A Review on Pharmacological and Therapeutic Properties of Echinacea

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Abstract

The botanical supplement market is growing at a rapid rate and this trend is expected to continue to progress. In the world of Nutraceuticals Echinacea plant is widely used for medicinal and commercial purposes. This Native American herb has a remarkable record of clinical and laboratory study, as well as a long history of medicinal use in the management of a variety of conditions. Phytochemical preparations from the genus of Echinacea are widely used for the protection and the treatment of common cold and upper respiratory tract infections. However, most of the uses of Echinacea are based on the reported immunological properties; there is a large body of evidence, based on in vitro and animal studies, demonstrating that Echinacea possess anti-inflammatory, anti-oxidative, and anti-microbial properties. It has also been suggested that this plant is a potential therapeutic agent for cancer, diabetes and skin problems. From the other point of view, on the basis of the available safety data, Echinacea has little adverse effects and is well tolerated.

This paper reviews the pharmacological properties of Echinacea genus and its individual active components.

Keywords: Echinacea; Common Cold; Coneflower; Inflammation; Review

Abbreviations

ABTS: 2,2'-Azino-Bis(3-Ethylbenzothiazoline-6-Sulphonic Acid); AP: Activator Protein; ATF-2: Activating Transcription Factor-2; cAMP: cyclic Adenosine Mono Phosphate; CB : Cannabinoid Receptor; CCL: Chemokine (C-C motif) Ligand;
CCR: C-C Chemokine Receptor; CD: Cluster of Differentiation; C-EBP: CCAAT-Enhancer-Binding Protein; COX:Cyclooxygenase; CREB-1: cAMP Responsive Element Binding Protein-1; CYPs: Cytochrome P450 Enzymes; ERK: Extracellular Signal-Regulated Kinase; G-CSF: Granulocyte-Colony Stimulating Factor; GSPx: Glutathione Peroxidase; G: Gray; HO-1, heme oxygenase-1; hsp: Heat Shock Protein; H2O2: Hydrogen Peroxide; IFN-y: Interferon-Gamma; IL: Interleukin; iNOS: inducible Nitric Oxide Synthase; JNK: c-Jun N-terminal Kinase; LDL: Low-Density Lipoprotein; LPS: Lipopolysaccharide; MAPK: Mitogen-Activated Protein Kinase; MCP: Monocyte Chemotactic Protein; MDR: Multiple Drug Resistance; MHC: Major Histo Compatibility Complex; MP-1: Macrophage Inflammatory Protein-1; NF-kB: Nuclear Factor-Kappa b; NK cells: natural Killer cells; NO: Nitric Oxide; PARP: Poly-ADP-Ribose Polymerase; PBMCs: Peripheral Blood Mononuclear Cells; PG2: Prostaglandin E2; PI3K: Phosphatidylinositol-3-Kinase; PPAR-y: Peroxisome Proliferator-Activated Receptor-Gamma; SOD: Superoxide Dismutase; sRBC: sheep Red Blood Cells; STAT: Signal Transducer and Activator of Transcription; T-Bars: Thiobarbituric Acid- Reactive Substances; TGF-β: Transforming Growth Factor-beta; TLR4: Toll-Like Receptor 4; TNF-α: Tumor Necrosis Factor-Alphal; UGT1A: UDP-Glucuronosyl Transferase 1A, URI: Upper Respiratory Infection

Introduction

Nowadays, the use of herbal/botanical products has gained growing acceptance by public due to the belief that they are natural and, therefore, safe [1]. Echinacea has become a best-selling medicinal herbal preparation of all time in North America and Europe [2]. Several species in the genus of Echinacea has been used for centuries, customarily as a remedy to treat a number of ailments including common cold, coughs, bronchitis, Upper Respiratory Infections (URI), abscesses, wound infections, gangrene, eczema, dizziness, sore eyes, snake bites, syphilis, typhoid, malaria, diphtheria, hemorrhoids, and tumors [3,4]. Numerous pharmacological investigations are available in literature and they are related to several kinds of preparations obtained from the species of Echinacea. Interest in Echinacea is focused on its immunomodulatory effects [5-9], and particularly several clinical trials have been done in the prevention and treatment of common cold and URIs [10-14].

The beneficial effects of Echinacea are also in a variety of disease states, such as inflammation [15,16], oxidative conditions [17,18], cancer [19-21], skin problems [22] and liver diseases [23]. In addition, Echinacea exhibit anti-microbial [24-27] and anti-diabetic properties [28-30]. This review focuses on the pharmacological benefits of Echinacea and its active ingredients in the context of its therapeutic potentials (Figure 1).
All of the relevant databases were searched for the term “Echinacea” and information on Echinacea was collected via electronic search by using PubMed and Science Direct.

Characteristics and Chemical Compounds

Echinacea, commonly called coneflower, is a genus of herbaceous perennial flowering plants in the daisy family, Asterales and originates in eastern North America [2]. Traditional taxonomic system has reported that nine species of Echinacea exist in nature [31] (Table 1), however, under a recent reclassification system, four species and eight varieties are categorized [32]. Among species of the Echinacea genus, E. purpurea, E. angustifolia, and E. pallida have been the most widely used in medicine for their pharmacological properties [33] (Figure 2).

The main bioactive compounds present in Echinacea species include alkylamides (alkamides), caffeic acid and its derivatives (caftaric, chlorogenic and cichoric acid, cynarin and echinacoside), polysaccharides, glycoproteins, lipoproteins, and acetylenes (polyacetylenes and polyenes) [34,35]. There are trace elements including Ca, Mg, Fe, Mn, Cu, Zn, Ni, and Li in root, stem, leaves, and flowers [36]. However the concentration of key compounds in species of Echinacea vary by plant age, plant parts used, growth conditions, geographical location, and method of extraction [37]. In addition, the distribution of chemical compounds and biological activities differ within the same plant (root, stem, leaves and flowers) [38]. For example, the alkylamide content in Echinacea species appears to be higher in roots, to increase with age and to differ with the geographical area of cultivation [38].

Several forms of commercial preparations are available that use different parts of the Echinacea plant such as roots, seeds, flowers, and leaves. The most commonly used form is the tincture, which is a liquid ethanol-water extract. Other forms include powdered ethanol-water extract, freeze-dried ethanolic or hydrophilic extracts, capsule and tablet, skin cream, ointment and gel, and pressed juice and tea.

Anti-Inflammatory Effects

Currently special emphasis has been given to the role of inflammation in the pathogenesis of diseases. For a long time, medicinal plants have been used as remedies for various inflammatory conditions.

The alcoholic extracts of E. angustifolia, E. purpurea and E. pallida significantly inhibited Nitric Oxide (NO) production by Lipo Poly Saccharide (LPS)-activated the RAW 264.7 macrophage cells, among which E. pallida was the most active. The enzymes Nitric Oxide Synthase (iNOS) and arginase metabolize a common substrate, L-arginine, but produce different biological effects. While iNOS is involved in inflammation, arginase contributes to anti-inflammatory response. Echinacea can modulate the iNOS/arginase balance due anti-inflammatory activation. The alcoholic extract of E. pallida inhibited iNOS enzyme at protein level in LPS-treated RAW 264.7 macrophages, whereas arginase activity of the cells was significantly improved by alcoholic extracts of E. angustifolia, E. pallida and E. purpurea. The hydrophilic fraction containing caffeic acid derivatives enhanced arginase activity, while the hydrophobic fraction containing alkamides inhibited iNOS expression and NO production [15]. The Echinacea-mediated decrease in NO production was generally associated with decreased protein level of iNOS, Echinacea present at the onset of LPS-induced iNOS expression led to a stronger inhibitory effect on NO production. An alcoholic tincture of E. purpurea roots considerably inhibited the nuclear expression of pro-inflammatory transcription factors NF-κB and STATs in rhinovirus-infected cells [39]. In a study using gene and protein array analysis the effects of Echinacea commercial preparations (E1 was an aqueous expressed juice of the aerial parts of E. purpurea, and E2 was a 50% ethanol tincture from E. purpurea roots) on rhinovirus infection was evaluated by BEAS-2B, a line of human tracheobronchial epithelial cells. It found that rhinovirus infection would increase some inflammatory cytokines at mRNA and protein levels, and that these effects could be reversed by E. purpurea. Substantial increases were observed about the pro-inflammatory cytokines IL-6 and IL-8 (CXCL8) at protein levels that was ameliorated by E. purpurea [40].

E. angustifolia preparation enriched fractions Bauer...
allyl amide 11 and Bauer ketone 23 showed anti-inflammatory effect in LPS-induced RAW264.7 mouse macrophage cell line. These treatments decreased Prostaglandin (PG)E2 production and inhibition of PGE2 production may be due to targeting of Cyclooxygenase (COX)-2 enzyme activity [41]. In macrophages subjected to Hydrogen Peroxide (H2O2), treatment by E. angustifolia extract reversed mRNA expression of COX-2, Interleukin (IL)-1β, NF-κB1, NF-κB2, and Tumor Necrosis Factor (TNF)-α, also Peroxisome Proliferator-Activated Receptor (PPAR)-γ to normal levels [42]. In a study, 50% ethanolic tinctures of E. tennessensis were prepared from roots, stems, leaves, and flowers of the plant. Fresh root, leaf, and flower tinctures stimulated human Peripheral Blood Mononuclear Cells (PBMC) proliferation in vitro, also fresh root tincture stimulated IL-10 production [43]. Oral administration of Echinacea alcoholic extract to mice increased production of anti-inflammatory cytokines IL-4 and IL-10, but decreased production of TNF-α and IL-1β in activated spleen cells [44].

