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Review Article

Commercial Herbal Products of Echinacea Nutrients

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Abstract

Echinacea preparations are among the most popular herbal products with immunomodulatory properties. While immunomodulatory aspects of an array of different biomolecules (e.g., phenolic compounds, alkamides, arabinogalactan proteins) occurring in Echinacea preparations. Echinacea and several other plants encompassed in herbal medicine (e.g., ginger, turmeric, and cannabis) have been shown to alleviate the effects of inflammation. It is interesting to note that these plants display enhanced antioxidant capacity, which could, in turn, be used to manage inflammation-related disorders induced by oxidative stress.

Fructan-related antioxidant capacity (and ability to act as ROS scavengers) has also been demonstrated in humans in both in vitro and in vivo studies, suggesting that the consumption of foods rich in fructans could exert beneficial immunomodulatory properties by acting as antioxidants. The ability of ITFs to bind to TLR2 suggests a potential role in anti-inflammatory pathways through the activation of regulatory T-cells.Echinacea, which was commonly used for the treatment of common cold, coughs, bronchitis, influenza and inflammation of mouth and pharynx, is found to rank in second position in the highest retail sales for over-the counter herbal products. It is found to be the most frequently used herbal remedies in case of the treatment for adults and children and hence consumed by approximately over 10 to 20% of the herbal users.

Echinacea purpurea root was found to reduce the oral clearance of substrates of CYP1A2 but not the oral clearance of substrates of CYP2C9 and CYP2D6. The ethanol and ethyl acetate-soluble fractions from the leaves and stem was found to contain a potent antiviral photosensitizer, which was absent in the flower extract. Dietary Echinacea did not enhance the growth, exhibit antiviral effects to porcine reproductive and respiratory syndrome virus (PRRSV), or show any evidence of immune enhancing properties. Echinacea purpurea was found to decrease the cadmium-induced mitotic activity of liver cells, and increased the apoptotic activity of these cells.

Key words: anti-inflammatory; PRRSV; T-cells.echinacea

Summary

Echinacea preparations are among the most popular herbal products with immunomodulatory properties (Barrett, 2003 and Sharma et al., 2006). While immunomodulatory aspects of an array of different biomolecules (e.g., phenolic compounds, alkamides, arabinogalactan proteins) occurring in Echinacea preparations have been highlighted before (Bruni et al., 2018; Classen, 2018;2019 and Pugh et al., 2013), here we review knowledge on Echinacea derived inulin-type fructans (ITFs) and highlight their presence in commercially available Echinacea products.

Echinacea is a plant genus within the family Asteraceae (previously termed the Compositae) and is comprised of 11 taxa of herbaceous and flowering plants (Kim et al., 2004 and Sharifi-Rad et al., 2018). Echinacea preparations (which are mainly based on three commercially important species; Echinacea purpurea, Echinacea angustifolia, and Echinacea pallida) are commonly used for preventing and alleviating the symptoms of bacterial and viral infections (Kim et al., 2004). Furthermore, some Echinacea preparations are known to exert antioxidant and anti-inflammatory activity espousing to its potential immunomodulatory activities (Sharifi-Rad et al., 2018 and El-Ashmawy et al., 2015).

Both in vitro and in vivo studies demonstrated that different extracts from Echinacea, either from roots, above-ground parts, or a mixture of both, could stimulate or signal immune responses (Goldrosen et al., 2004).

Immunological studies have used aqueous or alcoholic extracts, as well as purified polysaccharides. Their effects on monocytes, macrophages, natural killer (NK) cells, T cells, and dendritic cells (DC) have been

thoroughly studied (El-Ashmawy et al., 2015; Goldrosen et al., 2004 and Wang et al., 2006).

Further research concluded that several purified compounds from Echinacea (e.g., glycoproteins, soluble polysaccharides, caffeic acid derivatives, phenolic compounds and alkamides) could induce transcriptional changes that activate immunomodulation pathways (Dalby-Brown et al., 2005; Pillai et al., 2007; Ramasahayam et al., 2011; Rondanelli et al., 2018; Kour and Bani, 2011; Park et al., 2011 and Raduner et al., 2006).

In general, immunomodulatory and prebiotic polysaccharides have been implicated in the overall health and well-being of humans by (i) enhancing physiological parameters (e.g., blood pressure, hematological parameters), (ii) increasing tolerance against pathogens and, (iii) modulating immune responses (Vos et al., 2007 and Delgado et al., 2010).

However, an additional signaling pathway dependent on the peptidoglycan recognition protein 3 (PGlyRP3) has also been proposed (Zenhom et al., 2019). This recognition protein, which responds to bacterial cell wall peptidoglycan, forms part of a larger group of highly conserved host defense proteins in mammals and insects. It has been demonstrated that FOS enhances the activity of peroxisome proliferator-activated receptors (PPAR), a group of nuclear receptor proteins that function as transcription factors to modulate the expression of several genes involved in lipid and carbohydrate metabolism, as well as cell proliferation, differentiation, and death (Di Giacomo et al., 2017 and Dabrowski et al., 2019).

