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Medication of Human Diseases by Nutrients of Elderberry (Sambucus nigra)

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Abstract

Elderberry is thought to inhibit both bacteria and viruses, which could make it suitable for use when there are often secondary infections, such as when influenza is followed by bacterial pneumonia. It may also be effective for nosocomial infections (hospital "super-bugs"). Sambucus nigra is natively spread in European countries and is used as colorant or flavor in Juices and wines. Among different parts of Sambucus nigra, its flowers and berries are considered as medicinal parts, while elder flowers have been approved by German commission E for colds, while berries, leaves and barks are lack of approval by WHO, ESCOP, and German Commission. The potentially toxic cyanogenic glycoside "sambunigrin" is present in barks, leaves, seeds and unripe fruits. The amount of cyanogenic glycoside depends on growing conditions and the flowers have lower content of cyanogenic glycoside in comparison with other parts of plant. Elder flowers are rich of N-phenylpropenoyl-l-amino acid amides, which strongly stimulated the mitochondrial activity and cell proliferation of human keratinocytes and liver cells and deduced the adhesion of Helicobacter pylorito the human stomach without any necrotic toxicity effects. Elder-berries are containing the low amount of essential oil (0.01). Phenylacetaldehyde (32.3%), benzaldehyde (7.9%), ethyl linoleate (5.4%), 4-vinyl guaiacol (4.9%), linalool (4.5%), and phenyl ethyl alcohol (4.1%) were the main components of elderberry essential oil. Fruit ripening process can influence on the content of anthocyanin, soluble solid and titratable acid. The aroma characteristic of elderberries is used in different formulations. Aliphatic esters ((E)-β-damascenone, 2-phenyl ethanol, phenylacetaldehyde, dihy-droedulan, ethyl-9-decenoate, and nonanal) are responsible for fruity sweet characteristic aroma of elderberries. The presence of cyanidin-3-glucoside and cyanidin-3-sambubioside is responsible for dark color of European elder berries. Chemical composition of elder berries and flowers exhibited the presence of a number of health promoting compounds, which makes it as favorite supplements.

Elder flowers are generally regarded as safe. Black elder flowers are used for treatment of scarlatina and fever. Dried elder lowers have strong odor with sweet taste to slightly bitter and are used as diaphoretic agent in pharmaco-poeias and international systems for reducing the fever and chills. Elder flowers are used for treatment of conjunctivitis, constipation, diabetes, diarrhea, dry skin, headaches and rheumatism in folk medicine.Elderberry extract inhibited the Human infuenza A (H1N1) with IC50of 252 ± 34 µg/mL, the propagation of human pathogenic infuenza viruses, and immunod efficiency virus (FIV). In other study, elderberries had antiviral activity against infuenza A, infuenza B, HIV, Herpes sim-plex-1 viruses, and pathogenic chicken coronavirus. Elder flowers and leaves methanol extract had antiviral activity against dengue virus serotype-2 (400 µg/mL). Elderberry extract increased the influenza viral antibody in comparison with placebo group. Incubation of blood derived monocytes with elderberry extract significantly increased the production of IL-1β, TNF-α, IL-6, IL-8, and TNF-α. A significant increase in inflammatory cytokine of IFN-γ was observed after administration of elder in insulin deficiency diabetic and normal patients. Fever higher than 101 °F, headache, general aches; and pains are the characteristic symptoms of fu. Cough, chest congestion, sore throat, stuffy nose, fatigue, weakness, and extreme exhaustion are prevalent among patients. The antioxidant effects of elder extracts are responsible for their efficacy in reducing the pain, and fever.

The polyphenols), and anthocyanins in elders are strongly responsible for the anti-oxidant activities. A combination of echinacea herb and root extract supplemented with elderberry (Sambucus nigra L.) can be as effective as the conventional antiviral medicine oseltamivir for the early treatment of influenza. Elderberries have shown antibacterial and antiviral activities.
Key words: cough; chest congestion; sore throat; stuffy nose; fatigue; weakness

Introduction:

