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Echinacea – chemical composition, immunostimulatory activities and uses.

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Abstract: Immunostimulatory, anti-inflammatory, antioxidant and cicatrising activities are the main properties described, which make Echinacea useful in the treatment or the prevention of different pathological conditions. Nowadays is Echinacea used primarily to stimulate the immune system and to help prevent infections and colds. Echinacea is used less commonly as a topical preparation to enhance healing for minor wounds, eczema, burns, psoriasis, herpes, and other dermatologic conditions. It is also included in a number of dental and cosmetic preparations. *Echinacea angustifolia* DC, *E. pallida* (Nutt) Nutt., and *E. purpurea* (L.) Moench. are commercially important sources of phytopharmaceuticals and other medicinal preparations.
This report will discuss the recent literature on *Echinacea* plants, focusing on their biochemistry and therapeutic applications as immunostimulants.

Keywords: *Echinacea*, chemistry, immunostimulatory properties, therapeutic effectiveness.

Chemical composition

Echinacea species contain a great variety of chemical components that contribute to their activity. The most important components to which activity can be attributed include high molecular-weight polysaccharides, polyacetylenes, highly unsaturated alkamides, and caffeic acid derivatives (BAUER & WAGNER 1991). Some of the constituents are unique to one species, while others occur in two or more of the commercially important species.

Since *Echinacea* preparations may vary in chemical composition, their therapeutic effectiveness may be inconsistent. Factors that may influence the chemical composition of *Echinacea* preparations include what species of *Echinacea* is used (*E. purpurea*, *E. pallida* and *E. angustifolia*), what part of the plant is used (leaves, flowers, stems or roots), growing, drying and storage conditions and method of extraction (PERRY et al. 20001, KIM et al. 2000a,b, GRAY et al. 2003). Freshly harvested *Echinacea* is likely to be more effective than preparations that have been stored for long period of time since prolonged storage may result in the loss or damage of beneficial active constituents (PERRY et al. 2001).

Phenolic Compounds

Phenylpropanoids

Caffeic acid derivatives reported from *Echinacea* species include echinacoside, des-rhamnosylverbascoside and 6-O-caffeoylechinacoside, cynarin, cichoric acid, caftaric, chlorogenic and isochlorogenic acids, and others (BAUER & WAGNER 1991).

Echinacoside has been identified in the roots of *E. angustifolia* and *E. pallida* at concentrations of 0.3–1.3% and 0.4-1.7% of dry weight, respectively, but not in *E. purpurea*.

Many products are standardized for echinacoside content (found primarily in. *E pallida*), which was once thought to be major active ingredient, but is now believed to be minor, aside from its role in species identification (FOSTER 1990).

Cichoric acid is the major active compound found in the roots and flowers of *E. purpurea* with a concentration range of 1.2-3.1% and 0.6-2.1% of dry weight, respectively, and present in smaller amounts in *E. pallida* and *E. angustifolia* (BECKER & HSIEH 1985, BAUER et al. 1988a, BAUER & WAGNER 1991, AWANG & KINDACK 1991). The controlled drought stress can stimulate increased cichoric acid content in *E. purpurea* roots (GRAY et al. 2003). Quantitative determination of cichoric acid in numerous *Echinacea* extract by HPLC revealed big variation in content of this compound (BECKER & HSIEH 1985). Concerning cichoric acid stability, it was recently shown that enzymatic degradation by polyphenol oxidases occur in aquaeous extracts of fresh *E. purpurea* (KREIS et al. 2000, NÜSSLEIN et al. 2000).

Flavonoids

Rutoside is the major flavonoid found in the leaves and stems of *E. angustifolia*, *E. pallida* and *E. purpurea*. In addition, the following flavonoids have been reported, and occur as both the aglycones and as conjugates with various sugars: luteolin, kaempferol, quercetin, quercetagetin, apigenin, isorhamnetin. The flavonoid content of the leaves calculated as quercetin, has been estimated at 0.48% for *E. purpurea* and 0.38% for *E. angustifolia* (BAUER & WAGNER 1991).

