PHARMACOLOGICAL IMPORTANCE OF ECHINACEA PURPUREA

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ABSTRACT

Echinacea (E.) purpurea is a medicinal herb commonly known as the purple coneflower, red sunflower and rudbeckia. Echinacea purpurea, a plant is mostly used to treat respiratory infections. This paper reviews the history, chemistry and pharmacological action of Echinacea species. The Echinacea species, Echinacea angustifolia, Echinacea pallida and Echinacea purpurea have a long history of medicinal use particularly infections, and today Echinacea preparations are the best herbal medicine used in several countries like America, Germany, Australia, Thailand and some other European countries. Mainly Echinacea is focused on its immunomodulatory effects, anti inflammatory and antioxidant effects, anti viral effects, particularly in the prevention and treatment of upper respiratory tract infections. The chemistry and pharmacology action of Echinacea species is well documented and several groups of bioactive constituents, including alkaloids and lipophilic alkaloids, water-soluble phenolic compounds (mainly caffeic acid derivatives) and polysaccharides, benzalkonium chloride are considered important for its activity. The efficacy of Echinacea is not yet revealed completely. From the available data it is reported Echinacea appears to be well tolerated. However, further investigation and surveillance are necessary to establish the safety profiles of different Echinacea preparations. Safety issues include the possibility of allergic reaction, dose dependent adverse effects and overdose. In this article we have reviewed the role of bioactive compounds and the pharmacological properties of Echinacea purpurea.
KEY WORDS

Immunomodulatory, anti-inflammatory, anti-oxidant, Phenolic compounds and alkamides

INTRODUCTION

Echinacea is the composite family of Asteraceae, which is commonly known as purple cone flower. Echinacea is perennial, herbaceous plant mostly found in eastern North America. McGregor (1968) and Binns et al (2002) presented the detailed morphological classification as well as the numerical and statistical method of the Echinacea. According to McGregor and Binns there are 11 Taxa and 2 subgenera and four species with two botanical varieties were recognized.

Echinacea is an herbal medicine, which is used by native Americans for enhancing the human immune system, the herbal product which is found in the Echinacea was isolated for the roots of Echinacea angustifolia Dc and form the nut of Echinacea Pallida which has consistently one of the top species in the U.S herb market. In Europe and North America they widely used the Echinacea purpurea (L) Moench as the herbal medicine for most of the remedies. Due to the increased market demand, economic value and its potential benefits to human health make increased cultivation of Echinacea. As well as, a little effort has been directed in the field of genetic improvement of Echinacea for medicinal use. Beside this, Echinacea purpurea is used for both ornamental use and phytochemical use has been conducted in Europe, United States and Australia.

Three groups of phytochemicals are determined such as caffeic acid derivatives, polysaccharides and lipophilic alkamides, which are responsible for the genus medicinal properties. Both immunological and pharmacological studies showed that the importance of caffeic derivatives and cichoric acid, more over the result demonstrated immunological activity of alkamides both invitro and invivo. Most recent studies of placebo-controlled clinical studies identified that the liquid extraction of freshly harvested flowering top of Echinacea purpurea contains alkamides(0.25mg), cichoric acid(2.5mg) and polysaccharides(25.5 mg.ml-1) respectively, which is used to treat common cold in adults thus Echinacea purpurea is widely utilized and cultivated species, accounting for 80% of commercial production.

Due to the human health benefits of Echinacea, it is vital to increase the bioactive compounds of the plant by doing breeding and selection for extract preparation, the roots and above ground parts are used, which is potentially useful to evaluate the relationship between the roots and above ground parts to know the production of phytochemicals as well as variation among individual plants. The significant variations were found in caffeic acid and alkamides in different plants and its developmental stages were reported by Li, Binns et al and Stuart et al.

