

Plant raw materials and natural substances influencing the immune system

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Summary

The herb and the root of purple coneflower, the root of pale coneflower as well as narrow-leaved coneflower have a very well-documented immunostimulating activity. Among the other medicinal plants influencing the immune system there are also the herb of pale coneflower, the leaf of *Aloe arborescens* and the mistletoe herb. Both macromolecular compounds such as glycoproteins and polysaccharides and the micromolecular derivatives of caffeic acid, alkalamides and unsaturated alkyl ketones, are listed among active immunostimulators.

Key words: herbal medicine, immunity

INTRODUCTION

The most important and most common causes of the immune system weakness are alcohol abuse, the cooling of the organism, antibiotic- and chemo-therapy, recurring infections and bad diet. Natural medicaments can influence the unspecific and antigens-independent defense system of the organism. They have immunostimulating activity on the entire immunity regulation system and they enhance immunological response through such factors as macrophages, leukocytes and granulocytes as well as through mediators which are released by cell immune system [1]. In phytotherapy, two notions are applied for plant materials influencing immune system: immunostimulants or immunomodulators. Both denote unspecific stimulation therapy which includes stimulating the defense system, manife-

sting itself with the humoral immune response (immunoglobulins produced by lymphocytes B) and the cell response (macrophages and granulocytes produced by lymphocytes T) and/or modulation of autonomic nervous system to restore natural and regular functions of the organism.

The abuse of immunostimulating medicaments (overdosage or overlong administration) may cause immune system inefficiency or even its elimination, which may lead to intensification of chronic inflammatory condition and in turn to such stimulation of the immune system which turns against its own cells, in a slow process of destruction. The constant stimulation of lymphocyte B and T production [1] is likely to cause such autoimmune diseases as multiple sclerosis.

Among the raw plant materials pharmacologically proven to have an immunostimulating effect there are the herb and root of purple coneflower, the root of pale coneflower and, to a lesser extent, the root of narrow-leaved coneflower as well as the leaf of *Aloe arborescens*. The composition of various complex preparations with the declared immunostimulating activity is often completed by extracts from the root of *Baptisia tinctoria* and the branch of *Thuja occidentalis*. So far, they have been not documented to have curative properties as separate herbs. The polysaccharides they possess are ascribed the function of increasing the lymphocyte number and sensitivisation of alien substances to the phagocytosis effect (opsonisation). This is the most probable mechanism of the immunostimulating activity of polysaccharides in the roots of ginseng, *Eleutherococcus senticosus*, common nettle as well as in the root of marshmallow and in other raw plant materials which in practice are not applied in the treatment of weak immunity of an organism. In *in vivo* tests, the immunostimulating activity of polysaccharides of the aforementioned species was most often proved after parenteral application.

Glycoproteins constitute another group of macromolecular compounds with immunostimulating activity. They influence the division and simulation of lymphocyte B and T activity as well as immunoglobulin and interferon synthesis and the phagocytar activity of leukocytes. The immunostimulating effect of glycoproteins, applied parenterally, occurs the minimal dose of 1 ng/kg of body weight. Higher doses might cause immunosuppressive effect.

Several antitumor herbal compounds also exert immunostimulating action: the root of Indian ginseng (containing steroid sesquiterpenes), the bark and root of cats claw (oxindole alkaloids), the herb of mistletoe (glycoproteins and polysaccharides), the leaf of *Aloe arborescens* (glycoproteins and polysaccharides) or the polysaccharides from several fungi like *Schizophyllum commune* [2].

