023**, *13*, 6477. https://doi.org/10.3390/app13116477

Academic Editor: Emanuel Vamanu

Received: 20 April 2023
Revised: 24 May 2023
Accepted: 24 May 2023
Published: 25 May 2023

1. Introduction

Plant raw materials have been extensively studied since the time of ancient civilizations and many bioactive chemical constituents with high therapeutic potential have been discovered [1,2]. In the past 30 years, a significant increase in new "natural" medicines developed as very effective drugs has been observed [3]. Plant constituents, due to their great biological and structural diversity, are a unique and renewable source for the discovery of new natural medicines. Identified phytochemicals, including polysaccharides, lactones, glycosides, terpenoids, and alkaloids, have been reported to be primarily responsible for the immunomodulation activity of plants. The stimulation of the body's defense mechanism has been proven to be an effective approach to counteracting viral and bacterial infections [1]. Herbal preparations, including those using plant extracts, are widely known and increasingly used due to their significant immunostimulant properties [4]. Immunomodulators, defined as helpful compounds which are derived naturally from plants, have been proven to fight against invaders by producing antibodies as well as by maintaining the homeostasis of the immune system [5]. The most common and important causes of reduced immunity are chemotherapy and antibiotic therapy, cooling of the organism, alcohol abuse, recurrent infections, poor diet, and recurrent COVID-19 [6–8]. The terms immunostimulants and immunomodulators are used interchangeably in phytotherapy for plant materials that affect the immune system. Both define non-specific stimulatory therapy, which consists of stimulation of the defense system, manifested by a specific humoral response (stimulation of B lymphocytes to produce immunoglobulins) and the so-called cellular response (stimulation of T lymphocytes to produce macrophages and

granulocytes, among others) and/or modulation of the autonomic nervous system to restore the normal, natural functions of the body [9,10]. Its central element is the activation of macrophages—cells produced by the bone marrow that primarily stimulate the process of phagocytosis [11]. They are also responsible for releasing numerous substances with vast biological properties affecting the immune system, such as tumor necrosis factor (TNF-α) and interleukins (IL). TNF-α (tumor necrosis factor) is a protein substance involved in the immune response and inflammatory process [12]. Essential biological functions of the factor are stimulation of B, T, and natural killer (NK) lymphocytes, stimulation of the immune response to the presence of tumor cells by affecting apoptosis (programmed cell death process), and inhibition of proliferation of tumor cells [13]. The stimulus for its production is also provided by bacterial lipopolysaccharides, interleukin 1, and γ-interferon (IFN). More recently, the possibility of TNF influencing the regeneration of nerve cells in the brain has been identified. However, it should be noted that negative aspects of this factor—induction of tumor cell proliferation and enhancement of the inflammatory process—are also suggested. For this reason, great caution should be exercised against compounds that contribute to increased secretion of the TNF factor [14]. Interleukins (IL) are cytokines involved in the inflammatory process, with a broad spectrum of action. IL-1 affects the formation of B and T lymphocytes (specific immune response). IL-6 stimulates B lymphocytes formation and inhibits TNF reflux. IL-10, an anti-inflammatory cytokine, inhibits the production of pro-inflammatory cytokines such as IL-2, IL-3, γ-interferon, and TNF. Finally, IL-12 differentiates T lymphocytes and activates NK cells [15,16].

The use of immunostimulants inconsistently with treatment (too high doses and excessive duration of use) can cause the immune system to become deregulated or even shut down, leading to increased chronic inflammation. Consequently, the body's defense system is activated and the destructive process can gradually be directed against the body's cells. The continued stimulation of B and T lymphocyte production can lead to autoimmune diseases such as multiple sclerosis [17].

Among the plant raw materials that have so far been proven, by pharmacological and clinical studies, to have an immune-stimulating effect are, first of all, *Echinaceae purpureae herba recens* and *radix* [18] and *Echinaceae pallidae radix*, and to a lesser extent, *Echinaceae angustifoliae radix* and *Aloe arboreae folium*, as well as *Panax quinquefolii radix.* Polysaccharides in these plant raw materials increase the number of lymphocytes and sensitize foreign substances to the effect of phagocytosis (opsonization) [19].

The second group of macromolecular compounds with immunostimulating effects are glycoproteins [20]. They affect the division and stimulation of the activity of B and T lymphocytes, the phagocytic activity of leukocytes, and the synthesis of immunoglobulins and interferon [21,22]. The immunostimulatory effect of parenterally administered glycoproteins occurs after minimal doses—1 ng/kg body weight. Larger doses can cause an immunosuppressive effect and are used in transplants to prevent rejection by the immune system [23]. Some anti-tumor raw materials and plant compounds have an immunostimulatory mechanism of action. Among them, *Uncariae tomentosae cortex* (pentacyclic oxindole alkaloids) [24] and polysaccharides from some species of fungi, such as *Schizophyllan commune* [25], can be mentioned.