HISTORY

The Echinacea plant have been used since 1600 by native Americans, the Echinacea used for a variety of medical problems like sore gums, coughs to bowel trouble and snake bites. Echinacea purpurea is one of the most popular herbal plants cultivated in North America. Other name of Echinacea is 'Echinos' (the word comes from Greek) and also named as perennial herbs, Indianhead, comb flower and hedgehog. Echinacea have close relationship with Asteracea family members like sunflowers, ragweed and daisies. The general
treatment of Echinacea did not occur until 1800’s. The root extract used as a blood purifier\textsuperscript{21,22} also marketing as anti-infective agents\textsuperscript{20}. Echinacea purpurea is very popular in beginning of this century and starts from 1916 to 1950. Recent studies have been focused on Echinacea to treat upper respiratory problems, urinary tract infections, chronic wounds, and snake and mosquito bites\textsuperscript{24}.

CHEMISTRY

The active substances of Echinacea are polysaccharides, flavonoids, chicoric acid, alkyl amides, polyacetylenes and essential oils\textsuperscript{20,23}. Polysaccharides and chicoric acid glycosides have immunostimulatory activity in Echinacea. Based on the composition, extraction method and time of harvest the Echinacea purpurea is differ from other Echinacea species. Part of the plant using can mainly affect the amount of active substance\textsuperscript{21}.

PHARMACOLOGY

The number of polysaccharide have been isolated and analysed its pharmacological effects on the immune system. The high molecular weight polysaccharide heteroxylan has potential to activate phagocytosis. Other polysaccharide arabinogalactan induces the release of tumour necrosis factor (TNF) that increases the level of macrophage interlekin-1 and interferon beta-2. Alkylamide and chicoric acid glycosides also stimulate phagocytosis. Isobutylamide is one of the alkylamides which gives pungent smell and distinct taste for Echinacea\textsuperscript{25}. Echinacea have an antibacterial or antiviral activity through the immune system modulation, thus indirectly it acts on infection. Several studies on pharmacology of Echinacea used the parenteral formulation, because it is unclear activity of orally administered preparations\textsuperscript{21,26}.

MEDICINAL USES

Echinacea angustifolia, Echinacea Pallida and Echinacea purpurea are used medicinally. The constituents of each species of herb are similar with slight variations but they varied each other according to the active compounds present in roots, leaves and whole plant. Most of American Indians have been used medicinal preparation of Echinacea purpurea for the treatment of many diseases, including colds, toothaches, snake bites, headache and wound infections\textsuperscript{27}. It is the most effective antioxidant and it has immunoenhancing effects\textsuperscript{28}. The roots of Echinacea are used to treat blood poisoning, snake poisoning, skin disease, syphilis and rabbis. Echinacea purpurea herb is also used to treat chronic infections of respiratory tract and lower urinary tract (viral and bacterial origin). The polysaccharide from Echinacea purpurea used to kill bacteria such as staphylococci. Arabinogalactan, a high molecular weight purified polysaccharide from plant cell cultures of Echinacea purpurea has potent to activate macrophage cytotoxicity actions against tumor cells and micro organisms\textsuperscript{27}.

BIOACTIVE COMPONENTS OF ECHINACEA PURPUREA

Earlier studies reported that many bioactive components have been identified in Echinacea.

Above ground parts of Echinacea plant have less oils and pyrrolizidine alkaloids, such as tussilagine and isotussilagine than the root parts. The active components of the upper plant are thought to be caffeic and ferulic acid derivatives (such as cichoric acid and echinacoside) and complex polysaccharides (such as acidic arabinogalactan, rhamnoarabinogalactans, and 4-O-methylglucuronylarabinoxylans).

Alkamides and alkamide-rich alcohol extracts of Echinacea inhibit production of inflammatory mediators\textsuperscript{29,30}. Lipophilic alkamides, water-soluble phenolic compounds (mainly caffeic acid derivatives) and polysaccharides are the most recognized for their immunomodulatory properties\textsuperscript{31}.
Glycerin extract of *E. purpurea* increases in immunoglobulin (Ig) M response against sheep red blood cells (sRBC) in the mice. Polysaccharides were considered critical for stimulation of nonspecific immune responses.