The immunostimulating effect of purple coneflowers and their compounds has been proven in many pharmacological and clinical studies. The phagocytic capacity was tested both *in vitro* on yeast incubated human granulocytes and *in vivo* on macrophages of liver and spleen as well as in Carbon Clearance Test on the phagocytosis in reticuloendothelial system of animals. The clinical studies of purple coneflowers concerned mainly their influence on pulmonary airways and the results were positive. Seven symptoms of cold were controlled: weakness, the

pain in the limbs, headache, nasal mucosal inflammation, cough, inflammation in the oral cavity and reddening of the throat. In all the tests a quick effect (within 8 days) was expected. The results of almost all clinical studies indicate that the appropriately early start of purple coneflower treatment shortens the therapy by $1/3 - 1/4$ and that the optimal administration period should last for 7–10 days [2]. The compounds contained in purple coneflower influence the neutralization of several viruses and pro-inflammatory factors. The extract from the root and herb of purple coneflower was proven to be active against a few viruses responsible for infection of pulmonary airways such as *Herpes* and influenza as well as pro-inflammatory cytokines (chemokines) [3].

Not all the clinical studies were unambiguous about the efficacy of the *Echinacea* medications. The results of one analysis indicated the purple coneflower preparations only diminishing the number of secondary infections [1]. The discrepancies might result from the inaccuracies in the methodology in several studies. It is difficult to find an analysis with 65% recoveries after the application of purple coneflower and 74% recoveries after *placebo* wholly credible.

***Echinaceae purpureae herba recens* – purple coneflower herb**
***Echinacea purpurea* (L.) Moenh. – purple coneflower**

It occurs in North America and is grown in other continents, in Poland regarded as a decorative plant.

The characteristic constituents:

- a series of alkamides (fig. 1)
- caffeic acids derivatives - cicchoric acid
- polysaccharides (a 4-O-methyl-glucuronoarabinoxylan)

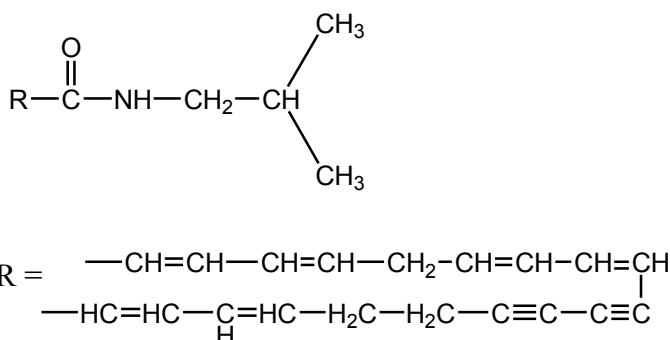


Figure 1. Alkamides

Pharmacological properties

The juice of the purple coneflower herb in the concentration of 5 mg/ml significantly increased the phagocytosis level in human granulocytes. In the transformation test, the lymphocyte T stimulation was also observed. The juice of the purple coneflower herb in the concentration of 50–500 µg/ml stimulated the incorporation of the ³H-thymidine, while in higher concentrations (>2500 µg/ml) showed a suppressive or cytotoxic effect. The same preparation inhibited the invasion of the viruses of flu, *Herpes* and of the oral cavity mucosa into the isolated animal cells and *in vivo* it also increased the level of γ-globulin after intraperitoneal application and stimulated the leukocytosis and granulocytosis by 55%. Furthermore, the juice of the herb which was applied to record-seeking sportspeople significantly changed the concentration of interleukin 6 and influenced the receptors of interleukin 2 – two cytokines (of protein structure) which stimulate the functions of the immune system in blood serum. Intense exercises cause the increase of cortisone which usually diminishes the NK concentration and inhibits the macrophage activity. In the group of the sportspeople a decrease of NK one hour after the event was not observed which might indicate that the herb of purple coneflower counteracts the immunosuppressive activity of cortisone and reduces the risk of upper airways infection [4].