Plant immunostimulants are a unique group of drugs, as they affect the physical and mental functions of the body. Dysfunction of the immune system causes a gradual decrease in the quality of life and often leads to depressive states. Therefore, early diagnosis of a decrease in immunity and its proper prevention is vital. However, a related problem is that it is not advisable to use prophylaxis, which is favored by the availability of herbs and the natural need to be resistant to all infections. Uncontrolled use of plant immunostimulants may lead to a gradual decrease in the concentration of factors responsible for the immune system and to difficult-to-cure rheumatoid conditions.

The inspiration for the current review article is the threats caused by the COVID-19 pandemic. The proper functioning of the immune system is important in limiting the effects of viral infection and restoring the normal functioning of the body. This work describes

the immunomodulation potential of the chosen 12 plant species, along with their bioactive chemical constituents. The relevant literature was searched from scientific databases. This work also emphasizes the importance of skillful use of plant immunostimulants by potential patients, but also by those who prescribe drugs. It is important not only to choose the right plant drug but above all to choose its correct dose and duration of treatment.

2. Materials and Methods

To write this study, articles were selected that reliably, primarily on the basis of clinical trials, described the possibility of using an effective and safe plant drug. The date of publication was not a criterion. The selection was based on plant raw materials presented in the ESCOP monograph and articles in renowned journals. The whole was still verified by the EMA monograph. There, the latest data on individually selected plant raw materials were found with the possibility of their practical application to ensure the reliability of the study.

3. Plant Raw Materials and Compounds with Proven Immune-Enhancing Effects

3.1. Echinaceae Purpureae Herba Recens—Echinacea purpurea (L.) Moenh

The characteristic compounds of *Echinaceae purpureae herba recens* are alkylamides (alkamide complex), polysaccharides (4-O-methylglucuronoarabinoxylan, arabinorhamnogalactate acid), and glycoproteins. The chemical structure and the immunostimulating effect of alkylamides and other natural compounds are presented in Table S1 [26–38]. Meanwhile, in Figure 1, the scheme demonstrating the postulated molecular mechanisms of action of plant-derived immunomodulators is presented.

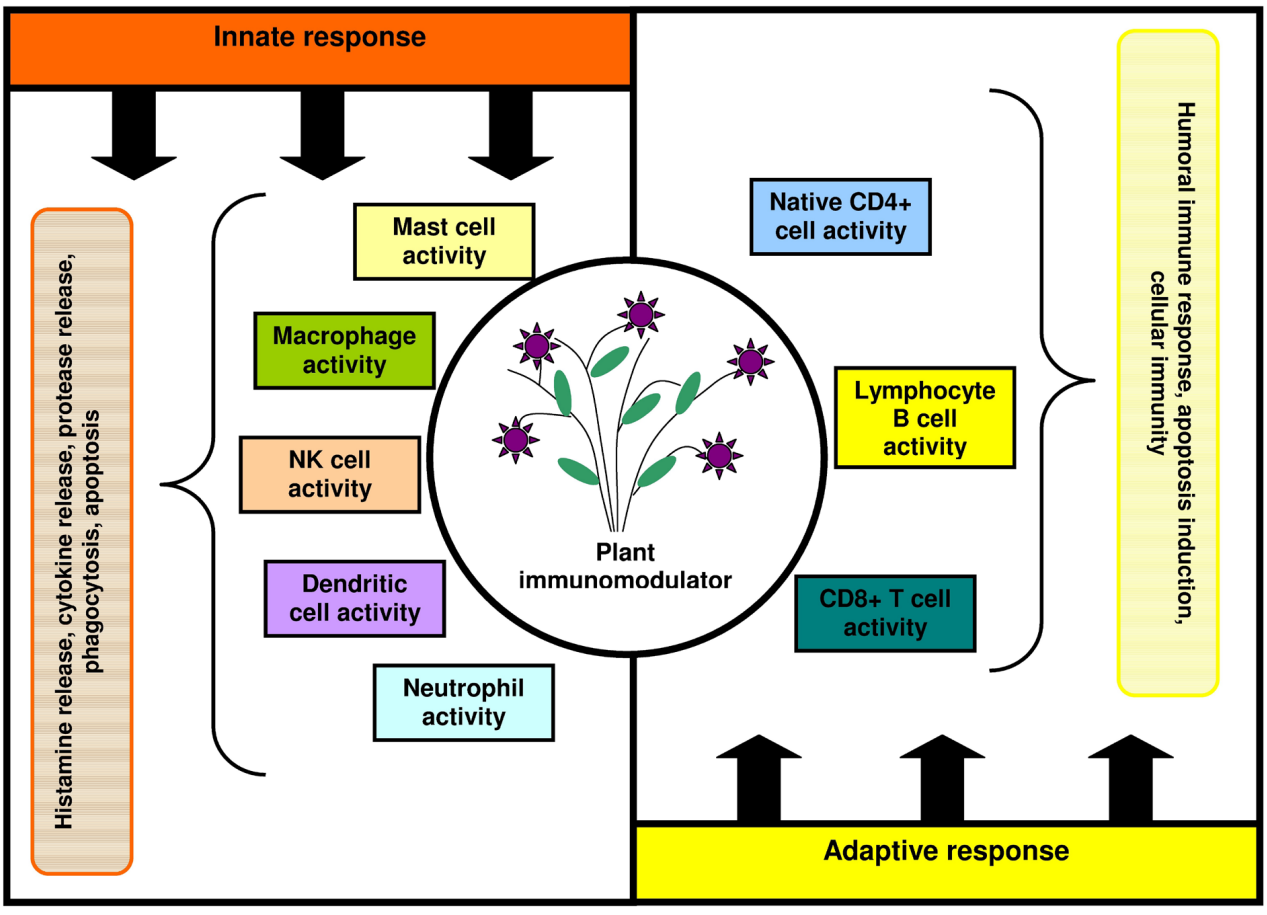

Figure 1. The scheme demonstrating the influence of plant-derived immunomodulators on the human immune system functioning. Prepared on the basis of [39].