Respiratory infections, such as the common cold and the seasonal flu, are often infectious diseases caused by different viruses (Roxas et al., 2007).

In this context, Echinacea extracts show profound antiviral activity against several viruses (including human and avian influenza viruses, H3N2-type IV, H1N1-type IV, herpes simplex, and rhinoviruses), and reversed virus-induced pro-inflammatory responses (Pleschka et al., 2009; Senchina et al., 2010 and Vimalanathan et al., 2013). It is necessary to better understand what role ITFs and other fructans may play in immunomodulation, when administered as part of a collective plant extract, given the knowledge that a variety of other herbal medicines (such as the Indian Ayurveda and Japanese Chikuyo–Sekko–To) with well-established immunomodulatory effects have been identified to contain fructans as key compounds (Lee et al., 2011 and Thakur et al., 2012).

A fructan isolated from Welsh onion (Allium fistulosum L.) demonstrated an inhibitory effect on influenza A. virus replication inmice (Hayashi et al., 2012). Intriguingly, fructans from burdock (Arctium lappa L.) strongly stimulate NO synthesis and defense signaling in plants (Guo et al., 2013), suggesting that the overall underlying mechanisms and pathways may be similar in all multicellular organisms. Both high and low DP fructans from aged and fresh garlic (Allium sativum) have the capacity to activate macrophages and subsequently phagocytosis, again in combination with a release of NO (Chandrashekar et al., 2011; 2016). Garlic is also an important component of the traditional Ayurveda Rasayana drugs, together with the Inula racemosa and Bombax ceiba. The immunomodulating properties of these three plants were attributed to their high fructan content (Balasubramani et al., 2011; Mishra et al., 2016 and Li et al., 2017). Fructans were also shown to be important immunomodulatory compounds in extracts of onion (Allium cepa), yacon (Smallanthus sonchifolius), Curcuma (Curcuma kwangsiensis), blue agave (Agave tequilana), and mugwort (Artemisia vulgaris) (Dong et al., 2015; Kumar et al., 2015; Corrêa-Ferreira et al., 2017; Gutiérrez Nava et al., 2017 and Paredes et al., 2019).

Echinacea and several other plants encompassed in herbal medicine (e.g., ginger, turmeric, and cannabis) have been shown to alleviate the effects of inflammation. It is interesting to note that these plants display enhanced antioxidant capacity, which could, in turn, be used to manage inflammation-related disorders induced by oxidative stress (Geronikaki and Gavalas, 2006).

Fructan-related antioxidant capacity (and ability to act as ROS scavengers) has also been demonstrated in humans in both in vitro and in vivo studies, suggesting that the consumption of foods rich in fructans could exert beneficial immunomodulatory properties by acting as antioxidants (Peshev et al., 2013; Shang et al., 2018 and Petkova et al., 2019). The ability of ITFs to bind to TLR2 suggests a potential role in anti-inflammatory pathways through the activation of regulatory T-cells (Tregs) (Zhang et al., 2017).

In line with this reasoning, inulin was shown to create an immunosuppressive environment in human peripheral blood mononuclear cells (PBMC) by promoting the expression of forkhead box P3 (FOXP3; a Treg biomarker) and the secretion of the anti-inflammatory cytokine IL-10 (Amarante et al., 2018). TLR2 signaling is also known to decrease intestinal permeability, a condition directly linked to inflammatory intestinal diseases such as celiac disease, inflammatory bowel disease (IBD), and irritable bowel syndrome (IBS) (Cario et al., 2007 and Suzuki, 2013).

It is well-known that ITFs indirectly influence AMP-activated protein kinase (AMPK) signaling through modulation of the microbiota, for instance, by stimulating the growth of Lactobacilli and Bifidobacteria, producing short-chain fatty acids (SCFAs) that activate AMPK (Peng et al., 2009). Metformin, a popular antidiabetic drug, is known to activate AMPK and to inhibit NF-B activation (Kim et al., 2011). Surprisingly, ITFs and metformin have very similar physical outcomes (Xue et al., 2019). PPAR, modulated by ITFs, is also known to influence AMPK signaling (Lee and Kim, 2010). These properties of ITFs make them good candidates for the treatment of current inflammatory diseases such as diabetes, obesity and IBD (Tak and Firestein, 2001 and Peng et al., 2019). The immunomodulatory and anti-inflammatory properties of Echinacea preparations are well-known and have been ascribed to the myriad of compounds that display antioxidant activity (Manayi et al., 2015). Both Echinacea angustifolia and Echinacea preparations were also reported to reduce inflammatory conditions caused by insulin resistance and induced by pathogens, respectively (Sharma et al., 2009; 2010; Gargari et al., 2013; Mao et al., 2018 and Chambers et al., 2019).

Echinacea preparations were reported to stimulate increases in both the number of white and red blood cells (Modaresi, 2013). In line with the possible anticancer activities of Echinacea preparations (Miller, 2012), it has been demonstrated that Echinacea extracts are potent activators of NK cell cytotoxicity. Echinacea extracts increase the frequency of NK cell target conjugates and speed up their lytic activities (Gan et al., 2003).