In the clinical studies, 120 patients with initial symptoms of acute upper airways inflammation were given 20 drops every 2 hours on the first day and eventually 20 drops of juice of the purple coneflower herb. A significantly shorter therapy span in the treatment group was observed as compared to the *placebo* group (4 and 8 days, respectively) [5]. In pharmacological studies, 559 adults with propensity for cold sores were applied 3 purple coneflower preparations: (1) dry extract from the herb (95% of the raw material) and the root (5%) in pills (6.78 mg in one pill), (2) the same extract in 48.27 mg and (3) dry extract from the root in 29.60 mg pills. The participants were applied the medication at the initial stage of cold (one pill three times a day) and continued until the withdraw of the symptoms, but no longer than for 7 days. The treatment with preparations (1) and (2) resulted in significant differences of efficacy as compared to *placebo*. A similar number of recoveries ensued after the treatment with (3). It should be stressed that despite the fact the dose in (1) was 27 times as high as in (2), both produced a similar clinical effect [6]. The effect of the treatment with purple coneflower juice applied intramuscularly was compared with the efficacy of one antibiotic at a great number of patients with pulmonary airway infection. It turned out that after a 10-day therapy there were 81% recoveries of the patients treated with the herbal preparations and 41% in the antibiotic group [7].

Several review studies and meta-analyses imply that the raw material can be recommended in the treatment of initial symptoms of cold as well as in the prophylaxis of recurrent infections and the infections [8, 9] of genitourinary system [7].

Dosage

Adults: 6–9 ml of juice or dry juice equivalent 2–3 times daily in divided dose during the day [7, 10].

Children: the doses adjusted to the body weight [7]. Some sources suggest that application in at the age under 1 is contraindicated due to the lack of research and not advised for children between 1 and 12 for the same reason [10].

Dosage safety

Purple coneflower preparations are well-tolerated, however, there is a risk of an allergy especially in people with atopic diseases and of leucopenia. Undesirable effects might be also triggered by autoimmunological diseases (in the treatment exceeding 8 weeks). Aggravation of symptoms or a sudden temperature surge during treatment must be immediately consulted with a pharmacist or a doctor. Undesirable effects during pregnancy have not been observed, but the drug must not be applied without doctor's consent.

The application of purple coneflower (and every other medicine affecting the immune system) is contraindicated for people with progressing systemic and immunological diseases such as tuberculosis, AIDS, immunosuppression, leukocyte diseases and for children under 1 year old. Clinical studies have not indicated interactions with other medicaments or food [7]. The efficiency of purple coneflower preparations is determined by the applications commencing at the first symptoms of cold [7, 10].

To be applied no longer than 10 days [10].

Echinaceae purpureae radix - purple coneflower root

The characteristic constituents

- caffeic acid derivatives - cichoric acid (fig. 2)
- alkamides
- polysaccharides
- glycoproteins

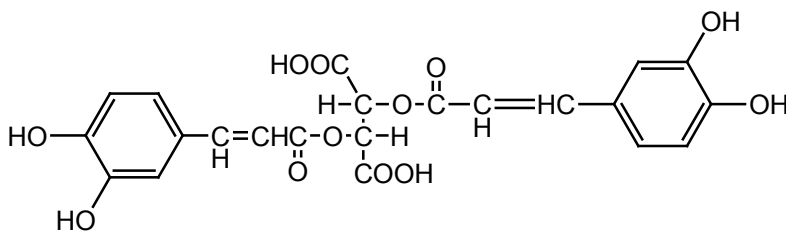


Figure 2. Cichoric acid

Pharmacological properties

Ethanol extracts of the raw material increased granulocyte phagocytosis (by 33%), which was enabled by alkamides, polysaccharides and glycoproteins. These compounds enhance the activity in a colony of macrophages (isolated from secretion from a mouse spleen) towards interferon biosynthesis as well as Tumor Necrosis Factor. Such a defense mechanism was confirmed *in vivo* after an intravenous application of polysaccharides and glycoproteins with a dose-dependent interleukin increase. In an animal study, after the oral application of purple coneflower root extract, new NK (Natural Killer) cells were proven to be created in bone marrow. Furthermore, the powdered root, applied parenterally to mice with leukemia enhanced their survival as compared with the control group [11]. In a recent *in vitro* trial, the synergistic effect of methanol extracts from purple coneflower root and herb was implied. The authors point out that the alkamides contained in these extracts cause superadditive effect on type 2 endogenous cannabinoid receptors through the intracellular release of calcium cations which suggests anti-inflammatory and immunomodulating effect of the extracts in question. In the same study, the synergistic effect of the extract on the secretion of the anti-inflammatory interleukin 10 was confirmed as well as the increased inhibition of TNF- α (also pro-inflammatory protein) expression [12].