Hippocrates in the fifth century BC is said to have called elderberry his medicine chest, implying that he used it for a great many conditions as did, later, Blochwich (Wells, 2010). In the mid-17th century the German Martin Blochwich wrote a whole book about elderberry's medicinal properties, The Anatomy of the Elder (Blochwich, 2010).
Kšonžeková (2015) suggests it is good for new-borns because of its high anthocyanin content. Elderberry is used as a strong food preservative (Mohammadsadeghi, 2013).
Zakay-Rones et al. (2004) conducted another RCT on 60 patients and found that influenza symptoms were relived on average four days earlier, and rescue medication was significantly less in those receiving elderberry extract compared with placebo. Kong et al. (2009) also conducted a pilot RCT with 64 participants on influenza and found similar results.
Tiralongo et al. (2016) conducted a randomized trial of 312 airplane passengers, 29 of whom went on to develop colds (coronavirus) and found that elderberry supplementation reduces cold duration and symptoms in air-travellers.
Levine et al. (2014) conducted a randomized trial of 54 patients and found that a herbal product which included S. nigra is a safe and effective anti-bacterial and anti-inflammatory mouth rinse, which significantly reduces the progression of gingivitis, dental plaque formation and spontaneous bleeding.
For viruses such as influenza, neuraminidase inhibitors such as Tamiflu and Relenza at first seemed very promising, but are proving to be a disappointment (Jefferson et al., 2014). Elderberry has also been shown to be a neuraminidase inhibitor but one which may have more promise and to which resistance is unlikely to ever occur due to the shape of the bioactive molecule (Swaminathan, 2013).
Elderberry is thought to inhibit both bacteria and viruses, which could make it suitable for use when there are often secondary infections, such as when influenza is followed by bacterial pneumonia. It may also be effective for nosocomial infections (hospital "super-bugs") (Hearst et al., 2010).
Preliminary research suggests elderberry may aid the efficacy of other anti-retrovirals (Manganelli, 2005).
Some research suggests that elderberry always increases the immune effects whereas others think it may sometimes damp en them down (Voldvik, 2015).
Research in Norway, where it is commonly used, show no adverse consequences when it is used in pregnancy (Rødahl, 2011).
Amongst all fruits, elderberries are the most concentrated source of anthocyanins (Mateus, 2004).
In addition to polyphenols, lectins are found in many plant extracts including S. nigra and often show anti-viral activity by binding to viral proteins or host receptors, preventing their interaction (Chen et al., 2014).
In the recent journal Feed Additives 2020, Yasmin et al. discuss the use of elderberry as a food additive, one of a number of herbal extracts, with use as anti-virals for farm animals to reduce the amount of antibiotics used in the food chain.
Sambucus nigrais natively spread in European countries and is used as colorant or flavor in Juices and wines (Atkinson and Atkinson 2002). Among different parts of Sambucus nigra, its flowers and berries are considered as medicinal parts, while elder flowers have been approved by German commission E for colds, while berries, leaves and barks are lack of approval by WHO, ESCOP, and German Commission E (Ulbricht et al. 2014).
The potentially toxic cyanogenic glycoside "sambunigrin" is present in barks, leaves, seeds and unripe fruits. The amount of cyanogenic glycoside depends on growing conditions and the flowers have lower content of cyanogenic glycoside in comparison with other parts of plant (Senica et al. 2017).
Cyanogenic glycosides are hydrolyzed in the gastrointestinal tract to hydrogen cyanide (Vlachojannis et al. 2010).
Elder flowers are rich of N-phenylpropenoyl-l-amino acid amides (Hensel et al. 2007), which strongly stimulated the mitochondrial activity and cell proliferation of human keratinocytes and liver cells and deduced the adhesion of Helicobacter pylorito the human stomach without any necrotic toxicity effects (Hensel et al. 2007). Elder-berries are containing the low amount of essential oil (0.01) (Knudsen and Kaack 2015). Phenylacetaldehyde (32.3%), benzaldehyde (7.9%), ethyl linoleate (5.4%), 4-vinyl guaiacol (4.9%), linalool (4.5%), and phenyl ethyl alcohol (4.1%) were the main components of elderberry essential oil (Duymus Agalar et al. 2014). Fruit ripening process can influence on the content of anthocyanin, soluble solid and titratable acid (Rodrigues et al. 2018). The aroma characteristic of elderberries is used in different formulations. Aliphatic esters ((E)-β-damascenone, 2-phenyl ethanol, phenylacetaldehyde, dihy-droedulan, ethyl-9-decenoate, and nonanal) are responsible for fruity sweet characteristic aroma of elderberries (Kaack 2008). The presence of cyanidin-3-glucoside and cyanidin-3-sambubioside is responsible for dark color of European elder berries (Mateus et al. 2004). Chemical composition of elder berries and flowers exhibited the presence of a number of health promoting compounds (Vlachojannis et al. 2010), which makes it as favorite supplements.
Black elder flowers are used for treatment of scarlatina and fever (Kaur et al. 2014).Dried elder lowers have strong odor with

sweet taste to slightly bitter and are used as diaphoretic agent in pharmaco-poeias and international systems for reducing the fever and chills (Organization 2004). Elder flowers are used for treat-ment of conjunctivitis, constipation, diabetes, diarrhea, dry skin, headaches and rheumatism in folk medicine (Organization 2004).