In murine macrophages, the alkamides significantly inhibited COX-2 activity and suppressed the LPS-induced expression of COX-2, iNOS, TNF-α, IL-1α, IL-6, and Monocyte Chemotactic Protein (MCP)-1, but elevated Heme Oxygenase-1 (HO-1) protein expression [16]. In RAW264.7 macrophage cells, chemically synthesized Bauer Ketones 21 and 23 from E. palida each significantly inhibited both PGE2 and NO production; as well Bauer Alkylamide 11 repressed production of PGE2 and NO [45]. Other results showed that polysaturated alkamides, undeca-3Z-ene-8,10-diynoic acid isobutylamide (A5), dodeca-2E-ene-8,10-diynoic acid isobutylamide (A7), and dodeca-2E,4Z-diene-8,10-diynoic acid 2-methylbutylamide (A8), isolated from roots of E. angustifolia were efficient inhibitors of COX2 activity and suppressed PGE2 formation in H4 human neuroglioma cells [46]. Ethanol extracts of E. paradoxa var. paradoxa, rich in polyenes/polycatlenes suppressed LPS-induced production of NO, PGE2, IL-1β and IL-6 in stimulated RAW264.7 macrophage. Pentadeca-8Z-ene-11, 13-diyn-2-one (Bauer ketone 23) and pentadeca-8Z, 13Z-dien-11-yn-2-one (Bauer ketone 24) from E. paradoxa were found mainly responsible for inhibitory effects on NO and PGE2 production [47].

A polysaccharide from water extract of E. purpurea roots inhibited Pam3CSK4-stimulated release of TNF-α by human THP-1 acute monocytic leukemia cells. This anti-inflammatory activity was shown to be mediated by the Phosphat Idlylnositol-3-Kinase (PI3K)/Akt signaling pathway [48]. The cichoric acid from E. purpurea extract has anti-inflammatory activity in rheumatoid arthritis by collagen-induced arthritis rat model. Administration of cichoric acid for 4 weeks significantly decreased the paw swelling, restored body weight gain, and decreased the organ index of the thymus and spleen compared with that of the arthritis group. The cichoric acid reduced the TNF-α, IL-1β and PGE-2 levels in serum; also decreased the levels of NF-kB, TNF-α and COX-2 in synovium tissues of the ankle joint compared with the arthritis group [49]. A polysaccharide fraction obtained from E. angustifolia root extract (0.5 mg/kg) inhibited the carrageenan-induced rat paw edema in intravenous injection and the croton oil-induced mouse ear dermatitis when applied topically. Polysaccharide fraction also reduced the leukocytic infiltration of the croton oil dermatitis, evaluated both from histological and peroxidase activity aspects [50].

These studies suggest that Echinacea influences inflammatory pathways and may modulate pro-/anti-inflammatory ratio.

Echinacea as an Anti-Oxidant

The relationship between free radicals and the incidence of various types of diseases has led to considerable interest in preventive medicine in assessing the free radical scavenging activity of medicinal plants and other nutritional anti-oxidant supplements. There have been several reports on anti-oxidative benefits of Echinacea species.

Methanolic extracts of freeze-dried E. purpurea, E. angustifolia and E. pallida roots have anti-oxidant activities and were capable of scavenging Hydroxyl Radical ([OH]·). Similar scavenging capacities for each extract were found for both 1,1-Diphenyl-2-Picrylhydrazyl (DPPH) radical and ABTS radical. Moreover all these species were found to delay the formation of conjugated diene hydroperoxide-induced by the thermal decomposition of 2, 2’-azobis(2-amidinopropane) dihydrochloride and extend the lag phase of peroxidation of soybean liposomes. Each root extract suppressed the oxidation of human Low-Density Lipoprotein (LDL), following oxidative modification by Cu²⁺ [17]. The efficacy of the extracts from the stems, leaves, and roots of E. purpurea in the reaction with DPPH correlated well with the amount of cichoric acid present in the extracts. The alkamides from E. purpurea alone showed no anti-oxidant effect; however, alkamides present in the extract improved the anti-oxidative activity of cichoric acid in the peroxidizing lipid emulsion [51]. In another study the anti-oxidant activities of echinacoside and caffeic acid was compared by measuring their inhibition of Cu²⁺-catalyzed oxidation of human LDL. The efficiency of anti-oxidative activity of the tested substances was: cichoric acid had the highest capacity, the second was echinacoside, and finally caffeic acid. Synergistic anti-oxidative effects of Echinacea components were found when cichoric acid (major caffeic acid derivative in E. purpurea) or echinacoside (major caffeic acid derivative in E. pallida and E. angustifolia) were combined with a mixture of alkamides and/or an aqueous extract containing the high molecular weight polysaccharides [52].

E. purpurea was given to mice at a dose of 30 mg/kg body weight for 14 days before and after irradiation with 3 Gy of γ-rays. The results reflected the reduced effects of γ-rays on peripheral blood hemoglobin and red blood cells, differential white blood cells and bone marrow cells counts in γ-irradiated mice. The changes observed in Thiobarbituric Acid-Reactive Substances (TBARS) level, Superoxide Dismutase (SOD) and Glutathione Peroxidase (GSPx) activities, as well DNA fragmentation were ameliorated by E. purpurea administration [18]. In a study the radio-protective properties of E. purpurea tablets in a group of radiation workers who were identified as carrying dicentric chromosomes in their lymphocytes were
investigated. All radiation workers were taking two 275 mg Echinacea tablets for two week treatment. At the end of period, lymphocyte chromosome aberrations frequency dropped significantly, and the number of apoptotic cells increased [53]. E. purpurea administration had a suppressive effect on radiation-induced lymphocytopenia and monocytopenia, and resulted in a faster recovery of blood cell counts. E. purpurea activated macrophages to stimulate IFN-γ production in association with the secondary activation of T lymphocytes, and cytokines released from macrophages in mouse peripheral blood after E. purpurea administration activated helper T cells to proliferate. In addition, SOD activity in peripheral blood was increased because of echinacoside and caffeic acid as anti-oxidants which eliminate superoxide (02) [54].

These results indicate that Echinacea and its derivatives are a good source of natural anti-oxidants and could be used to prevent the damaging effects of free-radicals.

Immunomodulatory Activities

Herbal medicine provides several remedies for strengthening the body’s resistance to illness by acting on various components of the immune system. A class of medicinal plants, known as immunomodulators, alter the activity of immune function through the regulation of molecules such as cytokines, chemokines and immunoglobulins. Echinacea is a wide-spectrum immunomodulator that regulates both innate and adaptive immune responses.

In normal rats oral administration of Echinacea preparations (containing its components cichoric acid, polysaccharides and alkylamides) two times/day for 4 days improved phagocytic activity of alveolar macrophage, also TNF-α and NO release by the LPS-stimulated alveolar macrophages. An enhanced release of TNF-α and IFN-γ in response to Echinacea was apparent in spleen macrophages [55]. In a study, extract of Echinacea aerial parts (50 mg/ kg) was administered over an 8-week period to male Sprague-Dawley rats. This treatment significantly increased circulating total white cell counts, and IL-2 level [56]. Normal human peripheral blood macrophages cultured in presence of Echinacea ethanolic extract produced higher amounts of IL-1, TNF-α, IL-6 and IL-10 than unstimulated cells. E. purpurea increased the number of cytotoxic T cells and suppressor T cells. An increase was observed in IFN-γ levels which activated cell-mediated immune responses, such as proliferation and activation of type I helper T (Th1) cells [57]. Sullivan, et al. [58] examined the effects of polysaccharides isolated from E. purpurea on macrophages. Murine peritoneal macrophages were cultured with E. purpurea extract enriched for polysaccharide. The results showed an E. purpurea extract stimulated production of IL-6, IL-12, and NO from macrophages. E. purpurea triggered a signaling cascade within macrophages through both TLR4-dependent and -independent mechanisms, involving ERK, p38 and c-Jun N-terminal Kinase (JNK), and ultimately the activation of NF-kB.

E. purpurea whole herb and root powders were found to stimulate murine macrophage for TNF-α, IL-1α, IL-1β, IL-6, IL-10, and NO secretion, as well as to significantly enhance the viability and/or proliferation of human Peripheral Blood Mononuclear Cells (PBMCs) in vitro [59]. Randolph, et al. [60] in a preliminary study in six healthy individuals found that in vitro exposure of THP-1 peripheral leukocytes to Echinacea extract induced expression of the IL-1α, IL-1β, IL-8, TNF-α, Intra Cellular Adhesion Molecule (ICAM), and IL-10 genes. Serum and hematological values were not different from baseline, suggesting that liver or bone marrow responses were not involved in acute responses to Echinacea. Echinaforce® is the standardized E. purpurea preparation from combined root and aerial ethanolic extract, from Bioforce, Switzerland. In an ex vivo study oral administration Echinaforce® reduced the pro-inflammatory mediators TNF-α and IL-1β, and increased anti-inflammatory IL-10 levels. Chemokines Macrophage Inflammatory Protein-1 (MIP-1α) and IL-8 were up-regulated in blood samples from subjects treated with Echinaforce® [61]. Polinacea® is a standardized hydroethanolic extract obtained from E. angustifolia roots containing echinacoside, the high molecular weight polysaccharide IDN 5405 and an isobutyramide fraction. Polinacea® in 10 healthy subjects was administered as herbal syrup once a day for 30 days (containing 100 mg). Results showed the up-regulation of mRNA expression of IL-2 and IL-8 and the down-regulation mRNA levels of the pro-inflammatory cytokines TNF-α and IL-6; these changes positively correlated with the protein levels detected in the plasma [62].