3.1.1. Pharmacological Properties

Purple coneflower herb juice at the concentration of 5 mg/mL significantly increased phagocytosis in human granulocytes. Stimulation of T lymphocytes in their transformation assay was also observed [26,40]. The juice of fresh purple coneflower herb at a concentration of 5 to 500 g/mL stimulated the incorporation of labeled 1H-thymidine, whereas the concentration exceeding 2500 g/mL caused its suppression. The same preparation inhibited the intrusion of *influenza*, *Herpes*-type viruses, and oral mucosal viruses into isolated animal cells. Moreover, the increased globulin levels after intraperitoneal administration as well as the stimulated leukocytosis and granulocytosis by 55% were observed in vivo [27].

It is also worth noting that the fresh herb juice administered to professional athletes significantly altered the concentration of interleukin 6 and affected the receptor for interleukin 2, two cytokines (with a protein structure) that stimulate serum immune function and increase serum immune concentrations. It has been observed that intense exercise causes an increase in cortisone levels, which tends to reduce NK (natural cytotoxic cell) levels and inhibit macrophage activity. In a group of athletes taking the plant-based drug, no decrease in NK was observed one hour after the sporting event. This experience may suggest that purple coneflower herb counteracts the immunosuppressive activity of cortisone and reduces the risk of upper respiratory tract infections [41].

In clinical trials, 120 patients with the first symptoms of acute inflammation of the upper respiratory tract were administered 20 drops of purple coneflower herb juice every 2 h on the first day, followed by 20 drops three times daily. A significantly reduced treatment period was observed in the treated subjects versus the placebo group (4 and 8 days, respectively) [42].

In pharmacological studies with humans (559 adults prone to colds), three preparations of purple coneflower were administered: 1. dry extract of the herb (95% of the raw material) and root (5% of the raw material) in tablet form (6.78 mg per tablet); 2. the same extract in a tablet of 48.27 mg of the drug; 3. dry extract of the root in tablet form of 29.60 mg per tablet. Participants used the drugs at the first symptoms of a cold (three times, one tablet per day) and dosed them until the symptoms disappeared, but for no longer than 7 days. Treatment with preparations 1 and 2 yielded significant differences in efficacy compared to placebo. A smaller number of cures were obtained after treatment with formulation 3. It should be noted that despite the use of 7× higher dosage in formulation 2 compared to 1, both had almost the same effect. The therapeutic effect of the intramuscularly administered fresh purple coneflower herb juice was compared with the effectiveness of antibiotic treatment in patients with respiratory tract infections. It has been demonstrated that after 10 days of therapy, an 81% cure rate in patients treated with the plant preparation and 41% in those taking the antibiotic was observed [43]. However, it should be noted that coneflower herb can be contaminated with mold and common mycotoxins, which has been recently reported [44].

Several review studies and clinical meta-analyses suggest that the serum can be recommended for the treatment of the first symptoms of the common cold, but also for the prevention of recurrent respiratory tract infections and urinary tract infections [45].

3.1.2. Safety of Use

Purple coneflower herb juice significantly increased phagocytosis in human granulocytes and shortened the first symptoms of acute inflammation of the upper respiratory tract [26,39]. Preparations of purple coneflower herb are well tolerated, but there is a risk of sensitization, triggering an allergic reaction in people with atopic diseases. There may be side effects associated with autoimmune diseases and leukopenia (when used for longer than 8 weeks). Deterioration of disease symptoms or a sudden increase in temperature during treatment with purple coneflower herb preparations should be addressed with a doctor or pharmacist. No adverse effects have been reported during pregnancy in women and born children, but the drug should not be administered without consulting the doctor [46].

Preparations of *Echinacea purpurea* herb can be administered to children under one year. Interactions with other drugs and food were not observed in clinical trials. Only weak interactions were observed with some liver enzymes: cytochrome 450, CYP1A2, and 3A. The efficiency of purple coneflower preparations is determined by their rapid administration along with the first symptoms of a cold. The raw materials can be used for 10 days without interruption and should not be taken for longer than 10 days [46,47].

3.2. Echinaceae Purpureae Radix

The characteristic compounds of *Echinaceae purpureae radix* are cichoric acid, a caffeic acid derivative, alkamides, polysaccharides, and glycoproteins. The chemical structure of cichoric acid and its immunostimulating effect are presented in Table S1.

