Review Article

ECHINACEA PURPUREA – A POTENT IMMUNOSTIMULANT

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ABSTRACT

Medicinal plants possess several pharmacological activities that have immense application in present pharmaceutical field in order to explore natural drugs of lesser side effects and also the lesser cost. *Echinacea purpurea* L. is one among the plant with both pharmacological and the properties of the aesthetic enjoyment. It was found to contain immunostimulant, antileishmanial, cytochrome p450, apoptotic – mitotic and anti-microbial activities. It also effective on antibody and immune cell response and on the markers of aging and possess total antioxidant capability. It has contained several phytochemical compounds such as alkamides, caffeic acid esters (cichoric acid), polysaccarides, polyacetylenes etc. The plant was traditionally used for the treatment of respiratory infections, snake bite, tumour treatment, inflammation etc. and was particularly used for the stimulation of immune system.

Keywords: *Echinacea purpurea* L, Immuno stimulant, Pharmacological activities, Phytochemical compounds, Antitumour effect.

INTRODUCTION

Echinacea purpurea L. (EP) belongs to the family of *Asteraceae* is one of the most important medical herb with enormous pharmacological and aesthetic properties. During the year 2005, products obtained from the above plant were ranked among the top botanical supplements in United states. The roots and subterranean stems of the plant were used by the North Americans for the treatment of trauma and also to alleviate symptoms of infection and inflammation. The EP was found to show good immunoregulatory, anti-inflammatory and antioxidant capacity[1,2] with neither the symptoms of hypersensitivity nor the side effects during the clinical trial stages[3]. The important components in the plant were found to be caffeic acid derivatives, alkamides, flavonoids, essential oils and polyacetylenes[4]. Among them, caffeic acid derivatives and alkamides were proved to have immunoregulation effects[5]. The caffeic acid derivatives, alkamides and polysaccharide fractions were found to show inhibition against in vitro Cu(II)-catalyzed oxidation of human low-density lipoprotein (LDL) that proves the presence of antioxidant property[6]. The plant is grown mainly for its ornamental value because of its showy flowers[7]. The allergic reaction is the most common adverse effect that occurs in adults who are sensitive to plants belonging to the daisy family. Other side effects include the activation of autoimmune disorders such as multiple sclerosis and collagen disease. *Echinacea* was found to be safe for oral and topical use, except for the patients who are allergic to it.

Alternative names

Echinacea, snakeroot, kansas snakeroot, narrow-leaved purple coneflower, scurvy root, Indian head, comb flower, black susans, and hedge hog.

DESCRIPTION

Echinacea purpurea belongs to sunflower family is a perennial herb of about 1.5-6 dm (0.5-2 ft) tall, with a woody rhizome or tough caudex. The plant has rough-hairy stems that is mostly unbranched. Basal and lower cauline leaf blades are ovate to ovate-lanceolate with serrate edges, up to 2 dm long and 1.5 dm wide, and slightly heart-shaped at the base. Cauline leaves are similar but become smaller as they extend up the stem. The flowers are in heads like sunflowers with the disk up to 3.5 cm across. The drooping ray florets have ligules 3-8 cm long, and are reddish-purple, lavender, or rarely pink. The disk florets are 4.5-5.5 mm long, and are situated among stiff bracts. Flowers bloom from June to August. Pollen grains are yellow. Fruits are small, dark, 4-angled achenes.

DISTRIBUTION AND ESTABLISHMENT

The purple coneflower grows in rocky prairie sites in open, wooded regions. *Echinacea purpurea* extends eastward through the Great Plains bioregion from northeast Texas, Missouri, and Michigan. Native *Echinacea* species are dwindling in the wild from loss of habitat and over-harvesting. *E. purpurea* is not as threatened as *E. angustifolia*. In the wild, *E. purpurea* grows sporadically along waterways, with a few scattered individuals. Plant densities are too low for efficient harvest for commercial purposes. *E. purpurea* is the most widely adaptable species for cultivation. It is cold and heat hardy, easy to grow, and boasts high yields. Bioactive constituents *of E. purpurea* compare favorably with *E. angustifolia*, although there are proportional differences. *E. angustifolia* has more of the alkylamides, while *E. purpurea* has more of the equally immune enhancing caffeic acid derivatives. They are both effective medicines. A combination of both probably affords the most broad-spectrum immune-enhancing effect.

Historically, *E. purpurea* was rarely utilized by pharmaceutical companies.