E. purpurea ethanolic extract can regulate the differentiation of Dendritic Cells (DCs), which are known as professional antigen-presenting cells. Alkylamide-rich root extract promoted maturation of human DCs in a similar manner as LPS; however, the stem plus leaf extract inhibited DC maturation. Down-regulation the mRNA expression of chemokines MIP-1α, and MCP-2, and receptors CD191 (CCR1) and Cdw199 (CCR9) were observed in stem plus leaf extract-treated DCs. Regulatory molecules MIP-1β and MCP-1 involved in the c-Jun pathway were found to be up-regulated in root extract-treated DCs [5]. The polysaccharide-rich root extract of E. purpurea increased the expression of MHC class II, CD86, and CD54 surface biomarkers after 48 hours of exposure, whereas the alkylamide-rich leaf extract inhibited the expression of these molecules. Production of IL-6 and TNF-α increased with exposure to the root, in contrast, the leaf extract inhibited COX-2 activity. While both extracts decreased the uptake of ovalbumin by murine Bone Marrow-Derived Dendritic Cells (BMDCs), the leaf extract inhibited the antigen-specific activation of naïve CD4+ T cells from OTII/Thy1.1 mice [7].

Echinacea is found to be a potent activator of Natural Killer (NK) cells; these cells are active in non-specific immunity against virus-mediated infections and tumors. Mice immunized with sheep Red Blood Cells (sRBC) were gavaged for 7 days with each of the alcohol extracts from E. angustifolia, E. pallida, and E. purpurea. The three extracts increased percentages of CD4+ and CD19+ lymphocytes in spleen and NK cell cytotoxicity. Antibody response to sRBC was improved equally by extracts of all three Echinacea species. In addition, each extract significantly increased IFN-γ production, but inhibited the release of TNF-α and IL-1β. E. angustifolia- and E. pallida-treated mice demonstrated
higher production of IL-4 and increased IL-10 production [44]. *E. purpurea* may be capable of stimulating non-specific immunity in the elderly. *E. purpurea* after two weeks of administration had the capacity to increase the number of NK cells in aging mice, reflecting increased new NK cell production in their bone marrow generation site, leading to an increase in the absolute numbers of NK cells in the spleen, their primary origin [63]. Administering root extract of *E. purpurea* daily for 50 days from the onset of leukemia in mice augmented NK cells and prolonged life span. Treatment had an increasing effect on the absolute numbers of NK cells in spleens in 9 days (intermediate stage leukemia). Three months after leukemia beginning, *E. purpurea*-treated leukemic mice had 2-3 times the normal numbers of NK cells in their spleens, also all the major hemopoietic and immune cell lineages in their bone marrow origin site were recorded at normal numbers [64].

*Echinacea* increased the frequency of NK target conjugates and activated the programming for lysis of NK cells. *Echinacea* resulted in the activation of CD69 expression and increased mean fluorescence intensity in both the CD16+ and CD56+ NK subsets. As well, the frequency of CD56+ killer cells in the conjugates was also significantly increased by *Echinacea*. There was recruitment of non-conjugated CD56+ cells into CD16+ NK-target conjugates and activation of the NK-target non-killer conjugates into killer cells [65].

Water-soluble extract from *E. purpurea* fresh aerial parts (containing 80% polysaccharides, phenolic compounds, cinnarin, cichoric and caftaric acids) strongly enhanced T-cell production of IL-2 and IFN-γ in response to Phorbol 12-Myristate 13-Azetate (PMA) plus ionomycin stimulation [66]. The addition of cichoric acid from a root extract (prepared from both *E. angustifolia* and *E. purpurea*) and 2,4-diene alkylamide-derived from combination of both species induced NFκB expression after PMA stimulation of Jurkat T-cell line [67]. In a study by Sasagawa et al. Jurkat cells were treated with ethanolic extract prepared from dried leaves and flowers of *Echinacea* with alkaloids or caffeic acid derivatives. *E. purpurea* 95:5 ethanol/water extract inhibited phytosomatammagillin-dependent production of IL-2, and this inhibitory activity correlated with the presence of alkaloids but not caffeic acid derivatives [9]. A mixture of *E. purpurea* and *Glycerrhiza glabra* root (Revitoni® tablets) showed a stimulatory effect on human granulocytes, and notable stimulating activity was observed in the T-lymphocyte CD69 bioassay [68]. It found that decreased number and function of regulatory T cells (Tregs) in association with the enhanced feeder function of Antigen-Presenting Cells (APCs) may contribute by improving immune function by *E. purpurea*. The CD4+FoxP3+ and CD4+CD25+ Tregs incidence was attenuated and CD4+CD25+ Tregs function was decreased, while the feeder function of APCs was enhanced in the mice spleens administered with *E. purpurea* for 3 weeks [69].

*Echinacea* has the potential for enhancement of humoral immune responses as well as innate immunity. An alcohol extract of *Echinacea* improved the T cell-dependent antibody response to immunization with sRBCs in mice and increased splenic T cell production of IL-4 and IL-10 suggesting that *Echinacea* stimulation of both Th-2 and Th-1 cytokine production improved B cell function and increased antibody formation [44]. A diet supplemented with 1% w/w *Echinacea* for 28 days can enhance immune function by increasing antibody production which resulted from augmenting both Th1 and Th2 cytokine production. Production amount of IgA, IgG, and IgM was higher in the splenic lymphocytes of rats fed with *Echinacea* [70]. Arabino Galactan-Proteins (AGPs) purified from roots of *E. pallida* and suspension culture of *E. purpurea* induced the IgM-production of mouse lymphocytes and stimulated IL6-production in alveolar mouse macrophage culture [71]. A study by Rehman and colleagues [6] demonstrated that oral administration *E. angustifolia* root extract of rats for a period of 6 weeks which were injected with the antigen Keyhole Limpet Hemocyanin (KLH) and re-exposed to KLH after the initial exposure, showed a significant augmentation of their primary and secondary IgG response to the antigen. Extract of *E. purpurea* enhanced cellular immune function of PBMC both from normal individuals and patients with either the chronic fatigue syndrome or the Acquired Immuno Deficiency Syndrome (AIDS). The addition of herb significantly increased both antibody-dependent and NK-mediated activities against cells infected with herpes virus [72].

Polysaccharides isolated from *E. purpurea*-activated peritoneal macrophages after administration of cyclophosphamide or Cyclosporin A (CsA) in immunodeficient mice. *E. purpurea*-treated macrophages exhibited increased production of TNF-α and higher cytotoxicity against tumor target WEHI-164 as well as against the intracellular *Leishmania enrietti*. After a cyclophosphamide-mediated reduction of leukocytes in the peripheral blood, the polysaccharides induced an earlier influx of neutrophil granulocytes. *E. purpurea* treatment after cyclophosphamide or CsA restored their resistance against lethal infections with the macrophage-dependent pathogen *Listeria monocytogenes* and predominantly granulocyte-dependent *Candida albicans* [73]. Polinacea® administered orally showed an immune-stimulating activity by reducing the *C. albicans*-induced mortality both in normal and in CsA-treated mice. It enhanced T-cell function and proliferation by stimulating IFN-γ production in anti-CD3-treated murine T-cell cultures [74].

Echinacea-derived alkaloids have a structural similarity to anandamide, an endogenous ligand of cannabinoid receptors; consequently, it was found that alkaloids bind to Cannabinoid Receptor (CB) type-1 and -2, therefore suggested as a new class of cannabinomimetics [75]. CB2 receptor is abundantly expressed in some of inflammatory and immune cells, and there is evidence that the CB2 receptor plays a role in inflammatory also immune responses, as well as related pathophysiological conditions [76]. N-alkylamides from *E. purpurea* and *E. angustifolia* preparations are capable of stimulating IL-10, and inhibiting expression of TNF-α protein. N-alkylamides exerted pleiotropic effects modulating the endocannabinoid system by activating the CB2 receptor, endocannabinoid transport and degradation [77]. Alkaloids dodeca-2E,4E,8Z,10E/Z-tetraenoic acid isobutylamides (1/2), trienic (3) and dienoic acid (4) derivatives induced synthesis of TNF-α mRNA in primary
human monocytes/macrophages. This up-regulation was found to be mediated by CB2 receptors, increased cAMP, p38/MAPK and NK signaling, as well as NF-kB and ATF-2/CREB-1 activation [78].

A controversy result showed that cynarin isolated from E. purpurea down-regulated immune responses by binding to CD28, a receptor of T-cells on T-lymphocytes, and this interaction is stronger than the binding between CD28 and CD80, a co-stimulated receptor of antigen presenting cells. Cynarin’s function was proved by its ability to down-regulate CD28-dependent IL-2 expression in a T-cell culture line. It is believed that the immunomodulatory effects of Echinacea depend on the combined action of alkamides, polysaccharides, and chicoric acid. These components are potentially effective in stimulating humoral immunity as well as innate immune responses. It appears likely that Echinacea stimulates the immune system via multiple pathways. Echinacea can affect non-specific immune response, activate innate immune cells such as macrophages, polymorphonuclear leukocytes and NK cells, stimulate phagocytosis, and inhibit the production of inflammatory mediators by white blood cells.