*E. purpurea* found an increase in CD4+ T-lymphocytes in mouse peripheral blood but implied it is a secondary effect in association with macrophage activation. Alkamides and Caffeic acid derivatives are good antioxidants in cell-free free radical generation systems.

The main caffeic acid derivative (caftaric acid, chlorogenic acid and echinacoside) in EA and EPA, has been functionally linked to anti-inflammatory and wound healing properties of *Echinacea* when applied topically.

Caffeic acid derivatives are effective antioxidants in free radical generation systems. Groups of phenolic compounds and alkamides, which have demonstrated antiviral and antifungal properties, respectively. Benzalkonium chloride and phytochemicals derived from *Echinacea purpurea* was reported to have antiviral activity against herpes virus in a human cell model.

**PHARMACOLOGICAL ACTION**

**ANTI-INFLAMMATION ACTIVITY**

*Echinacea purpurea* is one of the main medicinal *Echinacea* species and have long been used to treat infections, to aid in wound healing and to enhance the immune system. Alkamides and caffeic acid derivatives are potent anti-inflammatory agents present in *Echinacea* derived alkamides have immunomodulatory and anti-inflammatory activity. *E. purpurea* (EP) have been used for wound healing, pain relief and alleviation of cold symptoms. Alcohol extracts of *Echinacea* offers anti-inflammatory effects through inhibition of production of inflammatory mediators tumor necrosis factor-alpha (TNF-α) and nitric oxide (NO). Prostaglandin E2 (PGE2) is a critical inflammatory mediator that is produced through the arachidonic acid cascade. The anti-inflammatory role of *Echinacea* is also mediated through own regulation of cyclooxygenase-1 and cyclooxygenase-2 through suppression of Prostaglandin E2 activation. COX-1 and COX-2 catalyze the reaction converting arachidonic acid, released by phospholipase A, to Prostaglandin E2. Wagner has reported lipoxygenase-inhibiting anti-inflammatory activity attributable to one of *E. purpurea*’s isobutylamides, dodecatetraenoic acid.

Alcohol extracts of *Echinacea* are composed of two classes of natural chemicals lipophilic alkamides and water-soluble caffeic acid derivatives. Caffeic acid derivatives have an antihyaluronidase activity. An inhibition of hyaluronidase leads to accumulation of enough hyaluronan in the extracellular matrix for wound repair. In rats, excision wounds treated with a caffeic acid derivative, showed a healing process characterized by reduced inflammatory response and higher hyaluronan content. These data indicate that *Echinacea* presents a clear anti-inflammatory activity that may promote wound tissue recovery. However, there are no studies that have tested the efficacy of oral administration of *Echinacea* or its chemical constituents in wound healing.

**ANTI-OXIDANT ACTIVITY**

*Echinacea* was found to be a very potent antioxidant. Arachidonic acid metabolism and prostaglandin E2 production were reduced by several *E. purpurea*. Alcohol extracts of *Echinacea* are typically composed of two classes of natural chemicals, lipophilic alkamides and water-soluble caffeic acid derivatives. Caffeic acid derivatives are effective antioxidants in free radical generation systems and have an anti-hyaluronidase activity. Enhancement of free-radical scavenging activity has been shown by laboratories in the U.S. and Canada. Hu and Kitts investigated anti-oxidant and free-radical
scavenging activity, including suppression of oxidation of human low-density lipoprotein.

**ANTI IMMUNOSUPPRESSANT**

Echinacea products are the most popular herbal immunostimulants in North America and Europe. In 1997 Echinacea may be best known as an immunostimulant. There have been numerous reports of immunomodulatory properties in various preparations derived from different parts of several species of Echinacea. A series of studies in mice using purified polysaccharides from Echinacea plant cell cultures showed a stimulatory effect when applied to immune cells in culture or injected intraperitoneally into mice. Mice with suppressed immunity due to treatment with cyclophosphamide or cyclosporin also had an increase in these immune functions when given purified polysaccharides from Echinacea. These studies suggest that Echinacea stimulates immune functions in healthy or in immunosuppressed animals. These immunologically active polysaccharides did not stimulate all immune cells. B cells were not activated, nor did the B cells produce more antibodies to sheep red blood cells. Apparently, Luetting et al purified polysaccharides from E. purpurea act on the nonspecific branch of immunity. Recent studies have been shown that rhinoviruses could stimulate the transcription of various immuneresponse genes in different types of cells. Furthermore the expression of cytokine genes and some of their secreted products in bronchial epithelial cells could be reversed by Echinacea preparations. Several animal and human studies have suggested that Echinacea stimulates neutrophil and macrophage phagocytic function. Other scientific studies suggest that the Echinacea purpurea possesses nonspecific, short-term immune system stimulant properties.

