Mechanism of action

In this guide

68. The exact mechanism by which *Echinacea* preparations exert their beneficial effect on the treatment and prevention of common cold is not known. Antiviral, immunomodulatory and anti-inflammatory effects of *Echinacea* were demonstrated in *in vitro*, *in vivo* and human studies referenced in the section below. However, the relevance of the *in vitro* and *in vivo* effects of *Echinacea* to clinical efficacy is not known and exact pharmacodynamic mechanism cannot be established (EMA, 2014).

In vitro and in vivo studies

Antiviral effects

69. 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), which can contribute to improved clinical outcomes of influenza infections by modulating the immune response (Fusco *et al*., 2010).

Immunomodulatory and anti-inflammatory effects

70. 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.

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 achieved 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

71. *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.

Human Studies

72. A meta-analysis (Schapowal et al., 2015) of six randomised control trials (RCTs) reported that Echinacea significantly reduced the relative risk (RR) of recurrent respiratory tract infections (RR = 0.649; 95% CI: 0.545–0.774; $p < 0.0001$). In individuals with high susceptibility to recurrent respiratory tract infections (e.g., stress, smoking, poor sleep, low T4/T8 ratio), the risk reduction was greater (RR = 0.501; 95% CI: 0.380–0.661; $p < 0.0001$). Echinacea treatment also halved the incidence of complications such as pneumonia, sinusitis, and bronchitis (RR = 0.503; 95% CI: 0.384–0.658; $p < 0.0001$), with pneumonia showing the greatest reduction (64.9%). The study concluded that Echinacea is an effective option for the management of recurrent respiratory tract infections and their related complications and that people with presumed lower immune function and high susceptibility to infection may benefit most. The authors attributed the increased resistance to viral infections observed in the human studies to the reported immunomodulatory effects of Echinacea in in vitro and in vivo studies.

73. Melchart *et al*. (1995) summarized the results of five placebo-controlled, randomized studies investigating the immunomodulatory activity of *Echinacea* extracts in a total of 134 healthy volunteers (18 females and 116 males) aged 18–40 years. The primary outcome measure was the relative phagocytic activity of polymorphonuclear neutrophil granulocytes (PNG). Two studies reported a significant increase in PNG phagocytic activity with *Echinacea* compared to placebo, while the remaining three found no significant effect. Peripheral blood leukocyte counts were unchanged across all studies. The review authors concluded that it was difficult to draw firm conclusions regarding *Echinacea*’s effect on PNG activity due to methodological differences in measuring phagocytosis, small sample sizes, and the absence of chemically defined, standardised *Echinacea* preparations.

74. A human study with 10 healthy subjects (5 male and 5 female) evaluated the immunomodulatory effect of a standardised E. angustifolia root

extract (Polinacea) by measuring the mRNA and protein levels of the cytokines IL-2, IL-8, IL-6 and TNF-α in plasma samples (Dapas et al., 2014). The subjects took 10 mL, equal to 100 mg E. angustifolia root extract containing 4.7 mg/10 mL of echinacoside and 8.0 mg/10 mL of high molecular weight polysaccharides, daily for 4 weeks. The study reported upregulated expression levels of IL-2 and IL-8 and downregulation of the pro-inflammatory cytokines TNF-α and IL-6 following Echinacea treatment. The maximal differential gene expression for the cytokines was observed after 14 days of Echinacea treatment. The authors acknowledge the study limitations such as small sample size and the lack of comparison to other Echinacea preparations.