The results about Echinacea immunomodulation seem inconclusive and controversial, some studies express that Echinacea is an immunostimulator and some of them state it is an immunosuppressor. It is noteworthy to mention that immunity is a two-edged blade that the body keeps under tight control; excessively strong immune reactions can be precarious. Based on this concern, Echinacea should be used with caution by individuals with autoimmune disorders such as rheumatoid arthritis and multiple sclerosis. On the other side, Echinacea can stimulate immunity and may be harmful where immunosuppression could be vital in some people such as in organ transplantation. Further studies are needed to clarify the mechanisms which are responsible for the beneficial effect of Echinacea observed in immune system.

Anti-Cancer Effects

Interest in herbal medicine for cancer therapy has dramatically grown over the past years. Cancer patients may wish to use natural botanicals to inhibit tumor growth and development. Echinacea and its compounds have shown promising anti-tumor effects.

Hexanic root extract of the E. purpurea, E. angustifolia and E. pallida reduced cell viability in human pancreatic MIA PaCa-2 and colonic COLO320 cancer cell lines in a concentration- and time-dependent manner. E. pallida extract induced apoptosis by increasing caspase-3 activity and the internucleosomal degradation of DNA, without evidence of necrotic cell death [79]. Five compounds, two polyacetylenes (namely, 8-hydroxy-pentadeca-(9E)-ene-11,13-diyne-2-one and pentadeca-(9E)-ene-11,13-diyne-2,8-dione) and three polyenes (namely, 8-hydroxy-pentadeca-(9E,13Z)-diene-11-yn-2-one, pentadeca- (9E,13Z)-diene-11-yn-2,8-dione and pentadeca-(8Z,13Z)-diene-11-yn-2-one) isolated from the n-hexane extract of E. pallida roots induced apoptosis in pancreatic MIA PaCa-2 and colonic COLO320 cancer cells [80]. Ethanolic extract of E. purpurea flowers and its major compound cichoric acid showed a significant inhibitory effect on proliferation of human colon cancer cells Caco-2 and HCT-116 in a dose- and time-dependent manner. Cichoric acid was able to decrease telomerase activity in HCT-116 cells. Moreover, cichoric acid effectively induced apoptosis in colon cancer cells, which were characterized by DNA fragmentation, activation of caspase-9, cleavage of Poly-ADP-Ribose Polymerase (PARP) and down-regulation of β-catenin [19]. An acetylenic constituent of E. pallida roots, namely pentadeca-(8 Z,13 Z)-diene-11-yn-2-one, revealed a concentration-dependent cytotoxicity on leukemia Jurkat and HL-60, breast carcinoma MCF-7, and melanoma MeWo cell lines. This component arrested the cell cycle in the G1 phase on HL-60 cells [20]. When a commercially extract of E. purpurea root was administered to mice immunized with killed leukemia cells in an erythroleukemic mouse model for 3 months the number of NK cells was elevated compared to animals without receiving the Echinacea. In the group fed with Echinacea product in the early phase of the tumor development the number of T- and B lymphocytes in the spleen was markedly enhanced [21]. E. purpurea had suppressive effects on spontaneously occurring leukemia caused by endogenous recombinant Murine Leukemia Viruses (MuLV). Female AKR/J mice were given oral 7.5 mg/ week dose of E. purpurea leaves powder for 8 weeks. Mortality from thymic lymphoma was delayed and enlargement of thymic lymphoma in experimental mice was suppressed with E. purpurea preparation. Proliferation of MuLV in the thymus was markedly inhibited after oral administration of the E. purpurea. Production of endogenous IFN-γ in mice was also effectively augmented by the oral treatment with herb [81]. The administration of 50 mg/kg E. purpurea extract to rats with Benign Prostate Hyperplasia (BPH) for 4 and 8 weeks gradually and considerably reduced the prostate mass and reversed the degenerative changes in the structure of the prostate [82].

Gastrointestinal mucositis is a common complication of chemotherapeutic drugs and there is currently no effective long-term treatment. SAMITAL® is an oral suspension formulation based on the combination of three standardized extracts from Vaccinium myrtillus, Macleaya cordata fruits and E. angustifolia roots designed for the relief of oral mucositis-induced by chemotherapy and/or radiotherapy in cancer patients. 20 pediatric patients undergoing chemotherapy initially received oral SAMITAL® to treat gastrointestinal mucositis and were then given SAMITAL® prophylactically to prevent recurrences with successive cycles of chemotherapy. SAMITAL® significantly decreased gastrointestinal mucositis grade, reduced pain, mucosal erosions, bleeding and dysphagia [83]. Phase II trials with SAMITAL® as part of an overall clinical development program are currently ongoing [84].

These results represent scientific evidence on the possible role of Echinacea species in medical oncology. Because the agents used for cancer chemotherapy are known to be highly toxic towards normal cells, immune-enhancing activities by Echinacea is looked into with interest and more research is needed in this area.
Anti-Microbial Properties

Several anti-microbial agents are available but have some side effects. To overcome this problem, many natural sources particularly medicinal plants can be considered as alternatives.

*E. pallida* and *E. purpurea* inhibited NO production and TNF-α release from LPS-stimulated RAW 264.7 macrophage cells in response to infection of *Salmonella enterica*. Upon bacterial infection, RAW 264.7 cells produced high levels of NO; however, alcoholic extract of *Echinacea* administered orally for one week decreased NO production in a dose-dependent manner [85]. The use of *E. purpurea* extract had prophylactic effect on the development of *Pseudomonas aeruginosa* infection. *E. purpurea* feeding resulted in diminishing bacterial number in livers of C57Bl/6 (susceptible strain) and B6C3F1 (relative resistant strain) mice. *Echinacea* feeding of the second relative resistant strain (BALB/c x C3H) F1 resulted in stimulation of granulocytes chemiluminescent and lymphocytes proliferative response [86]. *Echinacea* could inactivate certain respiratory bacteria and could also reverse inflammatory effects caused by these bacteria in epithelial cells. Echinaforce® inactivated *Streptococcus pyogenes* (Group A streptococcus), which is often associated with sore throat and more severe pulmonary infections. *Hemophilus influenzae* and *Legionella pneumophila* were also readily inactivated, and their cellular pro-inflammatory response completely reversed. Moreover *Staphylococcus aureus* (methicillin-resistant and sensitive strains) and *Mycobacterium smegmatis* were also sensitive to Echinaforce® [24].

Influenza infection is an important clinical problem. *Echinacea* extracts and active components have the potential for being used in improving the pathology of influenza infections. Echinaforce® has potent anti-viral activity against the IV strains, human Victory (H3N2) and PR8 (H1N1), avian strains KAN-1 (H5N1) and FPV (H7N7), and the pandemic S-OIV (H1N1). Human H1N1-type IV, highly pathogenic avian IV (HPAIV) of the H5 and H7 types, as well as swine origin IV (H1N1) were inactivated in treatment by Echinaforce®, Haemaggulination assays showed that Echinaforce® inhibited the receptor binding activity of the virus, suggesting that the extract restricted the viral entry into cells. In sequential passage studies under *in vitro* treatment with the H5N1 virus no Echinaforce®-resistant variants appeared, in contrast to Tamiflu, which produced resistant viruses upon passing. In addition, the Tamiflu-resistant viruses were susceptible to Echinaforce® as well as the wild type viruses [26]. The alkylamides undeca-2,4E-diene-8,10-diyonic acid isobutylamide, dodeca-2E,4E,8Z,10E/Ztetraenoic acid isobutylamide, dodeca-2E,4E-dienoic acid isobutylamide, and undeca-2E-ene-8,10-diyonic acid isobutylamide suppressed production of TNF-α and PGE2 from RAW 264.7 macrophage cells-infected with the H1N1 influenza A strain PR/8/34. Dodeca-2E,4E-dienoic acid isobutylamide especially inhibited production of these mediators and also strongly suppressed production of Granulocyte-Colony Stimulating Factor (G-CSF), MCP-1, MIP-1α and CCL5 (RANTES) [87]. In the context of influenza virus-stimulated human PBMCs from older individuals vaccinated against influenza, *E. tennesseensis* root tinctures augmented IL-10 production, diminished IL-2 production, and had no effect on IFN-γ production [88].

Results indicated that rhinovirus infection of epithelial cells treated with *Echinacea* led to profound effects on numerous mediators. An alcohol tincture from *E. purpurea* roots increased the expression of several transcription factors in non-activated human bronchial epithelial BEAS-2B cell line, but inhibited the expression of these when the cells were infected with rhinovirus. The BEAS-2B cells were used as the model, and nuclear extracts of uninfected cells and rhinovirus-14 infected cells were examined with and without treatment with *E. purpurea* extract. It was found that *Echinacea* increased the nuclear content of several transcription factors, including the pro-inflammatory factors such as Activator Protein (AP)-1, AP-2, NF-κB, and STATs 1-6. Infection by rhinovirus resulted in a more dramatic increase in these transcription factors; however, when rhinovirus-infected cells were treated with *Echinacea*, transcription factor levels were reduced to low levels [39]. Preparations include juice from the aerial parts of the plant (which contain polysaccharides) and alcoholic tinctures from roots (containing caffeic acid derivatives and alkylamides) stimulated the release of pro-inflammatory factors from uninfected BEAS-2B bronchial epithelial cells. Exposure to Rhinovirus 14 stimulated the release of several chemokines known to attract inflammatory cells, and most these effects were reversed by introduction either of the two *Echinacea* extracts [89]. These results could explain the anti-inflammatory effects of *Echinacea*. The rhinovirus type 1A (RV1A) resulted in increased mucopolysaccharide inclusions in the goblet cells of normal human airway epithelial cells; this change was reversed by *Echinacea* treatment. Mucus production during colds could be ameliorated by *Echinacea* because mucin secretion stimulated by RV1A is reversed by *Echinacea* treatment. *Echinacea* also inhibited secretion of substantial amounts of the pro-inflammatory cytokines IL-6 and IL-8 in RV-infected tissues [90].