A potent activity of the purple coneflower root on immune system was confirmed in pharmacological studies on people and in clinical studies. Ethanol extract increased the volunteers' phagocytosis by 120% after being applied 3 times daily by 30 drops of the medicine for 5 days. The effect lasted 6 days [13]. Patients with flu were administered purple coneflower root tincture (1:5, 55%) for 8–10 days in daily doses equaling 480 mg and 900 mg of dry raw material. Only the higher dose led to statistically significant symptoms reduction [14]. Like the herb, the purple coneflower root has also been proven to be efficient in fighting the early symptoms of cold and in prophylaxis of recurrent infection of pulmonary airways [15]. Not surprisingly, in trials with an extract from the entire plant with standardized presence of alkamides, cichoric acid and polysaccharides, with people suffering from recurrent colds who were applied 8 x 5 ml of alcoholic extract on the first day and 3 x 5 ml daily for the following 6 days, a statistically significant difference in diminishing the symptoms of cold as compared with *placebo* group was obtained [16].

Dosage

3 x 60 tincture drops (1:5, 55%), which equals 3 x 300 mg of dry root daily [11] or a lozenge containing 40 mg of the extract (= 260 mg of dry root) every 2 hours and no more than 9 daily [17].

Dosage safety

Contraindications as in *Echinaceae purpureae herba* with one addition - purple coneflower root is contraindicated for children under 12 [17].

Administration must not last longer than for 8 weeks [11]. The lack of treatment effects within 8 days of application requires a consultation with a pharmacist [17].

Echinacea pallidae radix – pale coneflower root

Echinacea pallida Nutt. – pale coneflower

Characteristic constituents

- caffeic acid derivatives – echinacoside (fig. 3)
- essential oil – alkanes
- alkyl ketones – 8-hydroxyketoalkenynes (fig. 4)

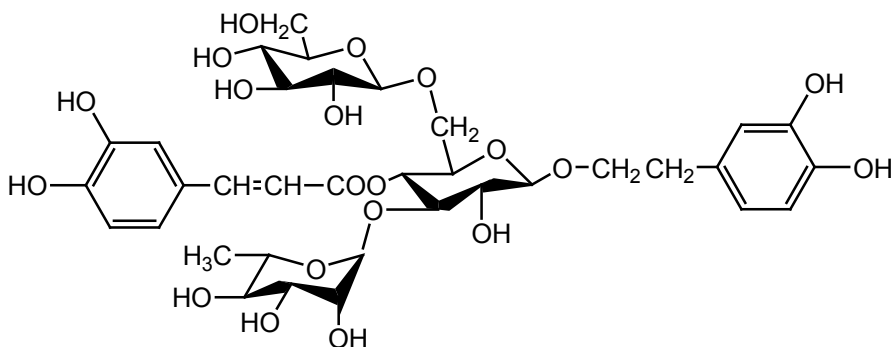


Figure 3. Echinacoside

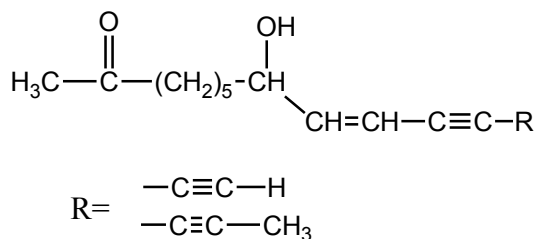


Figure 4. 8-hydroxyketoalkenynes

Pharmacological properties

An influence of ethanol extract and macromolecular compounds of the pale coneflower root on biosynthesis of the factors responsible for organism immunity has been investigated. *In vivo* and *in vitro*, an increase in phagocytosis and a higher concentration of interferon and immunoglobulins as well as cytokines such as interleukin 1 and 6 and TNF- α were observed [18]. Three kinds of pale coneflower root extracts (hot water, cold water and 50% alcoholic) were compared as for their influence on immune system factors: an increase in the number of interleukins 10

and 12 by monocytes TNF- α and proliferation of mononuclear peripheral blood cells. The cold water extract increased the TNF- α concentration of interleukin 12. However, proliferation of the peripheral blood cells was minimal [19].