Terpenoid Compounds

All three commercially important *Echinacea* species contain varying amounts of essential oils in the roots, leaves, flowers, and other aerial parts (MAZZA & COTRELL 1999). Concentrations of total essential oil vary widely from species to species. Typical concentrations for fresh materials range from 0.05-0.48% and in dried materials from <0.1 % to 1.25%, depending on the plant part (BAUER & WAGNER 1991, MAZZA & COTRELL, 1999). Essential oil of *E. purpurea* contains, among other compounds, borneol, bornyl acetate, pentadeca–8-(Z)-en-2-one, germacrene D, caryophyllene, and caryophyllene epoxide. Essential oil of *E. angustifolia* and *E. pallida* contains, among other compounds, pentadeca-(1.8-Z)-diene (44%), 1-pentadecene, ketoalkynes and ketoalkenes (MAZZA & COTRELL 1999, HUDAIB et al. 2002). Terpenoids previously isolated from *E. purpurea* (e.g. germacrene) have been attributed more recently to the similar appearing plant, *Parthenium integrifolium*, which is a frequent contaminant of *Echinacea* products (NEWALL et al. 1996).

Lipid Compounds

Polyacetylenes

Polyacetylenes are widespread in the Asteraceae, and there were determined the structures of 5 compounds in the series found in *Echinacea.* The main constituents were determined. as trideca-1-en-3,5,7,9,10-pentayne and pontica-epoxyde, present in *E. purpurea* and *E. angustifolia*. The content of polyacetylenes decreases markedly during long-term storage of the ground root (SCHULTE et al. 1967).

Polyacetylenes and polyenes are the major lipophilic constituents of *E. pallida* roots, which contain very low concentrations of amides (SCHULTE et al. 1967); the polyacetylenes are very susceptible to auto-oxidation, making the chemical composition of the roots highly dependent on processing and storage conditions (BAUER et al. 1988a).

Nitrogenous Compounds

Alkylamides

Natural alkylamides (or alkamides) are the principle lipophilic constituents of *E. purpurea* and *E. angustifolia* roots (BAUER et al. 1988b,c, He et al. 1998).The first alkylamide isolated from *Echinacea*, echinacein (dodeca-(2E,6Z,8E,10E)-tetraenoic acid), was reported in the roots of *E. angustifolia* (0.01%) and *E. pallida* (0.001%) (JACOBSON 1967). Numerous other alkylamides mostly isobutylamides of C11-C16 straight-chain fatty acids with olefinic or acetylenic bonds, or both, are found in the roots; the highest concentration is in the *E. angustifolia* (0.009-0.15%), followed by *E. purpurea* (0.004-0.039%), and the lowest is in *E. pallida*. The main alkamide is a mixture of isomeric dodeca-2,4,8,10-tetraenoic acid isobutylamides (JACOBSON 1967, BAUER et al. 1989).

The roots of the three *Echinacea* species.contain different structural types of alkamides, while the aerial parts yielded very similar alkamide patterns (BAUER & REMIGER 1989). Isobutylamides of C11-C16 straight-chain fatty acids with olefinic or acetylenic bonds (or both) are found in the aerial parts of *Echinaceae purpureae herba*, with the isomeric dodeca-(2E,4E,8Z,10E/Z)-tetraenoic acid isobutylamides (MÜLLER-JAKIC et al. 1994).

The alkamide content varies over *E. purpurea*`s life cycle, quantitatively and qualitatively (LETCHAMO et al.. 1998), gradually decreasing in the aerial parts and increasing in the roots as the plant matures (PERRY et al. 1997, EL-GENGAIHI 1998). PERRY et al. (2000) determined that levels of alkamides fell by over 80% during storage at 24°C for 64 weeks and also droppe d significantly during storage at –18°C.Alkamides are inducible defense co mpounds in *Echinacea* plants (BAUER 1998). Determination of the major alkylamides showed that they accumulate primarily in the roots and inflorescences (BRADLEY 1992). BAUER (1998) suggested alkamides as one of the classes of compounds most relevant for standardization of *Echinacea* preparations, but found that levels of some alkamides varied considerably between different commercial preparations of *E. purpurea*.

Alkaloids

Early reports of an „alkaloid“ in *Echinacea* species were subsequently shown to be due to the presence of betaine (*E. angustifolia*) and/or glycine betaine (*E. purpurea*).The pyrrolizidine alkaloids, isotussilagine and tussilagine, are found only in trace amounts (0.006% in dried materials) in both *E. angustifolia* and *E. purpurea*. At these concentrations, the alkaloids are considered to be non-toxic (RÖDER et al. 1984, BRADLEY 1992). According to structure/activity studies, a 1,2-unsaturated necine ring system is necessary for pyrrolyzidine alkaloids to be hepatotoxic. Since neither of the pyrrolizidines from *Echinacea* have this structure, there is little risk of liver damage for consumers (BAUER & WAGNER 1991, NEWALL et al. 1996).