The hydroalcoholic extract also pressed juice of *E. pallida* exhibited anti-viral activity against herpes simplex virus types 1 and 2 (HSV-1, HSV-2) in a dose-dependent manner. Plaque formation was significantly reduced by more than 99% or completely absent. In addition *Echinacea* juice revealed anti-viral activity during all phases of the viral replication cycle, protected cells against viral infection by interfering with virus attachment and could interact with herpes virus inside and outside the cell [91]. Polysaccharide isolated from *E. purpurea* promoted immune response, leading to a reduced latency phase, and it has a promising effect on latency prevention in HSV-1 when supplied prior to infection [92]. The rhinoviruses 1A and 14, influenza virus, Respiratory Syncytial Virus (RSV), adenovirus types 3 and 11, and HSV-1 induced secretion of IL-6 and IL-8, in addition to several other chemokines, depending on the virus; and Echinaforce® inhibited this induction. *E. purpurea* preparation effectively inhibited the virus-induced cytokine secretion and pro-inflammatory responses induced by all the viruses tested in BEAS-2B human bronchial epithelial cells. This preparation also showed potent virucidal activity against viruses with membranes such as RSV, HSV, and influenza virus, at the oral recommended dose [93].
In an open-label, fixed-sequence study, 50 patients infected by human immunodeficiency virus (HIV) received anti-retroviral therapy including 400 mg etravirine (a non-nucleoside reverse transcriptase inhibitor of HIV) once daily for 4 weeks. Capsules containing *E. purpurea* root extract were added to the anti-retroviral treatment (500 mg every 8 h) for two weeks. Results showed that the co-administration of *E. purpurea* with etravirine was safe and well tolerated in HIV-infected patients [94]. Chicoric acid has been shown to inhibit the HIV-type 1 integrase, improved the anti-HIV-1 effect of Zidovudine and protease inhibitor (AG1350) *in vitro* [95].

Echinaforce® inhibited growth of three species of trypanosomatids: *Leishmania donovani*, *Leishmania major*, and *Trypanosoma brucei*. *L. donovani* stimulated the production of the pro-inflammatory IL-6 and IL-8 cytokines in human bronchial epithelial cells and in skin fibroblasts, but Echinaforce® eradicated this stimulation by anti-inflammatory effect [96]. By application of purified polysaccharides from cell cultures of *E. purpurea*, peritoneal macrophages killed cells infected either with the parasite *Leishmania enrietti*, or with yeast *Candida albicans* [97]. Extracts from *Echinacea* inhibited the growth of several yeasts such as *Saccharomyces cerevisiae*, *Candida shehata*, *C. kefyr*, *C. albicans*, *C. steatolytica* and *C. tropicalis* [25]. The alkamides from *Echinacea* acted synergistically to disrupt the fungal cell wall and cell membrane, a target for specific inhibition of fungal pathogens. *S. cerevisiae* cells exposed to sub-inhibitory concentrations of synthetic alkamides and *Echinacea* extract exhibit increased frequencies of cell wall damage and death, which were comparable to caspofungin and significantly greater than hygromycin and nourseothricin, which inhibit protein synthesis [98].

These results provide evidence that bacterial, viral, and fungal infections could be halted by *Echinacea* administration.

**Common Cold and Upper Respiratory Infections**

The common cold is one of the most prevalent illnesses worldwide, coupled with a lack of specific treatment options which invites to evaluate alternative therapies such as herbal remedies. Nowadays, *Echinacea* is possibly the most recognized herbal supplement for prevention and treatment of colds. Many people believe that *Echinacea* can boost the immune system and reduce the severity and the frequency of cold symptoms. This plant is widely used to fight the common cold and other upper respiratory infections in United States and Europe, nevertheless, some studies of *Echinacea* for the common cold have not found that it real helps. The clinical effectiveness of *Echinacea* is controversial because clinical trials have had mixed results, some studies have shown clinical benefit, whereas others have not (summarized in Table 2).

Some studies showed that *Echinacea* could reduce duration, severity and frequency of symptoms of cold and URIs. Hoheisel et al. in a double-blind study found that *E. purpurea* pressed juice reduced the duration and the severity of colds. In this study, 120 people were given *E. purpurea* or a placebo as soon as they started showing signs of getting a cold. Treatment with *Echinacea* at early onset of cold or flu symptoms was effective for relieving these symptoms in a shorter period [11]. The results from a clinical study suggested that treatment with Echinaforce® can be recommended as a prophylactic treatment. Long-term treatment with Echinaforce® was associated with a significant reduction in both total number and severity of cold episodes, whereas it did not induce any health risk above that reported with the placebo treatment [99]. In a double-blind trial, 246 healthy adult volunteers with recent onset of a respiratory infection were given either Echinaforce®, *E. purpurea* concentrate (same preparation at 7 times higher concentration), special *E. purpurea* radix preparation or placebo until they felt healthy again but not longer than 7 days. Echinaforce® and its concentrated preparation were significantly more effective than the special *Echinacea* extract or placebo. All treatments were well tolerated, and among the *Echinacea* groups, the frequency of adverse events was not significantly higher than in the placebo group [100].

In a randomized, double-blind, placebo-controlled trial, 282 subjects with a history of two or more colds in the previous year, but otherwise in good health, were recruited. They were instructed to start Echinilin (a formulation prepared from freshly harvested *E. purpurea* and standardized on the basis of active components alkamides, chionic acid and polysaccharides) or placebo at the onset of the first symptom related to a cold for seven days. The total daily symptom scores were found lower in the Echinilin group, and the response rate to treatments was greater in the treated group. Early intervention with a standardized formulation of *Echinacea* resulted in reduced symptom severity in subjects with naturally acquired upper respiratory tract infection [101]. In a study, Echinilin was administered to 150 adults at the onset of their cold for one week, with eight doses (5 ml/dose) on day 1 and three doses on the subsequent days. Researchers observed decreased daily symptomatic scores and sustained increase in the number of circulating total white blood cells, monocytes, neutrophils, and NK cells in the *Echinacea* group versus placebo group. These results suggest that Echinilin, by enhancing the non-specific immune response and stimulating free radical scavenging properties, may have led to a faster resolution of the cold symptoms [102].

In one double-blind placebo-controlled study, a total of 95 subjects with early symptoms of cold or flu (runny nose, scratchy throat, fever) were randomly assigned to receive an *Echinacea* herbal tea preparation (*Echinacea Plus*) 5-6 cups/day titrating to 1 over 5 days or placebo, the study period was 3 months. There was a significant difference between the *Echinacea* and placebo group, also there were no negative effects reported by any of the subjects in either group [10]. 473 patients with early influenza symptoms randomized to either 5 days of oseltamivir followed by 5 days of placebo, or 10 days of an *E. purpurea*-based formulation called Echinforce Hot drink (Switzerland). According to the results, Echinforce Hot drink is as effective as oseltamivir in the early treatment of influenza infections with a reduced risk of complications and adverse events [103].

In a prospective, double-blind, randomized study, 62 patients with symptoms of the common cold were treated with a natural
A Review on Pharmacological and Therapeutic Properties of Echinacea

Table 2: Clinical trials and human studies on efficacy of *Echinacea* against common cold and upper respiratory tract infections