3.2.1. Pharmacological Properties

It was observed that ethanolic extracts of dry crude plant material stimulated granulocytic phagocytosis (by 33%). The effect was ascribed to the presence of alkamides, polysaccharides, and glycoproteins in the extract. The compounds increased the activity in a colony of macrophages isolated from the spleen of mice towards, among other things, the secretion of interferon. They stimulated the biosynthesis of interleukins (IL-1, IL-6) and tumor necrosis factor α (TNF-α). This mechanism of defense action of the raw material was confirmed in in vivo studies after intravenous administration of polysaccharides and glycoproteins in a dose-dependent manner. The increase in interleukin concentration resulted in the strengthening of the defense mechanism. The experiments performed using the animal model confirmed the formation of new NK cells in the bone marrow after oral administration of purple coneflower root extract. In addition, the powdered root, given parenterally to mice with leukemia, increased their survival rate compared to the control group [28,48,49].

One recent in vitro trial suggested a synergistic effect of methanolic extracts from purple coneflower roots and herbs, which are standardized for the presence of alkamides. The authors suggested that these compounds exert a super-addictive effect on endogenous type 2 cannabinoid receptors, such that there is an intracellular release of calcium cations, indicating an anti-inflammatory and immunomodulatory effect of the extracts studied [50].

Based on numerous clinical studies, the efficacy of purple coneflower root against early cold symptoms and in the prevention of recurrent respiratory infections was revealed. Not surprisingly, a statistically significant difference was observed in the reduction in cold symptoms compared to the placebo group during trials, with a whole plant extract standardized for the presence of alkamides, cichoric acid, and polysaccharides. People suffering from recurrent colds took eight times 5 mL of the alcoholic extract on the first day prophylactically and three times 5 mL daily for the next 6 days [51].

3.2.2. Safety of Use

The ethanolic extracts of dry crude plant material stimulated the granulocytic phagocytosis and stimulated the biosynthesis of interleukins (IL-1, IL-6) and TNF-α. The side effects and contraindications were the same as for *Echinaceae purpureae herba*, with one exception—*Echinacea purpurea* root was contraindicated for children under 12 years of age [52]. The plant material should not be administered for more than 8 weeks during one year [53].

3.3. Echinaceae Pallidae Radix—Echinacea pallida (Nutt.) Nutt.

The characteristic compounds of *Echinaceae pallidae radix* are echinacoside, a caffeic acid derivative, essential oil-containing alkenes, unsaturated ketoalkenes, and ketoalkinenes, as well as the products of 8-hydroxy-ketoalkene decomposition formed during the drying and storage of the raw material. The chemical structure of echinacoside and its immunostimulating effect are demonstrated in Table S1.

3.3.1. Pharmacological Properties

The effects of the ethanol extract and macromolecular compounds from pale coneflower root on the production of factors responsible for immunity were monitored. Increased phagocytosis and biosynthesis of interferon and immunoglobulins, as well as cytokines such as interleukin 1 and 6 and TNF-α, were observed in vitro and in vivo [29].

The strong effect on the immune system of purple coneflower root was confirmed by pharmacological studies with humans and clinical trials. The ethanolic extract increased phagocytosis by 120% in healthy volunteers after administering 30 drops of the drug three times daily for 5 days. This effect lasted for 6 days. Patients with flu-like symptoms used a tincture of purple coneflower root (1:5, 55%) for 8 to 10 days at a daily dose equivalent to 450 mg and 900 mg of the dry material. Only the higher dose produced a statistically significant reduction in disease symptoms [54]. In clinical trials, patients with flu-like symptoms treated with the extract equivalent to 900 mg of dry crude had a statistically significant effect compared to the placebo group on such cold symptoms as shoulder and limb pains, headache, and weakness. In addition, the administration of the extract resulted in a shorter recovery period for patients with the aforementioned cold symptoms. These studies indicate that the raw material can be used as an auxiliary agent in preventing and treating upper respiratory tract infections and the common cold [55].

3.3.2. Safety of Use

The ethanolic extract and macromolecular compounds from pale coneflower root on the production of factors responsible for immunity were monitored. Increased phagocytosis, biosynthesis of interferon and immunoglobulins, as well as cytokines such as interleukins 1 and 6 and TNF-α, were observed in vitro and in vivo [29].

The side effects were similar to those for *Echinaceae purpurea radix.* If disease symptoms do not resolve after 10 days of using preparations with *Echinaceae pallidae radix*, consultation with a doctor or pharmacist is required [56]. The raw material should be used for at least 8 weeks in the year [57].

3.4. Echinaceae Angustifoliae Radix—Echinacea angustifolia DC.

The characteristic compounds of *Echinaceae angustifoliae radix* are echinacoside and cynarin (caffeic acid derivatives), polysaccharides (composed mainly of inulin and fructans), glycoproteins, and alkamides. The chemical structure of cynarin and its immunostimulating effect are shown in Table S1.

3.4.1. Pharmacological Properties

An alcoholic extract of the plant material, at a concentration of 1 µg/mL, increased the phagocytosis in smears of human granulocytes by 17%. Similar results were observed using an aqueous extract (at the same concentration). In contrast, the chloroform fraction stimulated phagocytosis at a tenfold lower concentration by 34% [30].