MEDICINAL USES

The *Echinacea* was traditionally used by the native Americans as a anti-infective and snake-bite remedy and also to assuage coughs associated with colds[8]. *Echinacea purpurea* root was commonly used all around the world for the stimulation of the immune system [9]. It was used as the herbal medicine in treating the respiratory infections, against malignant tumors and several other inflammatory conditions[10-13]. *Echinacea purpurea* was appeared to activate the non-specific cellular and humoral immunity and the complement system. The species was found to stimulate the immune system by means of increasing the production and activation of leukocytes, lymphocytes, monocytes and cytokines[14]. *Echinacea*, which was commonly used for the treatment of common cold, coughs, bronchitis, influenza and inflammation of mouth and pharynx, is found to rank in second position in the highest retail sales for over-the-counter herbal products[15-18]. It is found to be the most frequently used herbal remedies in case of the treatment for adults and children and hence consumed by approximately over 10 to 20% of the herbal users[19-23].

Purple coneflower (*Echinacea purpurea*) which is a medicinal plant was found to be used widely Plains Indians as a painkiller and for the treatment of the varied ailments, including toothache, coughs, colds, sore throats, and snake bite[24]. The Choctaw use the purple coneflower as a cough medicine and the gastro-intestinal aid[25]. The Delaware used an infusion of coneflower root for the treatment of gonorrhea and found it to be highly effective. The purple coneflower was popularized as a medicine by the folk practitioners and doctors and was found to be the only native prairie plant and was used extensively as a folk remedy[24]. The most important property of the plant was found to be the immuno-stimulatory property that involves in the stimulation of the immune system based on the dose level[26,27].

Echinacea has also been used to treat other conditions such as infections of the urinary tract and is applied topically for the healing of the wounds and burns. However, the Primary use of the plant remains to be the prevention and treatment of upper respiratory tract infections (URTI) and other purported benefits such as the prevention and treatment of viral, bacterial and fungal infections such as otitis media, pharyngitis, sinusitis, candidiasis, cystitis, chronic fatigue syndrome, acquired immunodeficiency diseases (AIDs), snake bites[28-30]. A perennial plant native to North American, *Echinacea* was used by the Plain Indians for the treatment of fever and respiratory infections and by the Delaware Indians to the treatment of venereal disease[31]. A paste that was made out of the entire mashed plant was used topically for the treatment of snake bites, stings, burns, and swelling of the lymph glands (“mumps”). The roots were asked to chew or the juice is ingested in order to treat sore gums, toothaches, and sore throats[32].

PHYTOCHEMICAL CONSTITUENTS

Commercial preparations of the medicinal plant *Echinacea purpurea* are among the most popular herbal medicines in North America for the treatment of colds and flu[17]. The major chemical components of *E. purpurea* have been well characterized[33] and various biological activities that were associated were found out. For example, the polysaccharide fraction was found to stimulate the macrophage activity and several other functions that were related to the cytokine production[33-36] and certain groups of the phenolic compounds and alkamides was found to demonstrate the antiviral and antifungal properties[37,38]. *Echinacea purpurea* contains alkamides, caffeic acid esters (cichoric acid), polysaccarides and polyacetylenes[6,39].

Cichoric acid was found to be the main phenolic compound (2.27%) and the highest contents of caffeic acid derivatives were also found in *E. purpurea* roots[40]. Cichoric acid and verbascoside was found to be predominated in the extracts of *E. purpurea* roots[41]. Extracts of the roots and leaves was found to have the antioxidant properties in a free radical scavenging assay and in a lipid peroxidation assay[42].

The ethanolic extract of *Echinacea purpurea* roots contains nearly 15 alkamides[43,44]. Amides were found to be the principle lipophilic constituents of *E. purpurea* roots[45,46]. Higher concentration of isobutylamide was present in the roots of *E. purpurea*[47] and found to inhibit arachidonic acid metabolism to inflammatory prostaglandins and may also account for some of *Echinacea*’s anti-inflammatory effects[48]. The alkylamide content gets varied over the life cycle of *E. purpurea’s* that was found to be gradually decreasing in the aerial parts and increasing in the roots as the plant matures[49]. The alkylamides from the roots of *E. purpurea* possess various structures, but the aerial portions contain the similar compounds. *Terpenoids* which were previously isolated from *E. purpurea* (e.g. germacrene) was found to be attributed more recently to the similar appearing plant, *Parthenium integrifolium*, which is found to be a frequent contaminant of *Echinacea* products[50].

The hydrophilic, highly polar constituents, remarkably polysaccharides and glycoproteins, were present most prominently in the expressed juice of the plant, and in aqueous and hydro alcoholic extracts of the aerial parts[51, 52]. In a phase-I clinical trial, a polysaccharide fraction was isolated from *E. purpurea* tissue culture, caused an increased production of leukocytes, segmented granulocytes, and tumor necrosis factor *alpha* (TNFa). In addition, certain high-molecular weight proteins were also isolated from the roots of *E. purpurea*[53].