Carbohydrates

Polysaccharides

Polysaccharides (inulin, arabinorhamnogalactans, heteroxylans) isolated from *Echinacea* have been shown to stimulate the activity of immune cells (ROESLER et al. 1991) and to exhibit anti-inflammatory activity (TUBARO et al. 1987). Two immunostimulatory polysaccharides were isolated from the aerial parts of *E. purpurea*: a heteroxylan of average relative molecular mass about 35 000 (e.g. PS I), and an arabinorhamnogalactan of average relative molecular mass about 50 000 (e.g. PS II). Structural studies revealed PS I to be a 4-0-methylglucuroarabinoxylan, while PS II is an acidic arabinorhamnogalactan. A xyloglucan of average relative molecular mass about 79 000 was also isolated from the leaves and stems of *E. purpurea*. None of these are identical to a pectin-like polysaccharide, isolated from the expressed juice, which possessed

only weak immunostimulatory activity (BAUER & WAGNER 1991). The immunostimulatory polysaccharides of Echinacea species can be produces in cell cultures of *E. purpurea* on an industrial scale (BAUER & WAGNER 1991).

Echinacea also contain fructose and fructan polymers. The total fructosan content of *E. purpurea* increased during the winter, whereas this process occurred later in the season in *E. angustifolia*. The fructan content of the aerial parts of *E. purpurea* was 10 times less than of the roots, and the leaves and stems of *E. angustifolia* contained practically none. Homeopathic tinctures were also found to contain fructans (GIGER et al. 1989).

Other Constituents

Aside the published *Echinacea* constituents a number of other, including reducing sugars, phytosterols, a series of n-alkanes and inorganic constituents (potassium, calcium, magnesium, iron (III), aluminium sulphate, carbonate, chloride, and silicate) are believed to contribute to the pharmacological activity of *Echinacea* (BAUER & WAGNER 1991, BAUER 1999).

Ascorbic acid has been found in the leaves of *Echinacea purpurea* (0.214% of dry weight). Sitosterol, myristic, and linoleic acid were detected in E. angustifolia. Cyanidin glycosides have been isolated from the flowers of *E.purpurea* and *E. pallida*. Three glycoproteins (MW 17.21 and 30 kDa) were isolated from *E. angustifolia* (BAUER & WAGNER 1991).

The sesquiterpene esters, echinadiol-, echinaxanthol-, and dihydroxynardol-cinnamate were originally described by (BAUER et al. 1986) as constituents of *E. purpurea* roots. These compounds are in fact derived from the adulterant, *Parthenium integrifolium*, which was mistakenly processed at the time when adulteration by this species was common in commercial *Echinacea* products (HOFFMAN 1998). It has been postulated that the polyacetylenes are artifacts formed during storage, since they are found in dried but not fresh roots of *E. pallida* (BAUER et al 1986, AWANG & KINDACK 1991).

Activities and uses

Immune functions

While there is some controversy about which of the constituents of *Echinacea* contribute to the immunostimulatory activity, there is a consensus that the lipophilic alkylamides, as well as the polar caffeic acid derivative, probably make the primary contribution to the activity of alkoholic extracts by stimulating phagocytosis of polymorphonuclear neutrophyl granulocytes (BAUER & WAGNER 1990 BAUER & WAGNER 1991, MELCHART et al. 1994, RININGER et al. 2000, GOEL et al. 2002, BARNES et al. 2002). In addition to these constituents, polysaccharides are implicated in the activity of the expressed juice and aquaeous extracts, and in the response to the powdered whole drug (BAUER & WAGNER 1991).

The overall immunostimulant activity of the alkoholic and aquaeous extracts appears to depend on the combined effects of several constituents (BAUER & WAGNER 1990, BAUER & WAGNER 1991, BISSET 1994). Alkoholic extracts of *Echinacea* roots are more active than aquaeous extracts of the aerial parts (BODINET 1993). All of these extracts caused phagocytosis to increase by 20% to 30%, which corresponded well with in vivo results (BAUER & WAGNER 1991). *E. purpurea* root extract was also found to be more potent than those of *E. angustifolia* or *E. pallida* at increasing host resistance and in stimulating macrophages, production of IL-1, IL-6, TNF-£ and INFa,b, in vivo and in vitro (BODINET 1993).