Similarly, as in the case of pale coneflower root, three types of extracts of narrow-leafed coneflower root, namely cold water, hot water, and 50% alcohol extract, were compared for their effects on immune system factors. The increase in TNF-α, IL-10, and IL-12 production by monocytes and the proliferation of peripheral blood mononuclear cells were taken into consideration. All the extracts tested increased the TNF-α level, whereas only the alcoholic extract significantly increased the concentration of IL-12 [31,58].

Alkamides and polysaccharides isolated from the plant material increased the immune response in vitro. Furthermore, alkamides inhibited the lipo- and cyclooxygenases, suggesting their anti-inflammatory effects. In in vivo tests examining the rate of carcinoid particle elimination, the ethanolic extract was shown to increase phagocytosis. Clinical studies of coneflower roots showed a reduced incidence of upper respiratory tract infections. However, neither this effect nor a prophylactic effect in protecting against rhinovirus infection were statistically significant against the placebo group [59].

3.4.2. Safety of Use

An alcoholic extract of the plant material increased phagocytosis in smears of human granulocytes by 17%. Similar results were obtained using an aqueous extract [43].

The side effects are similar as they were noted for *Echinaceae purpureae radix*. The therapy should last up to 8 weeks in the year [60].

3.5. Aloe Arboreae Folium—Aloe arborescens Mill.

The characteristic compounds of *Aloe arboreae folium* are aloemannans, neutral polysaccharides composed of arabinopyranose, galactopyranose, and mannopyranose chains, and lectins from the group of glycoproteins.

3.5.1. Pharmacological Properties

Aloemannans, at the dose of 100 mg per kilogram body weight, administered parenterally, showed antitumor activity in in vivo experiments [61]. In another animal study, various parameters of immune, cellular, and humoral responses were investigated in mice following the administration of an aqueous extract originating from the greenhouse cultivation of *Aloe arborescens* in Poland. The preparation exerted a stimulatory effect on the migratory activity of mouse splenocytes, the chemiluminescent activity of mouse blood granulocytes, and the production of anti-SRBC antibodies. It stimulated the cutaneous angiogenesis response induced in mice by leukocytes isolated from healthy humans and patients with oral infections. The most beneficial effects of the extract were obtained after its oral administration at the doses of 2 and 4 µL. The administration of an 8 µL dose produced the placebo-level effect [62].

Increased phagocytosis was demonstrated in a clinical study in patients with upper respiratory tract inflammation after treatment with neutral polysaccharides and glycoproteins. Pharmacological and clinical studies of the aqueous extract of *Aloe arboreae folium* indicate the effectiveness of the preparation in low-immunity patients suffering from recurrent upper respiratory tract infections [63].

3.5.2. Safety of Use

Increased phagocytosis was demonstrated in a clinical study in patients with upper respiratory tract inflammation after treatment of aqueous extract [50].

The side effects are similar to those observed for *Echinaceae purpureae radix*.

3.6. Panax Quinquefolii Radix—Panax quinquefolius L.

The characteristic compounds of *Panax quinquefolii radix* polysaccharides (poly-furanosyl–pyranosyl saccharides with no ginsenosides) and quinquefolan A–C.

Pharmacological Properties

The immunomodulatory properties of polysaccharides present in *Panax quinquefolii radix* have been tested using crude aqueous extracts. It has been demonstrated that North American *Ginseng radix* polysaccharide extracts, not the ginsenosides, provided the immunostimulatory properties of the plant. The polysaccharide fraction of the extract was composed of glucose (Glc) (85.09%), galactose (Gal) (97.48%), arabinose (Ara) (5.89%), fucose (Fuc) (0.09%), rhamnose (Rha) (0.79%), and mannose (Man) (0.41%). The polysaccharides have been demonstrated to significantly stimulate the TNF-α in rat alveolar macrophages in vitro. Other studies have shown the induction of IL-6, IL-1β, TNF-α, and IL-10 production in human peripheral blood mononuclear cells (PBMC) by *Panax quinquefolii radix* aqueous and crude polysaccharide extracts [64]. This was probably due to the high molecular weight of the polysaccharides that triggered the immunomodulatory response characterized by a net Th_1 immune response in PBMC. It has been proven that the induction of the Th_1 transcriptional profile is triggered by mitogen-activated protein kinase (MAPK), nuclear factor-κB (NF-κB), and phosphoinositide 3-kinase (PI3K) signaling pathways. Furthermore, it has been demonstrated that the polysaccharides increased the nitric oxide (NO) and TNF-α

production in RAW 264.7 murine macrophage cells (in vitro) and rat alveolar macrophages (ex vivo) [65]. It has been shown that the NO and TNF-α plasma levels were significantly elevated in adult Sprague Dawley rats, orally administered with *Panax quinquefolii radix* polysaccharide extracts [66].

3.7. Withaniae Radix—Withania somnifera (L.) Dunal

The characteristic compound of *Withaniae radix* is withaferin A, the steroidal lactone from the withanolides group. The chemical structure of withaferin A and its immunostimulating effect are presented in Table S1.