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Study population</th>
<th>Type of study</th>
<th>Comparator</th>
<th>Dosage/Treatment period</th>
<th>Outcome</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tea preparation from aerial parts of <em>E. purpurea</em> and <em>E. angustifolia</em>, and <em>E. purpurea</em> root</td>
<td>patients with earliest symptoms of a cold</td>
<td>RCT</td>
<td>Placebo</td>
<td>5 to 6 cups day 1, titration to one cup on day 5/ 5 days</td>
<td>Positive</td>
<td>Lindenmuth [10]</td>
</tr>
<tr>
<td>Pressed juice of <em>E. purpurea</em> herb (<em>Echinacin®</em>)</td>
<td>patients with symptoms of a cold</td>
<td>RCT</td>
<td>Placebo</td>
<td>20 drops every 2 h on day 1 followed by 3 × 20 drops/ day/ 10 days</td>
<td>Positive</td>
<td>Hoheisel [11]</td>
</tr>
<tr>
<td><em>Echinaforce</em>® (alcoholic extraction from freshly harvested <em>E. purpurea</em> with 95% herb and 5% roots)</td>
<td>healthy adults</td>
<td>RCT</td>
<td>Placebo</td>
<td>for illness prevention: 3 × 0.9 ml/day; in case of cold: 5 × 0.9 ml/ day/ 4 months</td>
<td>Positive</td>
<td>Jawad et al. [101]</td>
</tr>
<tr>
<td>Echinaforce® tablets ( <em>E. purpurea</em> crude extract based on 95% herb/5% roots)</td>
<td>healthy volunteers</td>
<td>RCT</td>
<td>Placebo</td>
<td>2 × 3 (40.68 mg/ day)/ maximum one week</td>
<td>Positive</td>
<td>Brinkeborn et al. [102]</td>
</tr>
<tr>
<td>Freshly harvested <em>E. purpurea</em> and standardized on the basis of active components alkamides, cichoric acid and polysaccharides (<em>Echinillin</em>)</td>
<td>healthy adults</td>
<td>RCT</td>
<td>Placebo</td>
<td>10 × 4 ml the first day, then 4 × 4 ml/ 7 days</td>
<td>Positive</td>
<td>Goel et al. [103]</td>
</tr>
<tr>
<td><em>E. purpurea</em> ( <em>Echinillin®</em>)</td>
<td>adults at the onset of their cold</td>
<td>RCT</td>
<td>Placebo</td>
<td>8 × 5 ml for day 1, then 3 × 5 ml for 6 days/ one week</td>
<td>Positive</td>
<td>Goel et al. [104]</td>
</tr>
<tr>
<td>Syrup of <em>E. purpurea</em> herb harvested at flowering</td>
<td>healthy children</td>
<td>RCT</td>
<td>Placebo</td>
<td>3.75 ml twice a day for ages 2-5 years and 5 ml twice a day for ages 6-11 years/ 10 days</td>
<td>Negative</td>
<td>Taylor et al. [109]</td>
</tr>
<tr>
<td><em>Echinacea</em> fresh capsule (freeze-dried pressed juice from <em>E. purpurea</em>)</td>
<td>patients with cold</td>
<td>RCT</td>
<td>Placebo</td>
<td>3 × 1 capsule/ day/ maximum 14 days</td>
<td>Negative</td>
<td>Yale &amp; Liu [110]</td>
</tr>
<tr>
<td>Pressed juice of <em>E. purpurea</em> (<em>Echinacin®</em>)</td>
<td>patients with symptoms of a cold</td>
<td>RCT</td>
<td>Placebo</td>
<td>2 × 4 ml daily/ 8 weeks</td>
<td>Negative</td>
<td>Grimm &amp; Müller [111]</td>
</tr>
<tr>
<td>Capsules of <em>E. purpurea</em> dried plant</td>
<td>healthy adults</td>
<td>RCT</td>
<td>Placebo</td>
<td>3 × 2 capsules/ day (1 capsule containing 300 mg <em>E. purpurea</em>)/ 8 weeks</td>
<td>Negative</td>
<td>O’Neil et al. [112]</td>
</tr>
<tr>
<td>Tablets containing <em>E. purpurea</em> root and <em>E. angustifolia</em> root</td>
<td>individuals with cold symptoms</td>
<td>RCT</td>
<td>Placebo</td>
<td>4 × 2 tablet during first day, then 4 × 1 tablet per day for the next 4 days/ 5 days</td>
<td>Negative</td>
<td>Barrett et al. [113]</td>
</tr>
<tr>
<td>Capsules containing 50% <em>E. angustifolia</em> root, 25% <em>E. purpurea</em> root, 25% <em>E. purpurea</em> herb</td>
<td>patients with active cold</td>
<td>RCT</td>
<td>Placebo</td>
<td>6 × 4 capsules in the first day, then 3 × 4 capsules up to 10 days/ 10 days</td>
<td>Negative</td>
<td>Barrett et al. [114]</td>
</tr>
<tr>
<td><em>E. purpurea</em>/ <em>E. angustifolia</em> root alcoholic extract</td>
<td>healthy volunteers</td>
<td>RCT</td>
<td>Placebo</td>
<td>50 drops twice a day/ 12 weeks</td>
<td>Negative</td>
<td>Melchart et al. [115]</td>
</tr>
</tbody>
</table>

RCT = Double-blind, Randomized, Controlled trial

multitherbal formula Immumax (containing *Echinacea* extract, garlic powder, *Nigella sativa* oil, and *Panax ginseng* extract plus vitamin C and zinc) for the duration of their symptoms or a maximum of 2 weeks. The results indicated that Immumax was helpful in reducing the duration and severity of common cold symptoms, and the symptoms resolved faster in the Immumax group than in the placebo group. The median time to resolution of all symptoms was 8 days in the placebo group and 4 days in the Immumax group [104]. An herbal compound of *E. angustifolia*, Arabinogalactan, Vitamin C, Beta- Glucan Zinc (Imoviral® Junior) was given to 37 children affected by recurrent pharyngotonsillitis or otitis media. Almost all children after six months reported a reduction in frequency of acute episodes. Imoviral® Junior can improve the quality of life in pediatric patients affected by recurrent pharyngotonsillitis and otitis media without adverse effects [105]. URI frequently cause exacerbations of Chronic-Obstructive Pulmonary Disease (COPD). In a double-blind randomized placebo-controlled trial in COPD patients with acute URI, the combination of *E. purpurea* along with micronutrients zinc, selenium and vitamin C may alleviate COPD exacerbations caused by acute URI [106].

In contrast to abovementioned results, some studies have

reported no statistically significant improvement with *Echinacea* for the common cold. Taylor, et al. [107] using a large randomized controlled trial found no evidence of *E. purpurea* help in children suffering from URIs. Results of this trial do not support a benefit of *Echinacea* in the treatment of common cold symptoms in children, and its use was associated with an increased risk of rash. However, the authors concluded that their findings are not transferable to *Echinacea* use in adults or to other species/preparations of *Echinacea*. In another randomized double-blind placebo-controlled design, 128 adults received either 100 mg of *E. purpurea* (freeze-dried pressed juice from the aerial parts) or placebo 3 times daily until cold symptoms were relieved up to a maximum of two weeks. The time to resolution of symptoms was not statistically different and no significant difference was observed between treatment groups for symptoms including sneezing, nasal discharge, nasal congestion, headache, sore or scratchy throat, hoarseness, muscle pain, and cough [108].

A total of 109 patients with a history of more than three colds or respiratory infections in the previous year were randomly assigned to receive 4 ml *E. purpurea* fluid extract twice a day in a double-blind study. Treatment with *E. purpurea* did not significantly decrease the incidence, duration or severity of colds and respiratory infections compared to placebo. Adverse events were observed in 20% of patients in the *Echinacea* group compared with 13% patients in the placebo group [109]. In a randomized, double-blind clinical trial 58 subjects were assigned to survey the effects of *Echinacea* on the frequency of upper respiratory symptoms. Individuals in the *Echinacea* group reported 9 sick days during 8 weeks, whereas the placebo group reported 14 sick days. No difference was found in the frequency of upper respiratory tract symptoms and total symptom days reported 9 sick days during 8 weeks, whereas the placebo group reported 14 sick days during 8 weeks, whereas the placebo group reported 14 sick days. No difference was found in the frequency of upper respiratory tract symptoms and total symptom days reported 9 sick days during 8 weeks, whereas the placebo group reported 14 sick days during 8 weeks, whereas the placebo group reported 14 sick days during 8 weeks, whereas the placebo group reported 14 sick days during 8 weeks.

A total of 234 articles were identified through the literature search; and based on the analysis, the likelihood of experiencing a clinical cold was 55% higher with placebo than with *Echinacea*. This meta-analysis exhibited standardized extracts of *Echinacea* were effective in the prevention of symptoms of the common cold after clinical inoculation, compared with placebo [12]. Shah et al. did meta-analysis reviewed *Echinacea* clinical trials that examined both prevention and treatment in the incidence and duration of the common cold. The results supported *Echinacea*'s benefit in decreasing the incidence and duration of the common cold [13]. Evidence from another meta-analysis with a total of 2458 participants by Chapowal et al. [14] indicated that use of *Echinacea* potently reduced the risk of recurrent respiratory infections and development of complications. Ethanolic extracts from *Echinacea* appeared to be more effective than pressed juices, and increased dosing during acute episodes further enhanced these effects.

A Cochrane review by Karsch-Völk, et al. [114] compared the effect of *Echinacea* to placebo, in the treatment and the prevention of the common cold. They reviewed twenty-four double-blind controlled clinical trials with 4631 participants investigating the effectiveness of several different *Echinacea* preparations for preventing and treating common colds or induced rhinovirus infections. The authors concluded that *Echinacea* products have not proved statistically significant in reducing illness occurrence, although there might be a weak benefit from some *Echinacea* products.

Studies of *Echinacea* for the common cold have had mixed results, and whether or not *Echinacea* helps prevent or treat the common cold remains under debate. There are many variables in studying *Echinacea* for the common cold and URIs. All studies to date have had essential limitations, including differences in trial design, use of different species and/or plant parts (containing different constituents), various routes of administration, sample size, monitoring responses of healthy subjects, analytical methodology, and choice of biomarker and placebo. These differences make it hard to compare the results; consequently these data do not allow clear conclusions whether *Echinacea* might be effective for this purpose or not.

