Mechanism of action

In this guide

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75. The exact mechanism of action of Echinacea preparations in relation to common cold symptoms is not known. Antiviral, immunomodulatory and anti-inflammatory effects of Echinacea have been reported in in vitro, in vivo and human studies referenced below. However, the relevance of the in vitro and in vivo effects of Echinacea to clinical efficacy is not known and the exact pharmacodynamic mechanism cannot be established (EMA, 2014).

Antiviral effects

76. The Echinacea antiviral mechanism of action is not fully elucidated, but it is thought to be due to prevention of viral entry into the cells rather than inhibition of viral replication (Pleschka et al., 2009; Sharma et al., 2009), suggesting that Echinacea treatment is effective only at the very early stages in the infection process (Pleschka et al., 2009). The use of different species, extraction methods and preparations make it difficult to attribute the antiviral activity of Echinacea to specific compounds. Echinacea has also been reported to inhibit the induction of pro-inflammatory cytokines IL-6, IL-8 and TNF-α in vitro (Sharma et al., 2009) and IL-10 and IFN-γ in vivo (Fusco et al., 2010). The authors suggested that this immunomodulatory activity may contribute to improved clinical outcomes by moderating the inflammatory response (Fusco et al., 2010).

Immunomodulatory and anti-inflammatory effects

77. The immunomodulatory properties of Echinacea and its constituents have been extensively studied and reviewed in the literature. The studies reviewed in this statement reported that Echinacea stimulated the secretion of TNF-α (Burger et al., 1997; Rinninger et al., 2002; Goel et al., 2002), IL-1(Burger et al., 1997; Rinninger et al., 2002; Zhai et al., 2007) and IL-10 (Burger et al., 1997; Li et al., 2017) from macrophages and IFN-γ from lymphocytes (Li et al., 2017; Zhao et al. 2007). Echinacea has also been shown to increase the natural killer cells (NK) mediated cytotoxicity (See et al., 1997; Gan et al., 2003; Zhao et al. 2007), promote dendritic cells maturation (Li et al., 2017) and lead to changes in the percentage of immune cell populations, including T lymphocytes and NK cells (Zhao et al. 2007; Li et al., 2017; Gan et al., 2003). The immunomodulatory effects of Echinacea from in vitro and animal studies have been summarised in Table 2. The majority of the studies focused on E. purpurea preparations, with the exception of Zhao et al. (2007) where E. angustifolia and E. pallida were also tested.

78. Echinacea extracts have also been reported to exhibit anti-inflammatory properties due to their ability to inhibit cyclooxygenases (COX) I and COX II (Clifford et al., 2002) and 5-lipoxygenase (5-LOX) (Merali et al., 2003). Clifford et al. (2002) found that alkylamides from E. purpurea roots inhibited COX-I and COX-II by 36–60% and 15–46%, respectively, at 100 µg/mL, compared to higher inhibition by standard non-steroidal anti-inflammatory drugs (NSAIDs). Merali et

al. (2003) reported 5-LOX inhibition by root extracts of E. angustifolia, E. purpurea, and E. pallida attributing the activity to the presence of alkylamides in the extracts.

Table 2: Summary of the immunomodulatory effects of Echinacea

Echinacea **preparation**	**Concentration or dose**	**Test system**	**Summary of immune system effects**	**Reference**
Fresh and dried juice from EchinaFresh (*E. purpurea)* standardized for a content of 2.4% soluble β-1,2-D-fructofuranosides.	0.05-10 µg/mL fresh juice and 0.01-10 µg/mL dried juice.	Human peripheral blood macrophages	Statistically significant increase in the production of IL-1, TNF-α, IL-6 and IL-10 by the macrophages at all concentrations of *Echinacea.*	Burger *et al*., 1997
E. purpurea raw herb and root powders subjected to simulated digestion protocol in simulated gastric fluid.	5 – 320 µg/mL	RAW267.7 murine macrophages	Dose dependent induction of TNF-α, NO, IL-1α, IL-1β, and IL-6 with *Echinacea* treatment comparable to the results observed with the LPS positive control.	Rinninger *et al*., 2002