Pharmacological Properties

Withania somnifera (Ashwagandha) is reported to possess immunoprotective and immunoadjuvant properties. Its aqueous roots extract on T helper (Th) immunity using flow cytometry was examined. The extract was standardized with six withanolides as marker compounds using the high-performance liquid chromatography (HPLC) method. Daily extract dose ranging from 25 to 400 mg per kilogram body weight was administered orally to study the effect on Th1 (IFN-γ, IL-2) and Th2 (IL-4) cytokine modulation [32].

In in vivo studies, withanolides, at doses ranging from 0.5 to 2.0 mg/kg body weight, with dose-dependent potency, improved the physiological state of the organism under induced chronic stress, causing a decrease in the concentration of T lymphocytes. The therapeutic effect of the analyzed compounds was manifested by the increase in the levels of IL-2 and γ-interferon, whose increased concentration was found by measuring Th_1 cytokine (helper cells—white blood cells that affect the production of specific cytokines). The study also revealed the reduction in serum cortisone levels in the animals and a return to physiological levels of alanine, aminotransferase, hepatic peroxidase lipids, hepatic glutathione, and glycogen (their levels increased under stress). Withania root extract increased physical endurance and exhibited anabolic and immunostimulatory effects in vivo [67].

3.8. Eleutherococci Radix—Eleutherococcus senticosus (Rupr. and Maxim.) Maxim.

The characteristic compounds of *Eleutherococci radix* are lignans, syringin (the phenylpropane glycoside), and polysaccharides. The chemical structure of syringin and its immunostimulating effect are summarized in Table S1.

3.8.1. Pharmacological Properties

The aqueous–alcoholic extract of the raw material increased the phagocytosis of human leukocytes and granulocytes (by 60 to 240%). Polysaccharides present in the *Eleutherococcus* root were shown to be responsible for this effect [33].

The effect of the raw material on the immune system was also manifested by the increased levels of IL-1 and IL-6. The former cytokine is secreted in response to bacterial, viral, and fungal infections, influences the type of specific response, and activates T lymphocytes; the latter is secreted by macrophages and monocytes, activates T lymphocytes, and stimulates erythropoiesis through synergism with IL-3 and is a pyrogenic protein. In an in vivo study, the dry aqueous extract was shown to increase bone marrow production in a statistically significant manner and exhibited a cytotoxic effect on leukemia cells. The liquid alcoholic extract, on the other hand, inhibited the replication of rhinovirus, respiratory virus, and influenza A virus [34].

The *Eleutherococcus* root extracts also showed an immunizing effect on living animal cells against gamma-ray-induced changes and induced oxidative stress. Syringin present in the raw material showed similar properties. The compound was also characterized by the significant inhibition of TNF-α, a glycoprotein-like cytokine that is cytotoxic to cancer cells by activating the arachidonic acid breakdown cascade. In vivo studies have shown that syringin affects the release of acetylcholine and probably inhibits acetylcholinesterase [68,69].

3.8.2. Safety of Use

The aqueous–alcoholic extract of the raw material increased the phagocytosis of human leukocytes and granulocytes. Polysaccharides present in the *Eleutherococcus* root were shown to be responsible for this effect [33].

Medicinal preparations bearing the name "Siberian ginseng" may contain raw materials derived from six different plants, more or less morphologically similar to *Eleutherococcus senticosus* and certainly differing from it in chemical composition and pharmacological properties. The *Eleutherococcus* root can cause increased blood pressure, arrhythmia, headaches, and insomnia. It is, therefore, contraindicated in heart disease and hypertension, as well as for children under 12 and for women during pregnancy and lactation [70].

3.9. Visci Herba—Viscum album L.

The characteristic compounds of *Visci herba* are lectins belonging to the group of glycoproteins and polysaccharides.

Pharmacological Properties

Studies have shown that lectins are the main compounds in mistletoe herb that are responsible for the immunostimulatory effect, primarily by stimulating T-lymphocytes. Under in vivo conditions, they also stimulate phagocytosis, causing the biosynthesis of various cells as an immune response. Aqueous lectin-standardized extracts in pharmacological studies show dose-dependent stimulation of the immune system. Acidic polysaccharides present in the herb play an important role in supporting this effect [71].

Preparations of aqueous extracts of mistletoe herb are used in medicine. So far, about fifty clinical studies have been conducted. All of them concerned the effect of aqueous extracts of mistletoe herb, administered parenterally, in the treatment of various types of cancer [72,73].

The lectins present in the plant material show strong cytotoxicity and mutagenicity. Lectin ML I is an outstanding immunostimulator and an inhibitor of metastasis formation in some cancers. Aqueous extracts of mistletoe herb are components of preparations used in complementary and alternative medicine as immunomodulators in the treatment of certain cancers. The immune effect is closely correlated with the activity of lectins present in the raw material and depends on the dose. Therefore, it is necessary and very important to standardize preparations for the lectins they contain [74].

Numerous preclinical and clinical studies have proven that mistletoe herb extracts exhibit immunomodulatory effects. A key role in the cellular response against tumor cells is played by natural cytotoxic NK cells. According to the latest immunological research, from a scientific point of view, mistletoe herb is classified as a raw material that stimulates the immune system to control and inhibit the growth of tumors. It is not surprising that the smaller the tumor, the better the effects of the therapy. It should also be noted that the use of mistletoe requires a great deal of experience on the part of the doctor, particularly with regard to the source of the raw material, the size of the dose used, and the frequency and appropriate timing of its application. Failure of therapy is often the result of negligence of any of the factors mentioned above [75].