Low concentrations of polysaccharides are found in the expressed juice, and they are different in composition compared to those in the extract of the aerial parts (BAUER & WAGNER 1991). Low concentrations (0.012µg/mL) of the unpurified fresh pressed juice of *E. purpurea* above ground parts, as well as the dried juice cultured with normal human peripheral blood macrophages significantly increased production of IL-10, IL-6, IL-1 and TNF-£ (BURGER et al. 1997).

The standardized sap preparation of *E. purpurea* caused a greater in vitro stimulation of human white blood cells compared to the standardized extract. The sap may serve as an immunostimulant on resting human granulocytes when they are starting to act against foreign cells; at the same time may limit the damage to cells (free radical inhibition) at times when granulocytes are battling foreign cells (BROKOS et al. 1999). Pressed juices of the aerial parts of *E. purpurea* are used as non-specific immunostimulants and arabinogalactan-proteins (AGPs) have been shown to be part of the active principle (CLASSEN et al. 2004). Monoclonal antibodies against an AGP from pressed juice of *E. purpurea* showed the complement-stimulating activity (ALBAN et al. 2002).

Alkamides from *Echinacea* have been shown to inhibit enzymes (cyclooxygenase and 5-lipoxygenase) that are involved in the synthesis of leucotrienes and prostaglandins that suppress the production of NK cells (MÜLLER-JAKIC et al. 1994). Isobutylamides have been shown to stimulate immune cell activity (GOEL et al. 2002).

In human polymorphonuclear (PMN) cells, *echinacea*`s polysaccharides and the fresh juice enhanced spontaneous motility and phagocytosis (STOTZEM et al. 1992). Polysaccharides (xyloglucanes and arabinogalactane) and fresh juice of *E. purpurea* were also tested for their ability to activate human phagocytes in vitro and in vivo. They enhanced the spontaneous motility of PMN leucocytes and increased the ability of these cells to kill Staphylococci. Monocytes were activated to secrete TNF-£. IL-6, and IL-10 cytokines. Intravenous administration of 5 mg of polysaccharides to test subjects induced both the adherence of PMN to blood vessels and the migration of PMN and monocytes from bone marrow into the peripheral blood (STIMPEL et al. 1984, COEUGNIET & ELEK 1987, LUETTIG et al. 1989, ROESLER et al. 1991a, BURGER et al. 1997).

E. purpurea root extracts have been shown to stimulate the production of NK cells in the bone marrow and precursors cells of monocytes and NK cells of

experimental animals (SUN et al. 1999, CURRIER & MILLER 2000). Incubating mouse serum with polysaccharides from *E. purpurea*, *E. angustifolia* and *E. pallida* roots stimulated the proliferation of bone marrow cells and promoted phagocytosis by macrophages. There was no effect on T lymphocytes (STIMPEL et al. 1984, WAGNER 1985, BAUER et al. 1988, LUETTIG et al. 1989). Giving mice an ethanolic extract of *Echinacea* roots led to increased phagocytosis by macrophages and neutrophyls. The rate was tripled by *E. purpurea*, and doubled by *E. pallida* or *E. angustifolia* at dosages 1,66 mg/100 g p o 3x daily for two days (BAUER et al. 1989). Immunostimulant activity has been shown in mice, indicated by enhancened phagocytosis and increased elimination of carbon particles in serum (MILLS & BONE 2000). In isolated, perfused rat livers, echinacea extracts enhanced phagocytosis (VOMEL 1984).

The orraly applied extract of a mixture of *Thuja occidentalis*, *Baptisia tinctoria*, *Echinacea purpurea* and *Echinacea pallida* significantly enhances the antibody response to sheep red blood cells, induces an increase in the numbers of splenic plaque forming cells and increase in the titer of specific antibodies in the sera of treated animals (BODINET et al. 1999).

E. angustifolia root extract has shown a effect on antigen-specific immunity in male rats; specifically on immunoglobulins G and M. Compared to the control group, the *Echinacea* -treated rats showed significantly higher production levels of IgG antibodies (REHMAN et al. 1999). IgG makes up about 75% of the immunoglobulin in the serum of normal adults and can cross the human placenta. IgG protects newborns in their first month out of the womb and patients with a selective IgG deficiency suffer from recurrent infections of the respiratory tract. Selective IgM deficiency is also associated with susceptibility to current respiratory infections (STITES et al. 1994).