**Hepatoprotective Effects**

Chicoric acid may reduce acute alcohol-induced steatosis in mice through interfering with the induction of INOS and iNOS-dependent signaling pathways in the liver. Acute alcohol administration caused a significant increase in hepatic triacylglycerols accumulation, which was associated with increase in 4-hydroxyxynonenal protein adducts, and INOS and active plasminogen activator inhibitor 1 protein level in the liver; pretreatment with chicoric acid for 4 days before ethanol ingestion significantly attenuated these alcohol effects on the liver. In RAW264.7 macrophages, treatment with chicoric acid (4 mg/kg body weight) suppressed LPS-induced TNF-α and iNOS at mRNA expression level [23]. *E. purpurea* extract had a protective role on kidney and liver against Diethylnitrosamine (DEN) toxicity in rats. One month administration of DEN caused elevation in serum Alanine Transaminase (ALT), Aspartate Transaminase (AST), and Alkaline Phosphatase (ALP), creatinin and total and...
direct bilirubin levels in serum; however these factors decreased in E. purpurea administration. In addition, histopathological investigation revealed proliferation of hepatic stellate cells [115]. It was found that alkamide dodeca-2E,4E,8Z,10Z(E)-tetraenoic acid isobutylamides isolated from E. purpurea root has hepatoprotective effect against acute fulminating hepatitis induced by lipopolysaccharide/D-galactosamine (LPS/D-GaN) in mice. This dose-dependently induced HO-1 protein expression in LPS-stimulated murine macrophages that was regulated through increase in JNK phosphorylation, c-jun protein expression and phosphorylation, and transcription factor AP-1 binding consensus DNA activity. Besides, this alkamide suppressed serum aminotransferase activities, TNF-α expression, and damages to hepatocytes of LPS/d-GaN-treated mice [116]. Cadmium (Cd 2+) is toxic to a wide range of tissues. Prolonged intraperitoneal injection of E. purpurea extract combined with Cd(2+)+Cl(2) decreased the mitotic activity induced by Cd 2+, also increased apoptotic activity of hepatocytes of mice [117]. These data suggests a new application of Echinacea as a hepatoprotective agent, however further investigation is needed.

**Echinacea against diabetes**

Diabetes is a debilitating and often life-threatening problem with increasing incidence throughout the world. A scientific investigation of herbal remedies for diabetes may provide valuable alternative drugs and therapeutic strategies. Recent studies have indicated that *Echinacea* could have anti-diabetic activities.

Adipogenesis has been used to study the insulin signaling pathway and to screen anti-diabetic compounds. When adipocyte differentiation was induced with insulin plus 3-isobutyl-1-methylxanthine and dexamethasone, the accumulation of lipid droplets and the cellular triglyceride content were increased by ethanolic extracts of *E. purpurea* were found to activate PPAR-γ, to increase basal and insulin-dependent glucose uptake in 3T3-L1 adipocytes in a dose-dependent manner, and to exhibit characteristics of a PPAR-γ partial agonist [29]. The isomeric C12-alkamides isolated from a dichloromethane root extract of *E. purpurea* were found to activate PPAR-γ, to increase basal and insulin-dependent glucose uptake in 3T3-L1 adipocytes in a dose-dependent manner, and to exhibit characteristics of a PPAR-γ partial agonist [29]. The isomeric C12-alkamides isolated from the ethanolic extract of *E. purpurea* were found to activate PPAR-γ, to increase basal and insulin-dependent glucose uptake in 3T3-L1 adipocytes in a dose-dependent manner, and to exhibit characteristics of a PPAR-γ partial agonist [29]. The isomeric C12-alkamides isolated from the dichloromethane root extract of *E. purpurea* were found to activate PPAR-γ, to increase basal and insulin-dependent glucose uptake in 3T3-L1 adipocytes in a dose-dependent manner, and to exhibit characteristics of a PPAR-γ partial agonist [29]. The isomeric C12-alkamides isolated from the ethanolic extract of *E. purpurea* were found to activate PPAR-γ, to increase basal and insulin-dependent glucose uptake in 3T3-L1 adipocytes in a dose-dependent manner, and to exhibit characteristics of a PPAR-γ partial agonist [29].

**Effects On Skin Problems**

Several plants with effective properties may offer better alternative treatments for skin complications. *Echinacea* contains many valuable constituents for protection of skin from oxidative stress and for improving skin health. In a survey *E. purpurea* extract was incorporated into cream and gel bases and the effect of those formulations on skin irritation, hydration level and wrinkle reduction was evaluated in 10 healthy volunteers. According to results *E. purpurea* cream and gel were effective in improving skin hydration and reducing wrinkle, also both formulations showed no irritation to skin [118]. Acne is a chronic inflammatory disorder of skin follicles caused by the gram-positive bacterium *Propionibacterium acnes*. Echinaforce® might provide a useful safe treatment in the control of acne disease by preventing proliferation of the organism and inhibiting the bacterial-induced inflammation. In human skin fibroblasts *in vitro*, *P. acnes* induced the secretion of considerable amounts of pro-inflammatory cytokines IL-6 and IL-8; however, Echinaforce® completely reversed their level to normal [22]. *Echinacea* is purported to be beneficial for wound healing. It revealed that root extract of *E. pallida* and its constituent echinacoside has good wound healing properties in excision wounds treated topically. This activity probably related to the anti-hyaluronidase and anti-inflammatory activities of echinacoside [119]. Alcoholic extract of *E. pallida* accelerated cutaneous wound closure in the stressed mice, but had no curing effect for the non-stressed mice. The wound healing effect of *Echinacea* in stressed mice is not mediated through modulation of glucocorticoid signaling because plasma glucocorticoid in restraint stressed mice treated with *Echinacea* didn’t change [120].

**Effects On Nervous System**

Excitatory synaptic transmission in the hippocampus, a brain region that is involved in anxiety and anxiety-related behaviors, was suppressed by an *Echinacea* extract; but no change in inhibitory synaptic transmission could be detected upon application of this extract. In addition, at low concentration the *Echinacea* extract reduced the spiking activity of CA1 pyramidal cells, while at high concentration increased it, this was parallel to the reduction in the magnitude of the h-current-mediated voltage responses in pyramidal cells [121]. Anxiolytic potency of *Echinacea* preparations were consistently seen in three different laboratory tests of anxiety, the elevated plus-maze, social interaction and shock-induced social avoidance tests; these effects are comparable with chloridiazepoxide. *Echinacea* preparations had a considerable anxiolytic potential and it decreased anxiety-like behavior in all tests [122]. *E. angustifolia* extract decreased anxiety in the elevated plus-maze and ameliorated contextual conditioned fear. No lethality or behavioral signs of discomfort were noticed in rats treated with intragastric administration of 1000 and 3000 mg/kg *E. angustifolia*. A pharmacological formulation based on the same *E. angustifolia* extract was tested in healthy volunteers. One or two tablets (each contained 20 mg of the plant extract) per day were administered for 7 days to subjects scoring high on the State-Trait Anxiety Inventory (STAI). The high dose (2 tablets/ day) decreased STAI scores within
3 days in human subjects, an effect that remained stable for the duration of the one week treatment and for the 2 weeks that followed treatment [123]. The endocannabinoid system involves many pathophysiological activities including anagelsec action. Echinacea-isolated alkamides appear to exert psychoactive activities through the endocannabinoid system [77]. Alkamides from E. angustifolia roots showed psychoactive properties by binding to CB1 receptors predominantly expressed in the brain tissue [124]. The finding about the interaction of alkamides with CB receptors may help explain the traditional use of Echinacea for wound healing, pain relief and improvement of cold symptoms [125].

**Effects On Reproductive System**

Two study raised questions about possible anti-fertility effects of Echinacea. The histological changes were found after 4 or 8 weeks of using 50 mg/kg E. purpurea in Wistar male rats. Results of the study showed significant reduction in the testicle mass and the body mass, as well as changes in histological structures after eight weeks of E. purpurea administration. Consumption of the preparation for 8 weeks caused anti-androgenic variations in cells of spermatogonial epithelium of a testicle duct and consequently inhibited spermatogenesis [126]. An in vitro investigation by fresh sperm specimens exhibited E. purpurea at high-concentration interfered with sperm enzymes, possibly the Echinacea treatment may prevent sperm from fertilizing the oocytes. The beat cross frequencies were higher for Echinacea treatment group [127]. Echinacea extract can be useful medication for treatment of Benign Prostate Hyperplasia (BPH). Results of a work showed a significant decrease of prostate weight of BPH in rats, and reversed changes in the structure of the prostate gland after using E. purpurea extract for 8 weeks [82]. E. angustifolia extract enhanced cell viability and proliferation in mammary epithelial cells, HC11 mouse cell line and BME-UV bovine cell line. This effect may be modulated by MAPK and Akt activation and by a reduction of caspase-3 activity in Echinacea treatment. Moreover Echinacea was able to increase β-casein expression in association with prolactin (5 mg/ml). These data demonstrate that E. angustifolia extract can stimulate mammary epithelial cell physiology and may be considered a candidate to support mammary gland activity during mammogenetic and lactogenetic states [128].

**Metabolism and Pharmacokinetics**

It is found that application of herbal medicinal products and their components at the same time with substances that are Cytochrome P450 (CYP) enzymes substrates may cause herb-drug interactions. Since the use of herbal supplements continues to increase throughout the world, the potential for drug-herbal interactions also rises. Modified expression of CYP enzymes will affect drug metabolism in three different ways. It can alter drug elimination, pro-drug activation, or drug bioactivation (such as conversion to toxic metabolites), all of which can have serious consequences [129]. Echinacea is a widely used herbal medicinal product and consequently, studies of its interactions with conventional drugs are of particular importance.

It was demonstrated E. purpurea ethanolic extract can potently inhibit the expression of CYP3A1 and CYP3A2, also CYP2D2 and CYP2C6 activities [130]. CYP3A4 and CYP2C9 enzymes have been reported to metabolize one of the main alkamide constituents of E. purpurea extract in human liver microsomes [131]. Administration E. purpurea root extract for 8 days to healthy volunteers significantly decreased CYP1A2 activity, increased hepatic CYP3A4 activity, and there was little decrease in CYP2C9 activity. E. purpurea root reduced the oral clearance of substrates of CYP1A2 but not the oral clearance of substrates of CYP2C9 and CYP2D6 [132]. E. purpurea cause herb-drug interaction by up-regulating CYP1A2, CYP3A4 and MDR1 expression via Pregnane X Receptor (PXR) activation in human liver carcinoma HepG2 cells [133].