**ANTI FUNGAL ACTIVITY**

The Extract of E. purpurea has been shown to have antifungal activities in a series of in vitro experiments testing activity against various Candida species, and various Saccharomyces cerevisiae, Candida albicans the most common fungal cause of human skin disease. Antimicrobial actions were observed in various E. purpurea root and herb extracts. Other laboratories have also reported anti-Candida activity of extract of Echinacea purpurea. Phagocytosis of Candida by ex vivo human macrophages and natural killer cells was found to be enhanced following exposure to extracts of both E. purpurea and Gingseng. Mouse macrophage activity against Candida has also been observed to be stimulated by E. purpurea polysaccharide exposure. The polysaccharide rich Echinacea purpurea extract was found to decrease the infection and death rates of immunosuppressed mice infected with Candida. Coeugniet and Kuhnast demonstrated a human clinical trial testing an expressed juice of E. purpurea (Echinacin®) for ability to effect recurrent vaginal yeast infections. They found Echinacin®-treated groups demonstrated increased skin reactivity and decreased recurrence of vaginal candidiasis over the 6-month monitoring period while 60% of controls got new infections, only 5–17% of women in the treatment groups were diagnosed with recurrent vaginal infections (P < 0.05).

**ANTI VIRAL ACTIVITY**

Biological activity of the chemical Components of E. purpurea have been characterized. Eichler and Kruger reported Echinacea has antiviral and anti bacterial activity and they have found that cultured cells infected with virus and exposed to E. purpurea juice demonstrated an increased rate of presentation of viral antigen. Benzalkonium chloride and phytochemicals derived from Echinacea purpurea was found to have antiviral activity against herpes virus in a human cell model. Echinacea purpurea was also very effective.
against influenza virus. Skwarek et al revealed that the extract of E. purpurea has been found to inhibit viral replication in animal cell viral culture models. Eilmes demonstrated that complex hydrophilic and lipophilic extracts of Echinacea has more viral-infection- inhibitory activity fractions. Polysaccharide derived from Echinacea purpurea has been shown to stimulate macrophage activity and several functions related to cytokine production and groups of phenolic compounds and alkalamides, which have demonstrated antiviral and antifungal properties, respectively. These activities could be related to the reports that some E. purpurea preparations were able to prevent or control upper respiratory infections (URIs). Turner and colleagues have recently described a human trial testing the efficacy of Echinacea in preventing colds induced by a cultured rhinovirus. There are no reports on E. Purpurea in relation to HIV.

**CONCLUSION**

Extensive literature survey revealed that Echinacea has a long history of traditional use for a wide range of diseases. Much of the traditional uses have been validated by scientific research. It is the most important species that has more herbal medicinal value. The plant is used in common cold, coughs, bronchitis, upper respiratory infections, urinary tract infections and some inflammatory conditions. Studies suggest in this article that Echinacea possessed anti-inflammatory activity, antiviral activity, anti fungal activity, anti oxidant activity and anti immunosuppressant activity. Although many of the active compounds of Echinacea have been identified, the mechanism of action is not known, nor is the bioavailability, relative potency, or synergistic effects of the active compounds known. Existing literature suggests that Echinacea should be used as a treatment for illness, not as a means for prevention of illness. The studies reported in the present review confirm the medicinal value and pharmacological action of Echinacea purpurea. Future work needs to be carried out to identify the species of Echinacea and efficacy of the different plant parts (roots versus upper plant parts).

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