In clinical studies, patients with flu-like symptoms were treated with an extract equivalent to 900 mg of dry material, and a statistically significant effect as for such symptoms as the pain in the arms and limbs, headache and weakening was obtained as compared with the *placebo* group. The treatment span was also shorter in the treatment group.

The studies indicate that the raw material might be applied adjuvantly in the prophylaxis and treatment of upper pulmonary airways infections and of cold [18, 20].

Dosage

Adults: 90 – 96 mg of dry extract in tablets divided into 3–4 daily doses or 25 drops of the 1:5 tincture 5 times a day [18, 20].

Dosage safety

As in *Echinaceae purpurea radix*

To be applied no longer than for 8 weeks [18], lack of treatment resulting within 10 days requires a consultation with a pharmacist/doctor [20].

Echinaceae pallidae herba – pale coneflower herb

Characteristic constituents

- caffeic acid derivatives - cichoric acid and echinacoside
- alkamides

Pharmacological properties

Older studies indicated influence of the herb on immune system. The extract from the raw material increases the speed of the elimination of ink molecules through phagocytosis in the reticuloendothelial system of the tested animals (Carbon Clearance Test). The results have been not confirmed yet [21].

Dosage

No data

Echinaceae angustifoliae radix – narrow-leaved coneflower root *Echinacea angustifolia* DC.

Characteristic constituents

- caffeic acid derivatives - echinacoside, cynarin (fig. 5)
- polysaccharides
- alkamides

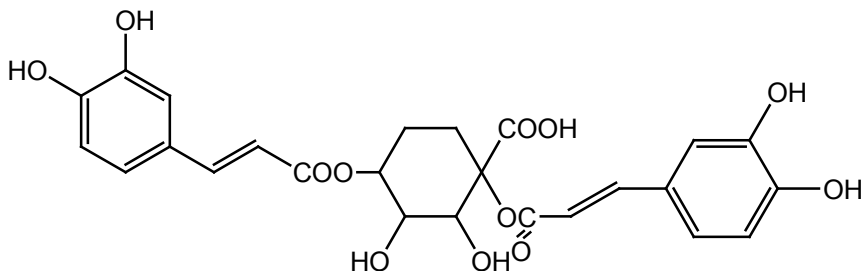


Figure 5. Cynarin

Pharmacological properties

The alcoholic extract at a concentration of 1 $\mu\text{g/ml}$ from the raw material increased the phagocytosis in the human granulocytes by 17%. Similar results were obtained for the water extract at the same concentration, whereas the chloroform fraction at tenfold lower concentration increased the phagocytosis stimulation by 34% [22]. Just like in the case of pale coneflower, three kinds of extracts (cold water, hot water and 50%-alcoholic) were compared as for the influence on immune system factors: the possible increase of interleukin 10 and 12 by $\text{TNF-}\alpha$ monocytes and proliferation of mononuclear peripheral blood cells. All the tested extracts increased the $\text{TNF-}\alpha$ concentration but only the alcoholic extract significantly increased interleukin 12 concentration [19]. Alkamides and polysaccharides isolated from the raw material in question increased the immunological response in *in vitro* tests. Moreover, alkamides inhibited lipo- and cyclooxygenase which implies anti-inflammatory activity. *In vitro* studies like Carbon Clearance Test showed that ethanol extract increased the phagocytosis of the test animals. Clinical studies of the narrow-lived coneflower root indicated diminishing of the frequency of upper pulmonary airways infections, but it was not statistically significant against *placebo* group nor prophylactically effective in rhinitis infections protection [23].

Dosage

Adults: daily dose 3 x 1 ml of ethanol extract or 3 x 60 drops of tincture (1:5, 50%).
Children: the dose adjusted to the age and body weight [22].