Glycoprotein-rich fractions of *E. purpurea* roots administered to mice (i.v.) have shown significant immunomodulating activity, resulting in the release of cytokines interleukin-1 (IL-1) and tumor necrosis factor-£ (TNF-£). The addition of the glycoprotein-rich fractions to mouse spleen cells in culture produced significant amounts of interferon £,ß, which showed activity against vesicular stomatitis virus (BODINET & BEUSCHER 1991).

Extracts of *E. purpurea* enhanced the cellular immune function of peripheral blood mononuclear cells from normal individuals and patients with either chronic fatigue syndrome or acquired immunodeficiency syndrome. At concentrations C0.1 &g/ml in vitro, *Echinacea* significantly enhanced NK cell function of all groups, concentrations C1 &g/ml significantly increased antibody-dependent cellular cytotoxicity (ADCC) of peripheral mononuclear cells from all groups (SEE et al. 1997).

Cancer

Due to *Echinacea*`s ability to modulate the immune response, it has been investigated as a treatment for cancer.The anticancer/antitumor effects of *Echinacea* are related to its general immunopotentiating actions and specifically

to its activation of macrophages (BAUER & WAGNER 1991, STEINMÜLLER et al. 1993).

In a series of an in vitro studies, acidic arabinogalactan, a purified polysaccharide from *E. purpurea*, was shown to be effective in activating mouse macrophages to cytotoxicity against tumor cells WEHI 164 fibrosarcoma (LUETTIG et al. 1989). Arabinogalactan induces peritoneal macrophages to produce tumor necrosis factor (TNF-alpha) and interleukin-1 (IL-1) (VIEHMANN 1978, HASS 1991). Interferon-beta2 was secreted by bone marrow macrophages in a dose-dependent manner after arabinogalactan activation. Arabinogalactan did not activate B cells but it did induce a slight increase in T cell proliferation. Arabinogalactan enhanced oxygen radicals release by macrophages both in vitro and in vivo (STIMPEL et al. 1984, LUETTIG et al. 1989). *Echinacea*`s polysaccharides also activated macrophages from mice previously treated with cyclophosphamide or cyclosporin A. The resulting cytotoxic activity was 80% of that observed with interferon-gamma and lipopolysaccharide, and more than four times that observed for control macrophages (STEINMÜLLER et al. 1993).

As are part of the first line of immunological defense of the body against virus-infected and tumor cells, the stimulation of monocytes and NK cells by *Echinacea* represents a chemopreventive action. Surgical interventions and stress have been shown in rats to cause a significant supression of NK cell activity which resulted in a greater incidence of death from mammary tumors and leukemia as a result of decreased host resistance (BEN-ELIYAHU et al. 1999).

Preliminary in vitro and animal studies suggest that *Echinacea* may have some anti-cancer properties (HAYASHI et al. 2001, CURRIER & MILLER 2001, 2002, KAPADIA et al. 2002). Administration of an *E. purpurea* extract for 50 days (beginning at the onset of leukemia) enhanced the immune status and significantly prolonged the life span of mice with leukemia (CURRIER & MILLER 2001). In another study, immunization (injection with killed tumor cells) and subsequent treatment with an *E. purpurea* root extract prolonged the life span of mice with leucemia to a greater extent than immunization alone (HU & KITTS 2000).

Intravenous administration of *E. purpurea*-derived polysaccharides to mice, once a day for three days directly following injection of cyclophosphamide, dramatically increased the number of PMNs as well as white blood cell count, compared to controls, for the nine days following treatment (STEINMÜLLER et al. 1993). Among rats undergoing experimental irradiation, dietary supplements with *E. purpurea* enhanced the mobilization of vitamin E mediated oxydation/reduction pathways, potentially protecting against radiation damage (PARANICH 1993).

At 400 mg/kg the pentane-soluble root oil from *E. angustifolia* and (Z)-1,8-pentadecadiene, a constituent of the oil, showed inhibitory activity in the in vivo mouse P-388 lymphocytic leukemia and the rat walker carcinosarcoma 256 tumor systems. An extract of *E. pallida* was inhibitory to the latter tumor type (VOADEN & JACOBSON 1972).