PHARMACOLOGICAL ACTIVITIES

Immunostimulant capacity *in vitro*

Echinacea purpurea L. (EP) is a medicinal plant originally used by native Americans in order to treat respiratory infections, wound healing and to enhance the immune system. A study was conducted to demonstrate the ability of EP extracts for stimulate the production of nitric oxide (NO) and TNF-α as well as to evaluate the cell viability by the use of chicken peripheral blood mononuclear cells (PBMCs) and RAW 264.7 macrophages *in vitro* which showed the polysaccharides content of EP was 162.2±8.4 mg/g dry weight (DW) when compared to the EP extracted with a 55% ethanol that contained only 22.3 ±1.0 mg gallic acid equivalent/g DW of total phenolic compounds and 86.0 ± 4.6 mg quercetin equivalent/g of flavonoid content. And also 89% and 81% of chicken PBMCs and RAW 264.7 macrophages showed positive for the cell viability under the treatment of 3.2 mg/ml of EP extracts and also the NO production and the release of TNF-α by RAW 264.7 goes linear to the dosage level. This shows the potential immunostimulant capacity of the EP extracts[54].

Effect of *echinacea purpurea* on antibody and immune cell response

A study tried to explore the effect of aqueous extract of *Echinacea purpurea* roots on the murine antibody response to *Bothrops asper* snake venom *in vivo* and they found remarkable increment in the level of anti-venom antibodies. Human lymphocytes that were activated with different lectins (Con A, PHA and PWM) for the study of the *In vitro* immune cell proliferation as a response to aqueous extract of *E. purpurea* root showed the increase in percentage of lymphoproliferation was greater when *E. purpurea* root extract was used in addition to individual lectins[55].

Effect of *echinacea* as antioxidant on markers of aging

Aging is found to be the multifactorial process that leads to the loss of function and the inability to adequately respond to external stress. The use of natural phytochemicals present in natural sources as antioxidants and functional foods has become the global trend. The effect of ethanolic and water extracts of *Echinacea purpurea* roots as natural sources of antioxidants on markers of aging was conducted in a study, where 24 Sprague-Dawley female rats were used. The activity of superoxide dismutase (SOD) and glutathione-s-transferase (GST), liver functions, total cholesterol, HDL, LDL, VLDL and triglycerides levels, blood hemoglobin and hematocrit counts were the parameters measured. Administering aged rats with *Echinacea* ethanolic and water extracts showed a significant improvement in increased and decreased levels of the above mentioned markers and returned the abnormal markers back to the normal levels[56].

Efficiency of *echinacea purpurea* on total antioxidant activity

The dried aerial part powder of *Echinacea purpurea* (EP) possess a significant efficiency on the total antioxidant activity (AOA) in serum of broiler chicks in comparison with an antibiotic (flavofosfolipol).The use of 10 g EP/kg diet was found to improve the total antioxidant activity in serum of broiler chicks. Hence, the plant with high potential to conduct assay on its antioxidant activity, with antioxidant activity assay further broken down to items of preventing oxidation and scavenging free radicals[57].

Immunological activity

The immunomodulating effects of *E. purpurea* were conducted in a study on female volunteers in the first clinical trial. Complement properdin was found to increase after four weeks of intervention. The increased complement properdin might be found as an indication of one of the aspect in immune system stimulation for patients who were treated with either *E. purpurea/E. angustifolia* or *E. purpurea/E. angustifolia* plus larch arabinogalactan[14].

Stimulatory effect

Several *Echinacea* species was used as botanical drugs for the purpose of “immunostimulation”. A phytocompound mixture extracted from butanol fraction of a stem and leaf extract of *E. purpurea* was investigated in a study for its transcriptomic and proteomic effects on mouse bone marrow derived dendritic cells primary cultures. The result showed no significant influence on phenotypic maturation activity of the dendritic cells (DCs). Affymetrix DNA microarray and bioinformatics analyses of genes that were differentially expressed in DCs treated with [BF/S+L/Ep] showed that the majority of responsive genes were related to cell adhesion or motility. A research with TRANSPATH database analyses of the gene expression and related signaling pathways in treated-DCs has predicted that the JNK, PP2C-a, AKT, ERK1/2 or MAPKAPK pathways as the putative targets of the mixture. The proteomic analysis showed that the expressions of metabolic, cytoskeleton or NF_B signaling-related proteins were actually regulated by the treatment with compound mixture. Thus, the mixture was found to modulate the DC mobility and related cellular physiology in the mouse immune system[58].