Alkylamide undeca-2 E,4 E/ Z-diene-8,10-diyanoic acid isobutylamide correlated well with inhibition of CYP3A4 by Echinaforce® [134]. In a clinical study, no significant effect of E. purpurea on midazolam pharmacokinetics was reported in healthy volunteers. E. purpurea selectively altered the catalytic activity of CYP3A in the liver vs. intestine, conversely, E. purpurea whole plant extract administration did not significantly alter CYP3A metabolic serum ratios of 1-hydroxymidazolam: midazolam in healthy volunteers [135]. E. purpurea significantly induced cytochrome CYP3A activity but does not alter lopinavir-ritonavir exposure in healthy subjects. Neither lopinavir nor ritonavir (400/100 mg) pharmacokinetics were significantly altered by 2 weeks of E. purpurea co administration in healthy volunteers. E. purpurea induced CYP3A activity but did not alter lopinavir concentrations, most likely due to the presence of ritonavir as a potent CYP3A inhibitor. E. purpurea is unlikely to alter the pharmacokinetics of ritonavir-boosted protease inhibitors but may cause a decrease in plasma concentrations of other CYP3A substrates [136]. In an open-label, fixed-sequence study the interaction of E. purpurea with etravirine, a non-nucleoside reverse transcriptase inhibitor of HIV was investigated. Fifteen HIV-infected patients receiving etravirine (400 mg once daily) for 4 week, and E. purpurea root extract (500 mg every 8 h) was added to the anti-retroviral treatment for 14 days. Results showed that the coadministration of E. purpurea with etravirine was safe and well tolerated in HIV-infected patients [94].

The multidrug transporter P-glycoprotein (P-gp), the product of the ABCB1 gene, involved in cancer Multi Drug Resistance (MDR) and in herb-drug or drug-drug interactions. Concomitant administration of medicinal herbs with drugs that are P-gp substrates may produce clinically significant herb-drug interactions. P-glycoprotein is responsible for exporting xenotoxins including pharmaceutical medicines from the cell. Alkamides isolated from E. angustifolia inhibited P-gp-mediated calcine transport a major constituent of the blood-brain barrier in isolated porcine brain capillary endothelial cells [137]. The n-hexane root extracts from E. pallida, E. angustifolia and E. purpurea reduced the efflux of the P-gp probe calcine-AM from human proximal tubule HK-2 cells (that constitutively expresses ABCB1). Pentadeca-(8 Z,13 Z)-dien-11-yn-2-one isolated from the n-hexane extract of E. pallida roots was an efficient compound that reduced P-gp activity and decreased the calcine-AM efflux [138]. The interaction of E. purpurea with P-gp transporter

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was studied in human adenocarcinoma colonic cell line Caco-2, as a standard rapid, reliable, and low-cost model for study the absorption of drugs by the intestine. In a study digoxin was used as a substrate and verapamil as a control inhibitor. At high concentrations of E. purpurea, a significant linear decrease was observed in the net digoxin flux, indicating a dose-dependent inhibitory effect of E. purpurea on P-gp [139].

Commonly used herbal supplements were screened for their potential to inhibit UDP-Glucuronyl Transferase 1A1 (UGT1A1) activity using human liver microsomes. Echinacea showed inhibition of UGT1A1 activity [140]. Alkamides and cinnamic acid have been shown to have good permeability through human Caco-2 cells, although caftaric acid, echinacoside and cichoric acid permeated poorly through the Caco-2 monolayers [141].

These findings suggest that Echinacea and components may influence metabolism of different drugs also alter their pharmacokinetics. However, further studies are also needed to confirm the potential of interactions between Echinacea and other conventional drugs.

Safety and Toxicity

The increasing use of medicinal herbs among the populations has created the need for scientific research to determine the safety of herbs. Herbal remedies and dietary supplements are not classified as drugs by the US Food and Drug Administration (FDA); therefore, although the 1994 Dietary Supplement Health and Education Act allows manufacturers to make claims intended to influence public opinion regarding the benefits of these products, herbs and supplements are excepted from the rigorous regulations required for drugs.

Echinacea has an excellent safety record and is well tolerated by most consumers. Oral administration of the E. purpurea expressed juice for 4 weeks proved virtually non-toxic to rats and mice, even in doses many times greater than human therapeutic dose [142]. There are reports of anti-apoptotic activity of E. angustifolia extract on noncancerous cells. The biological effect of E. angustifolia extract on cell viability and cell differentiation in mammary epithelial cells have been observed in two different cell lines HC11 and BME-UV. This herb activated MAPK/Akt pathway involved in cell viability and proliferation and prevention of caspase-3 accumulation that indicates an anti-apoptotic effect of Echinacea extract [130]. Moreover hydroalcoholic extract and pressed juice from E. pallida exhibited a low cytotoxic effect on monkey kidney cell cultures [143].

Cleft palate is one of the most common birth defects. E. purpurea extract had prophyllactic effect on incidence of phentoin-induced cleft palate. In a study the prophyllactic effects of levamisole and Echinacea extract on teratogenic effects of phentoin was compared. This study was performed on pregnant mice that received phentoin at 10th day of gestation. E. purpurea extract were administrated at dose of 360 mg/kg intraperitoneally, along with and 12 hours after phentoin injection. Cleft palate incidence decreased in fetuses of mice that received phentoin with Echinacea extract; also mean weight and length of fetuses of the ones that received Echinacea were significantly greater than those received only phentoin [144]. The teratogenic effect of phentoin on cleft palate is associated with inhibition of cell proliferation and increase in cell apoptosis of Mouse Embryonic Palatal Mesenchymal (MEPM) cells, and E. purpurea extract had the reverse effect [145].

On the other side of safety, there are rare cases of adverse effects. Such side effects include nausea, abdominal pain, diarrhea, itch, and rash. Echinacea has also been linked to allergic reactions, including asthma, shortness of breath, and one case of anaphylaxis [146]. Echinacea can be associated with allergic reactions that may be severe or exacerbate asthma [146]. Moreover, it has also been incriminated in causing contact dermatitis and anaphylactic reactions associated with the consumption of Echinacea [147]. In clinical trials, gastrointestinal symptoms were common. Echinacea supplementation has altered the gastrointestinal tract microbiota. In a study 50 human subjects consumed 1000 mg of standardized E. purpurea for 10 days. Significant increases were found for total aerobic bacteria, Bacteroides group and Bacteroides fragilis after E. purpurea exposure [148].

There are concerns that by stimulating immune function, Echinacea could potentially exacerbate autoimmune diseases and/or decrease the effectiveness of immunosuppressive drugs, but this warning is based on theoretical considerations rather than human analyses. Its immunostimulatory property may lead to interference with immunosuppressant agents; therefore a general consensus exists about the avoidance of Echinacea in patients who are being administered immunosuppressive drugs, especially in patients undergoing organ transplantation. However, despite the immunostimulatory effect that may be seen with short-term use, chronic long-term use (>6-8 weeks) of Echinacea may be immunosuppressive [149] which increases the risks of poor wound healing and opportunistic infections. Consequently its use in AIDS or autoimmune disorders such as multiple sclerosis and rheumatoid arthritis is controversial. Furthermore, there are also concerns about its potential hepatotoxicity, probably the use of Echinacea in combination with other drugs metabolized by the liver can cause possible unwanted effects; thus this plant should be used carefully in patients with pre-existing hepatic dysfunctions.

So altogether, while Echinacea administration appears to be without significant adverse effects, the full toxicological profile of Echinacea remains to be assessed.

Conclusions

Echinacea is one of the most important medical herbs. In a 2007 National Center for Complementary and Alternative Medicine survey, Echinacea was the third most commonly used non-vitamin, non-mineral natural product among adults, and the fifth highest selling herbal dietary supplement [150]. At present, extracts and plant products made from Echinacea purpurea, E. angustifolia, and E. pallida comprise one of the largest parts of the herbal medicine market, in North America as well as in Europe.

Echinacea is widely used as one of the treatments chosen by consumers with the belief that it will reduce the severity and duration of the common cold and because of its supposed...
beneficial effects on the immune system. There are multiple scientific studies published to evaluate the effects of Echinacea on common cold and immunity; however, results are controversial and inconclusive. It is well known that the effectiveness of distinct Echinacea products differ considerably, mainly due to the use of different parts of the plant (including leaves, flowers, root or rhizome), extraction protocols, and the addition of other components. These all have made their outcomes difficult to interpret and compare.

Different commercial products are likely to contain different relative concentrations of active constituents, and there are currently no regulated manufacturing standards for the amount of individual chemical compounds in commercial preparations. In addition, the dose and timing of administration also needs to be evaluated extensively.

Results show that among the bioactive compounds present in Echinacea, alkylamides, cichoric acid and polysaccharides have most effects. However the biological effects of unidentified compounds in this herb should be also investigated. Despite many pharmacological and clinical studies, the molecular mechanisms for Echinacea which exert its effects are not well understood. Additionally, more scientific research is required regarding its safety and adverse effects.

**Conflicts of interest**

None declared.

**References**

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