3.10. Uncariae Cortex—Uncaria tomentosa (Willd. Ex Schult.) DC.

The characteristic compounds of *Uncariae cortex* are uncarine and isopteropodine, being the pentacyclic oxoindole alkaloids and rhynchophylinne from the group of tetracyclic oxoindole alkaloids. The chemical structure of isopteropodine and its immunostimulating effect are presented in Table S1.

3.10.1. Pharmacological Properties

There are two chemical varieties of vilcacora in nature. One contains mainly pentacyclic oxoindole alkaloids, and the other contains tetracyclic alkaloids. The two groups of

these alkaloids act in different ways, and sometimes even in opposite ways. Oxoindole tetracyclic alkaloids affect the central nervous system, whereas oxoindole pentacyclic alkaloids affect the immune system. Therefore, determining the chemical variety of a plant is very important for unidirectional phytotherapy [76].

In Western Europe, the measurement of the content of isopteropodine—the alkaloid with the strongest immunostimulating properties—is used to standardize preparations. Extracts should contain 97% of pentacyclic oxoindole alkaloids from the sum of all oxoindole alkaloids found in the raw material, i.e., 1.3–1.75% [77,78].

The bark of vilcacora acts as an antioxidant and has immune-stimulating properties by stimulating and developing phagocytes and anti-tumor properties. In cases of existing cancer, it prevents metastasis and causes its regression. It also possesses anti-inflammatory and antiviral properties and promotes the production of white blood cells. In vitro studies have shown that an aqueous extract of the raw material inhibits the growth of cancer cells, and its mechanism of action is based on the selective induction of apoptosis, as explained by the so-called induction of DNA breaks. The compound that apparently showed this effect was unkarine F. In addition, pentacyclic oxoindole alkaloids present in the raw material stimulate the production of a factor that regulates lymphocyte proliferation, and tetracyclic oxoindole alkaloids have an antagonistic effect. Vilcacora alkaloids were also tested in two chemoluminescence models (granulocyte activation and phagocytosis) to determine their phagocytic capacity. Isopteropodine showed the strongest effect. In vitro studies also confirmed that the mechanism of the immunostimulatory effect of extracts from the bark of tansy capsicum is related to the stimulation of interleukin IL-1 and IL-6 production in alveolar macrophages and an increase in leukocyte and lymphocyte production [35].

In just two pharmacological studies involving healthy volunteers, the use of an aqueous extract of vilcacora at a dose of 350 mg per day, for 6 weeks, was shown to stimulate the immune system by increasing the number of leukocytes. Additionally, with a dose of 350 mg twice a day, an increase in peripheral blood lymphocytes and neutrophils was observed over a 5-month period. However, there are no controlled clinical studies to confirm this effect [36].

Thanks to its immune system-boosting properties, vilcacora is used in various cancers, mainly against leukemia and gastrointestinal cancers. Standardized preparations based on this raw material, registered as pharmaceuticals, are recommended by the World Health Organization for, among other things, cancer diseases for patients with a poor prognosis—not eligible for radical treatment—or to prolong life. Vilcacora preparations are helpful in reducing the side effects of chemotherapy and radiation therapy [79].

3.10.2. Safety of Use

The bark of vilcacora acts as an antioxidant and has immune-stimulating properties by stimulating and developing phagocytes and anti-tumor properties. In cases of existing cancer, it prevents metastasis and causes its regression. It also possesses anti-inflammatory and antiviral properties and promotes the production of white blood cells. In vitro studies have shown that an aqueous extract of the raw material inhibits the growth of cancer cells, and its mechanism of action is based on the selective induction of apoptosis, as explained by the so-called induction of DNA breaks [35].

Since vilcacora is used in traditional medicine as a menstrual inducer, the raw material should not be used in pregnant women. It is also not recommended in nursing mothers and children under the age of 12, due to the lack of any information on the safety of its use. Vilcacora should not be used in patients with hemophilia, in patients taking insulin and hormones, and in those undergoing internal organ or bone marrow transplantation. Preparations containing extract of the bark of tansy capsicum should be used under close medical supervision for patients who are concurrently taking drugs metabolized with cytochrome P-450 (protease inhibitors, warfarin, estrogens, theophylline), due to the fact that vilcacora inhibits its activity [80].

3.11. Filipendulae Ulmariae Flos et Herba—Filipendula ulmaria (L.) Maxim.

The characteristic compounds of *Filipendulae ulmariae flos et herba* are spiraeoside from the group of flavonoids and benzoic acid derivatives (methyl salicylate and salicyl aldehyde glycoside). The chemical structure of spiraeoside and its immunostimulating effect are summarized in Table S1.