Cytochrome p450 activity

Tinctures of *Echinacea* was found to inhibit the cytochrome P450 (CYP) *in vitro*. But, the effect of *Echinacea purpurea* root on the CYP activity in vivo was assessed by use of the CYP probe drugs caffeine (CYP1A2), tolbutamide (CYP2C9), dextromethorphan (CYP2D6), and midazolam (hepatic and intestinal CYP3A) on human. The study showed that the *Echinacea* administration was found to significantly increase the systemic clearance of midazolam by 34% and also significantly reduced the midazolam area under the concentration-time curve by 23% but no effect on the

oral clearance of midazolam. *Echinacea* dosing significantly reduced the oral clearance of caffeine and tolbutamide but no effect on dextromethorphan. Thus, *Echinacea purpurea* root was found to reduce the oral clearance of substrates of CYP1A2 but not the oral clearance of substrates of CYP2C9 and CYP2D6[59].

Anti viral activity

The aqueous fractions of the stems, leaves, and flowers of *Echinacea purpurea* possess potent anti-viral activity against herpes simplex virus and influenza virus. But, the activity was found to be attributed to the polysaccharide and cichoric acid components also. The ethanol and ethyl acetate-soluble fractions from the leaves and stem was found to contain a potent antiviral photosensitizer, which was absent in the flower extract[60]. Randomized controlled trials for the treatment of URTI (upper respiratory tract infection) was also supported the use of *Echinacea* at the first sign of a URTI treatment in adults[61]. In another study Dietary *Echinacea* did not enhance the growth, exhibit antiviral effects to porcine reproductive and respiratory syndrome virus (PRRSV), or show any evidence of immune enhancing properties[62].

Antifungal activity

The *in vitro* study data showed that the human granulocytes and monocytes which were treated with *E. purpurea* extracts showed the enhanced mobility and increased phagocytosis of *Candida albicans*[63]. Purified polysaccharides from *E. purpurea* was reported to inhibit *Candida albicans* growth *in vitro*[64].The Animal data study showed that the pre-treatment with polysaccharides from *E. purpurea* has provided significant protection against the injections of lethal doses of *C. albicans* in mice[65]. In German, a human study was conducted in 203 women who were suffering from the recurrent vaginal infections with *Candida albicans* was treated with topical econazole cream and Echinacin. In which, with Echinacin the recurrence rate was found to be only 16% in those who have received *Echinacea* by any of the routes[65].

Toxicology and adverse effects

The side effects and toxicological risks of *Echinacea* preparations were very low and the reports showed that *E. purpurea* root extract and *E. purpurea* aerial parts pressed juice was found to possess the acute toxicity in an extremely low level[66].

Antileishmanial effect

Search for useful medicinal plants for the therapy of leishmaniasis is necessary due to the limited availability of the effective pharmaceutical products and serious side effects that were caused by them. The immunologic stimulation of *Echinacea* against *Leishmania* infections was already reported. The concentrated ethanolic extract of the root of *Echinacea purpurea* preparation was also found to show the irreversible direct leishmanicidal activity against *Leishmania major* promastigotes at the crude concentration of 50 mg/ml[67].

Apoptotic - mitotic activity

Cadmium (Cd) is an important industrial pollutant and especially Cd^{2+} is much toxic to a wide range of organs and tissues such as liver and kidneys which are the primary target organs of cadmium toxicity. Cd^{2+} was found to induce apoptosis, mitotic activity of the cells and also causes necrotic cell death in case of certain pathophysiological situations. *Echinacea purpurea* is the stimulating agent for the production of immunoglobulins and/or interferons by means of stimulating one or another link of the immune system. The study showed that the long-term injections of *Echinacea purpurea* extract in combination with $CdCl_2$ lead to significant increase in cadmium concentration tested in the liver and kidney of experimental mice. *Echinacea purpurea* was found to decrease the cadmium-induced mitotic activity of liver cells, and increased the apoptotic activity of these cells.[68]

CONCLUSION

Medicinal plants were the potent source of the ancient people for the treatment of various diseases. They used the crude extract of the plant as such without knowing the actual mechanism of action and treated many diseases. But, the recent research involves in exploring the active principles of the plant that is responsible for a particular action and uses it in the pharmaceutical field to obtain drugs. These naturally available drugs are more potential in its targeted function and tends be of less manufacturing cost. Moreover, the drugs obtained from the medicinal plants of historical values doesn't cause any side effects that are caused by the synthetic drugs obtained from the chemical sources. The medicinal plant like *Echinacea purpurea* possess several pharmacological properties and contains a huge number of phytochemical compounds in it. Thus, these compounds could be used in the pharmaceutical industries to produce more drugs for the treatment of several diseases. This review encompasses on the advantage of using the above plant in further researches and its application in the pharmacy to produce drugs.

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