Leukopenia, which refers to a decrease in the number of circulating white blood cells in the body, is a side effect of many chemoterapeutic regimens used for the treatment of cancer. Leukopenia suppresses in immune response and increases the risk of infection. In a recent uncontrolled pilot study, *Echinacea* was investigated as a potential treatment for chemotherapy-induced leukopenia in 15 subjects with gastric cancer (MELCHART et al. 2002). Although treatment with 2 mg of *E. purpurea* polysaccharides per day for 10 days slightly decreases leukopenia in these subjects, the authors of the study concluded that the observed effects were unlikely to be of any clinical relevance.

Since these results are only preliminary in nature however, a great deal of research is needed before any conclusions can be made regarding the usefulness of *Echinacea* in a treatment of cancer.

Inflammatory response

Anti-inflammatory activities of *Echinacea* extracts have been attributed to direct inhibition of hyaluronidase (BAUER & WAGNER 1991). A number of *Echinacea* constituents have been shown to exhibit antihyaluronidase activity (MAFFEI-FACINO et al. 1993). Cichoric acid, cynarine and other compounds from *E. angustifolia* have anti-hyaluronidase activity, which may reduce inflammatory changes in damaged tissues (MAFFEI-FACINO et al. 1993). Several *Echinacea* constituents have protected collagen from degradation during exposure to free radicals, leading to suggestions that *Echinacea* may be helpful in protecting against sun damage to skin (MAFFEI-FACINO et al. 1995).

Topical applications of *Echinacea* extracts have been traditionally used to promote wound healing. The polysaccharide fraction (echinacin B) appears to promote wound healing by forming a hyaluronic acid-polysaccharide complex that indirectly leads to the inhibition of hyaluronidase (BONADEO et al. 1971) and stimulating the growth of fibroblasts (BAUER & WAGNER 1991, NEWAL et al. 1996). An *E. pallida* extract and echinacoside alone were shown to exhibit wound healing activity also (SPERONI et al. 2002)

In the *Croton* oil-induced edema model, swelling of the rat ear was significantly reduced by the polysaccharide fraction of. *E angustifolia* roots applied topically. In this test high molecular weight polysaccharides in the fraction were more active than lower weight polysaccharides (TUBARO et al. 1987).

Echinacea extracts have been shown to inhibit enzymes that involved in the synthesis of pro-inflammatory chemical mediators (MÜLLER-JAKIC et al. 1994, CLIFFORD et al. 2002). In a 1994 in vitro study, a n-hexane extract of *E. angustifolia* roots was shown to inhibit cyclooxygenase (by 62.4 % at 50 µg/ml) and 5-lipoxygenase (by 81.8 % at 11.5 µg/ml), which are involved in the synthesis of the pro-inflammatory eicosanoids prostaglandin E2 and leucotriene B4 respectively (MÜLLER-JAKIC et al. 1994). The inhibitory effect of the *Echinacea* extracts on these enzymes was attributed to its content of alkamides. The isobutylamides from *Echinacea purpurea* and *E. angustifolia* roots also inhibit arachidonic acid metabolism to inflammatory prostaglandines and may account for some of *echinacea*`s anti-inflammatory effects (WAGNER et al. 1989).

A number of *Echinacea* constituents (echinacoside in particular) have been shown to exhibit antioxidant and free-radical scavening activity in vitro (HU & KITTS 2000). Since free radicals are involved in the development of inflammation, the antioxidant and free radical scavening activity of *Echinacea* may contribute to its anti-inflammatory effects.

Viral infections

Methanolic and aquaeous extracts of *Echinacea* inhibit some viruses in cell culture, including influenza, herpes, and vesicular stomatitis viruses (VSV) (MAY & WILLUHN 1978, WACKER & HILBIG 1978, BODINET et al. 1993) The aquaeous extract of *E. angustifolia* root showed no activity against poliovirus type 1, influenza A, or Herpes simplex type 2 (HSV 2), but that of *E. purpurea* was moderately active against HSV 2 and influenza A2 (MAY & WILLUHN 1978).). The fresh juice of the whole *E. purpurea* plant is 30% more effective against the cytopathogenicity of VSV, influenza, and herpes viruses than the aquaeous or the alcoholic extracts (WACKER & HILBIG 1978).