3.11.1. Pharmacological Properties

The 70% extracts of *Filipendulae ulmariae herba*, corresponding to a dose of 1 g of plant material, revealed antimicrobial activity against *Staphylococcus aureus*, *Streptococcus pyogenes haemolyticus*, *Klebsiella pneumoniae*, and others. Aqueous extracts of *Filipendulae ulmariae* leaves showed anti-inflammatory activity by inhibiting 36% of cyclooxygenase in in vivo studies. Using the fluorescence method, an increased number of leukocytes were found after the application of extracts of *Filipendula ulmaria* flowers. Immunostimulatory effects have been demonstrated by several other studies with animals, in which the activity of extracts of *Filipendula ulmaria* herb was found to be higher than that of flavonoids isolated from plant materials [37]. *Filipendulae ulmariae flos et herba* are also used in pediatrics as antipyretics and diaphoretics, recommended for colds and flu [74,81].

3.11.2. Safety of Use

Aqueous extracts of *Filipendula ulmaria* leaves and flowers showed anti-inflammatory activity by inhibiting 36% of cyclooxygenase in in vivo studies [81].

A contraindication to the use of plant materials (especially flowers) is hypersensitivity to salicylic acid derivatives. No data on the possibility of plant material use during pregnancy and lactation without the knowledge of a doctor have been reported. They should not be used together with salicylates or other non-steroidal anti-inflammatory drugs without consulting a doctor. It is not recommended to use plant materials during pregnancy or lactation and in adolescents under 18 years of age [82,83]. It is recommended to use the preparations in the form of divided doses in a maximum hot (drinkable) infusion [82].

Methyl salicylate, one of the compounds found in aerial parts of *Filipendula ulmaria*, predominates in the essential oil (98%) of the leaves of *Gaultheria procumbens* L. This plant material is used primarily in Asian medicine in relieving muscle pain. It can be found in many forms: creams, lotions, ointments, smears, and even lozenges. It is also recommended for use by children. The toxic potential of this oil, which contains almost pure salicylates, remains neglected [84].

3.12. Sambuci Fructus—Sambucus nigra L.

The characteristic compound of *Sambuci fructus* is cyanidin 3-glucoside chloride from the group of anthocyanins. The chemical structure of this compound and its immunostimulating effect are presented in Table S1.

3.12.1. Pharmacological Properties

In vitro studies of an aqueous extract of elderberry fruit showed a stimulatory effect on the immune system through increased production of cytokines by monocytes. Further studies confirmed the antimicrobial and antioxidant properties of this plant material [38].

The results of two clinical trials showed the effectiveness of elderberry fruit aqueous extract in overcoming the influenza virus faster. Elderberry fruit is recommended for symptomatic treatment and prevention of colds and flu [85].

3.12.2. Safety of Use

In vitro studies of an aqueous extract of elderberry fruit showed a stimulatory effect on the immune system through increased production of cytokines by monocytes [85].

The plant's raw material is not recommended during pregnancy and lactation and in adolescents under 18 years of age. However, there are elderberry preparations on the pharmaceutical market for use in children over 3 years of age [86].

4. Discussion and Conclusions

Upper respiratory tract infections caused by viral infections and the common cold are ubiquitous. The use of modern synthetic drugs in such cases is not always effective. Alternative treatment is therefore necessary. Stimulation of the body's immune system can effectively prevent such infections. Numerous bioactive plant constituents revealed a potential immunomodulation effect when used in infectious diseases. They have been proven to stimulate and modify macrophages, lymphocytes, and cytokine production.

All plant raw materials (plant medicines) described in this review article are available on the herbal (pharmaceutical) market or in the form of herbs or ready-made commercial preparations. All of them have a proven effect on the immune system. Three species of the genus *Echinacea* are effective: *Echinacea purpurea radix et herba recens*, *E. pallida radix,* and *E. angustifolia radix*, as well as *Aloe arborescens folium*. The raw materials of these plants act mainly on the factors determining the functioning of the immune system. The article also presents plant raw materials that have an immunostimulating effect; however, this is not their main activity. Additionally, in the case of these plants, the immunostimulating effect derives from the impact on the factors of the immune system. Therefore, *Withaniae radix*, *Ginseng radix,* and *Eleutherococci radix* are used as strengthening drugs for psychophysical exhaustion. The flower and herbs of *Filipendula ulmaria* are used in colds and upper respiratory tract infections, whereas *Uncariae cortex* is a recognized anticancer drug.

The threat of the return of the pandemic infections still exists, and therefore, knowledge about the body's defense capabilities should be updated and recalled, particularly in case of situations such as the COVID-19 pandemic occurring. If phytotherapy is more accessible, patients can, with spontaneous and uncontrolled use of immunostimulants, cause the immune system to shut down and induce secondary chronic inflammation. Therefore, in this review article, we suggest following the rules for the use of immunostimulants, preferably after consulting a doctor or pharmacist.

It should be borne in mind that the limitations related to the usage of medicines of natural origin are the need to develop a procedure for standardization and appropriate quality control protocols.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/app13116477/s1, Table S1: Chemical structure of main active constituents in herbs with immunostimulating effect.

Author Contributions: Conceptualization, G.N., M.G.-M. and M.M.; writing—original draft preparation, G.N. and M.G.-M.; writing—review and editing, M.G.-M., M.M. and G.N.; supervision, M.G.-M. and M.M. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by Pomeranian Medical University (WFB-406/S/2023 and WFB-405/S/2023).

Conflicts of Interest: The authors declare no conflict of interest.

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