Additionally, the modulation of DC activity, important for Treg induction, has been reported (Benson et al., 2010).

Further research is necessary to decipher whether, and to what extent, ITFs contribute to the observed immunomodulatory effects of Echinacea preparations. The connection between the Echinacea polysaccharides and their immunomodulating properties has been suggested multiple times (Melchart et al., 2002).

The occurrence of ITFs in Echinacea (Wack and Blaschek, 2006) prompted us to investigate whether fructans were present in an array of commercial Echinacea preparations. A range of low and high DP ITFs was found (Dobrange et al., 2019).

More likely, ITFs present in Echinacea preparations stimulate the activity of immune cells directly by activating signaling pathways in vivo, as described (Hershberg et al., 2000 and Cario et al., 2002 and Forchielli, and Walker, 2006). Furthermore, it is important to note that the number of ITFs required for prebiotic effects (8 to 12 g a day) is much higher than the recommended daily intake of a commercially available Echinacea

preparation (Cummings et al., 2001; Lewis et al., 2005 and Welters et al., 2002).

The EP was found to show good immunoregulatory, anti-inflammatory and antioxidant capacity (Lee et al., 2009; Zhai et al., 2007) with neither the symptoms of hypersensitivity nor the side effects during the clinical trial stages (Saunders et al., 2007). The important components in the plant were found to be caffeic acid derivatives, alkamides, flavonoids, essential oils and polyacetylenes (Thygesen et al., 2007). Among them, caffeic acid derivatives and alkamides were proved to have immunoregulation effects (Matthias et al., 2008).

Echinacea purpurea was appeared to activate the non-specific cellular and humoral immunity and the complement system. The species was found to stimulate the immune system by means of increasing the production and activation of leukocytes, lymphocytes, monocytes and cytokines (Linda et al., 2002). Echinacea, which was commonly used for the treatment of common cold, coughs, bronchitis, influenza and inflammation of mouth and pharynx, is found to rank in second position in the highest retail sales for over-the-counter herbal products (Blumenthal, 2002 and Barrett, 2003). It is found to be the most frequently used herbal remedies in case of the treatment for adults and children and hence consumed by approximately over 10 to 20% of the herbal users (Tsen et al., 2000; Tsui et al., 2001; Planta et al., 2000; O'Dea, 2003 and Cala et al., 2003).

For example, the polysaccharide fraction was found to stimulate the macrophage activity and several other functions that were related to the cytokine production34-36and certain groups of the phenolic compounds and alkamides was found to demonstrate the antiviral and antifungal properties (Binns et al., 2002a and Merali et al., 2003). Echinacea purpurea contains alkamides, caffeic acid esters (cichoric acid), polysaccarides and polyacetylenes (Dalby-Brown et al., 2005 and Chen et al., 2005).

Cichoric acid was found to be the main phenolic compound (2.27%) and the highest contents of caffeic acid derivatives were also found in E. purpurea roots (Pellati et al., 2005). Cichoric acid and verbascoside was found to be predominated in the extracts of E. purpurea roots (Sloley et al., 2001).

Extracts of the roots and leaves was found to have the antioxidant properties in a free radical scavenging assay and in a lipid peroxidation assay (Pellati et al.,.2004). The ethanolic extract of Echinacea purpurea roots contains nearly 15 alkamides (Guiotto et al., 2008 and Spelman et al., 2009).

Human lymphocytes that were activated with different lectins (Con A, PHA and PWM) for the study of the In vitro immune cell proliferation as a response to aqueous extract of E. purpurea root showed the increase in percentage of lymphoproliferation was greater when E. purpurea root extract was used in addition to individual lectins (Fernando et al., 2007).

Administering aged rats with Echinacea ethanolic and water extracts showed a significant improvement in increased and decreased levels of the above-mentioned markers and returned the abnormal markers back to the normal levels (Nematalla et al., 2011).

The plant with high potential to conduct assay on its antioxidant activity, with antioxidant activity assay further broken down to items of preventing oxidation and scavenging free radicals (Gholamreza et al., 2011).

The proteomic analysis showed that the expressions of metabolic, cytoskeleton or NF_B signaling-related proteins were actually regulated by the treatment with compound mixture. Thus, the mixture was found to modulate the DC mobility and related cellular physiology in the mouse immune system (Shu-Yi et al., 2010).

Echinacea purpurea root was found to reduce the oral clearance of substrates of CYP1A2 but not the oral clearance of substrates of CYP2C9 and CYP2D6 (Christopher Gorski et al., 2004).

The ethanol and ethyl acetate-soluble fractions from the leaves and stem was found to contain a potent antiviral photosensitizer, which was absent in the flower extract (Selvarani Vimalanathan et al., 2005).

In another study Dietary Echinacea did not enhance the growth, exhibit antiviral effects to porcine reproductive and respiratory syndrome virus (PRRSV), or show any evidence of immune enhancing properties (Hermann et al., 2003). Echinacea purpurea was found to decrease the cadmium-induced mitotic activity of liver cells, and increased the apoptotic activity of these cells (Sara Soudi et al., 2007).

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