For purified caffeic acid derivatives, antiviral activities have been demonstrated (MAY & WILLUHN 1978), the components may block viral receptors on the cell surface (BAUER & WAGNER 1991). From the flowers and leaves of *E. pallida*, besides caffeic acid, the caffeic acid derivative echinacoside, and cichoric acid, a tartaric acid derivative, were reported to show in vitro virustatic and antiviral activity against vesicular stomatitis virus (CHEMINAT et al. 1988).

Incubation of vesicular stomatitis virus with 125 µg/ml of cichoric acid for 4 hours reduced the number of viral particles in mouse L-929 murine cells by more than 50% (MÜLLER-JAKIC et al.1994). In cultures of mouse cells, treatment with aquaeous *E. purpurea* extracts for four to six hours prior to exposure to influenza and Herpes viruses caused 50-80% resistance to infection for 24 hours after exposure; by 48 hours, the cells were again sensitive to infection (WACKER & HILBIG 1978, BEUSCHER et al. 1995, THOMPSON 1998).

NK cells are immune cells involved in the first line of defence against virus-containing cells. An *E. purpurea* extract enhanced the function of immune cells (NK cells and peripheral blood mononuclear cells) isolated from both normal subjects and subjects with either acquired immunodeficiency syndrome (AIDS) or chronic fatigue syndrome (SEE et al. 1997).Cichoric acid, a caffeic acid derivative abundant in *E. purpurea* has also been shown to inhibit human immunodeficiency virus (HIV) type 1 integrase, a viral enzyme that is involved in the integration of viral genetic material into the host`s genetic material during infection (MCDOUGALL & KING 1998, ROBINSON 1998). By inhibiting the HIV type 1 integrase enzyme, cichoric acid may help prevent HIV from infecting host cells.

Microbial infections

Echinacea has some mild antimicrobial activity which is attributed primarily to echinacoside, a caffeic acid derivative.Echinacoside has shown in vitro activity against the growth of *Staphylococcus aureus*, against which a concentration of 6 mg was found about as potent as one unit of penicilin (STOLL et a. 1950).

Polyacetylene compounds from the roots of *E. angustifolia* and *E. purpurea* have shown strong inhibitory activity in vitro against *Pseudomonas aeruginosa* and *Escherichia* (SCHULTE et al. 1967).

A multi-herb formula including *Echinacea* had in vitro activity against several bacteria including *Escherichia coli*, *Pseudomonas mirabilis*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus* (VOADEN & JACOBSON 1972).

Fungal infections

Human granulocytes and monocytes treated with *E. purpurea* extracts demonstrated enhanced mobility and increased phagocytosis of *Candida albicans* by 30%-45% (WILDFEUER & MAYERHOFER 1994). In vitro granulocytic phagocytosis of Candida albicans increased from 20% to 30% at the start to nearly 50% on days 3 or 4 of the treatment with the fresh expressed juice of E. purpurea aerial parts (MÖSE 1983).

Purified polysaccharides from *E. purpurea* inhibited *Candida albicans* growth in vitro (TRAGNI et al. 1988, ROESLER et al. 1991b). The polysaccharide mixture administered 24 hours prior to, at infection, and 24 hours post-infection (0.2 mg i.v.) protected mice infected with a lethal dose of *Candida albicans*. Colony forming units (CFUs) of *C. albicans* were reduced to 5% of the number found in yeast-infected, untreated control mice; however, when administered 18 hours following infection, there was little if any reduction in the growth of *C. albicans* by the polysaccharide treatment (94). Treatment with the polysaccharid mixture (0.2 mg i.v. on the same day, 24 and 48 hours following *C. albicans* infection) in cyclophosphamide-treated mice (200 mg/kg, 3 days prior to infection) resulted in a 36.9% to 80% reduction in CFUs of C. albicans in their kidneys (STEINMÜLLER et al. 1993).

N-Hexane extracts of *Echinacea* (*E. purpurea* roots and inflorescens, *E. pallida* roots and tops) variably inhibit growth of yeast strains of *Saccharomyces cerevisiae*, *Candida shehata*, *C. kefir*, *C. albicans*, *C. steatulica* and *C. tropicalis* under near UV irradiation (phototoxicity) and to a lower extent without irradiation (conventional antifungal activity). Phototoxic activity of *Echinacea* spp. is primarily attributed to the ketoalkenes and ketoalkynes abundantly present in the roots (BINNS et al. 2000).

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