Dosage safety

As in *Echinaceae purpureae radix*.

To be applied no longer than for 8 weeks [22].

Aloe arborescens folium – aloe arborescens leaf

Aloe arborescens Mill.

It occurs in Eastern and Southern Africa and in Arabian Peninsula. In many countries (including Poland) it is grown for medicinal and cosmetic purposes. It

has characteristic fleshy leaves with barbed edges and tubular red orange flowers gathered in ebracteate inflorescences.

Characteristic compounds

- polysaccharides – aloemannans, neutral polysaccharides (composed of chains of arabinopyranose, galactopyranose and mannopyranose)
- glycoproteins – lectins

Pharmacological properties

Aloe-mannans, in the dose of 100 mg/kg of body weight, applied parenterally, exhibited anti-tumor activity in an *in vivo* study [24, 25].

In another study, various parameters of immunological, cellular and humoral response were investigated in mice for water extract from *Aloe arborescens* leaves grown in a herbal institute in Poland. The preparation stimulated migration activity of mouse splenocytes and chemiluminescent activity of mouse blood granulocytes. It also increased the antibodies (SRBC) production and stimulated skin angiogenesis which was induced for mice with leukocytes, isolated from healthy people and from patients with oral cavity infection. The most efficient activity of the extract was obtained after oral application in the dose of 2 and 4 μl . The results of the treatment with an 8 μl extract were comparable to those of *placebo* [25].

A clinical study on patients with upper airways inflammation demonstrated increased phagocytosis after application of neutral polysaccharides and glycoproteins from the leaf of *Aloe arborescens*. Clinical and pharmacological studies on water extract indicate its efficiency in hyp immunity as well as in upper airways infections.

Dosage

In ready preparations, to be applied orally only.

Visci herba – mistletoe herb

Viscum album L. – mistletoe

It is a semi-parasite with bushy habit and dichotomically branched leaves occurring both in coniferous and in deciduous trees.

Characteristic compounds

- glycoproteins – lectins
- polysaccharides

Pharmacological properties

Research showed that lectins are main compounds of the mistletoe herb to be

responsible for immunostimulating effect, mostly through the increase of lymphocyte T concentration. In *in vivo* conditions they also stimulate phagocytosis causing biosynthesis of various cells as an immunological response [27]. The water extracts standardized for lectins exhibit dose-dependent stimulation of immune system. Acidic polysaccharides contribute significantly to this effect. Water extracts preparations from the mistletoe herb are used in medicine. So far, about 50 clinical studies have been carried out. All of them concerned the influence of the mistletoe herb, applied parenterally, in the treatment of various types of cancers [1].

CONCLUSION

Raw plant material with immunostimulating activity can be particularly effective for people prone to upper airways infections provided that the dosage rules should be strictly observed, so that the doses and the treatment span are not exceeded. The analysis of possible usefulness of purple coneflower raw materials suggests that they might be supportive in the treatment of early symptoms of cold, and furthermore they might be very effective in preventive activity. The four materials from the three purple coneflower species, used on their own or as part of complex preparations, have differentiated chemical composition both quality – and quantity – wise. Thus, literature might suggest different dosage of preparations including these herbs as well as different application periods.

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SUROWCE ROŚLINNE I NATURALNE SUBSTANCJE WPŁYWAJĄCE NA UKŁAD ODPORNOŚCIOWY

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Streszczenie

Ziele i korzeń jeżówki purpurowej oraz korzeń jeżówki białej posiadają bardzo dobrze udokumentowaną aktywność immunostymulującą. W grupie leków roślinnych wpływających na system odporności organizmu wymieniany jest też korzeń jeżówki wąskolistnej, ziele jeżówki białej, a także liść aloesu drzewiastego i ziele jemioli pospolitej. Wśród aktywnych immunostymulatorów znajdują się związki wielkocząsteczkowe – glikoproteiny i polisacharydy oraz substancje małowcząsteczkowe – pochodne kwasu kawowego, alkaloidy i ketoalkeny.

Słowa kluczowe: rośliny lecznicze, odporność