Plant parts extracted with aqueous ethanol, producing four different fractions with concentrations of chicoric acid, polysaccharide and alkylamides at basal level, 3, 20 and 50 times the basal level.	100 µL *via* oral gavage	Male Sprague-Dawley rats	*Echinacea* fractions at 20 and 50 times the basal dose levels significantly increased the phagocytic index in alveolar macrophages compared to basal and 3 times basal level dose. TNF-α secretion from alveolar macrophages showed a dose-dependent rise with 3 and 20 times basal level doses. Similarly, spleen macrophages exhibited dose-dependent increases in TNF-α and IFN-γ release.	Goel *et al*., 2002

Commercially available *E. purpurea* extracts with a defined chemical composition of chicoric acid (3.045%), caftaric acid (1.575%), chlorogenic acid (0.065%), dodeca-2E, 4E, 8Z, 10E/Z-tetraenoic acid isobutylamide (1.635%).	400 µg/mL	Bone marrow-derived dendritic cells (BMDCs) derived from femur and tibia of 6–8-week-old female C57BL/6 mice.	*Echinacea* treatment significantly increased percentage of CD40, CD80, CD83 and CD86 markers on BMDCs and increased the secretion of IFN-γ, IL-12, IL-10, and TGF-β1 by BMDCs. Endocytosis of fluorescently labelled dextran reduced by *Echinacea* treatment, similar to results observed with LPS control.	Li *et al*., 2017

Dried, ground preparations of fresh *E. purpurea* herb homogenized, filtered and used fresh the same day.	0.001 to 1000 pg/mL	Human peripheral blood mononuclear cells (PBMC) from healthy patients or patients with chronic fatigue syndrome (CFS) or acquired immunodeficiency syndrome (AIDS).	Significant increase in the NK cell activity from healthy patients and those with CFS and AIDS was observed following *Echinacea* treatment in a concentration dependent manner. A similar concentration dependent response was observed for the antibody dependent cell-mediated cytotoxicity in all three patient groups following *E. purpurea* treatment.	See *et al.*, 1997

			Increase in the NK-mediated cytotoxic activity was observed with *E. purpurea* treatment in a concentration dependent manner.	
E. purpurea dissolved in water and filtered to prepare a water soluble extract.	Concentrations up to 10 µg/mL	Human peripheral blood mononuclear cells (PBMC)	*Echinacea* treatment reduced CD16 expression (frequency and intensity) by lymphocytes, while increasing CD69 expression within $CD16^+$ populations, with over 90% $CD16^+$ cells expressing CD69 at the highest concentration.	Gan *et al*., 2003

Ground *E. purpurea* aerial parts and freeze dried into a powder. The preparation contained cichoric and caftaric acids, as well as cynarin, but not alkylamide.	Concentrations of up to 250 µg/mL	Human T-cell line Jurkat E6-1	*E. purpurea* induced a dose-dependent increase in IL-2 secretion and a five-fold rise of IFN-γ secretion by high-density T cells.	Fonseca *et al*., 2014

Alcohol extracts of *Echinacea*. *E. purpurea* contained chicoric acid and caftraic acid, no echinacoside. *E. angustifolia* contained echiancoside, cynarin, chlorogenic acid. *E. pallida* contained echinacoside, chlorogenic acid and caftaric acid.	130 mg/kg bw/day by gavage	Eight-week-old male BALB/c mice	All three *Echinacea* species increased IFN-γ production in mitogen-stimulated splenocytes, suppressed IL-1β and TNF-α. In non-stimulated splenocytes, *E. purpurea* significantly increased IL-1β secretion. *E. purpurea* increased the percentage of $CD49^+$ and $CD19^+$ splenic cells, while *E. angustifolia* only increased $CD49^+$; *E. pallida* had no effect on either. Only *E. pallida* significantly enhanced NK cell cytotoxicity.	Zhai *et al*., 2007