The use of elder flowers for cold is approved by Ger-man Commission E (Blumenthal et al. 2000), while berries, leaves and barks are lack of approval by WHO, ESCOP, Ger-man Commission E. Elder flowers are GRAS (Ulbricht et al. 2014) and have been approved for treatment of common cold, fever.

Elderberry extract inhibited the Human infuenza A (H1N1) with IC50of 252 ± 34 μg/mL (Roschek et al. 2009), the propagation of human pathogenic infuenza viruses in cats (Krawitz et al. 2011), and immunod efficiency virus (FIV) (Uncini Manga-nelli et al. 2005). In other study, elderberries had antiviral activity against infuenza A, infuenza B, HIV, Herpes sim-plex-1 viruses, and pathogenic chicken coronavirus (Barak et al. 2001; Chen et al. 2014). Elder flowers and leaves methanol extract had antiviral activity against dengue virus serotype-2 (400 μg/mL) (Castillo-Mal-donado et al. 2017).

The IC50 for 5, 7, 30, 40-tetra-O-methylquercetin and dihydromyricetin were 0.36 and 8.7 μM against H1N1infections and were comparable with oseltamivir (Tamifu; 0.32 μM) and amantadine (27 μM) (Roschek et al. 2009).

During the spread of Influenza viral infections, the secondary infections by bacteria can lead to severe pneumonia. Elderberry extracts (standard to minimum concentration of 3.2% anthocyanin) decreased the populations of Streptococ-cus pyogenes(groups C, G) and Branhamella catarrhal is more than 70% (Krawitz et al. 2011).

There is four properly randomized clinical trials and statistically good scientifc evidence of elder efficacy against influenza and influenza like diseases (Ulbricht et al. 2014).

The VAS score for cough increased from 2.19 ± 1.47 to 3.69 ± 1.25 in placebo group. No adverse effects related to elderberry were reported during the study (Kong 2009).

The elderberry syrup is effective against infuenza A virus, more than influenza B type, without any adverse effects (Zakay-Rones et al. 2004).

Elderberry capsules had no significant effect on mental health of participants. No adverse effects were reported for standard elderberry extract during the study (Tiralongo et al. 2016). No adverse or sedative effects were reported for elderberry extract during the study, and one complaint for taste of elderberry syrup was reported (Roschek et al. 2009).

The denaturalization of hemagglutinin spikes of influenza by elder extracts is associated with viral inactivation to pierce and enter the cells and replicate (Janeway et al. 2001).

The immune-modulatory effects of elderberry extracts are associated with cytokines production (cyanidin-3-glucoside and cyanidin-3-sambubioside), phagocytes activation and its immigration to inflamed tissues (Janeway et al. 2001).

Elderberry extract increased the influenza viral antibody in comparison with placebo group. Incubation of blood derived monocytes with elderberry extract significantly increased the production of IL-1β, TNF-α, IL-6, IL-8, and TNF-α (Barak et al. 2001).

A significant increase in inflammatory cytokine of IFN-γ was observed after administration of elder in insulin deficiency diabetic and normal rats (Badescu et al. 2015).

Furthermore, it is reported that the strong immunemodulatory effects of elder are related to pectic polysaccharides (Ho 2017).

Fever higher than 101 °F, headache, general aches; and pains are the characteristic symptoms of fu. Cough, chest congestion, sore throat, stuffy nose, fatigue, weakness, and extreme exhaustion are prevalent among patients (Fendrick et al. 2003). The antioxidant effects of elder extracts are responsible for their efficacy in reducing the pain, and fever. The polyphenols (Stoilova et al. 2007; Viapiana and Wesolowski 2017), and anthocyanins in elders (da Silva et al. 2019) are strongly responsible for the anti-oxidant activities. Elder berries are used as expectorant and mild anti-inflammatory agents in treatment of upper respiratory ailments (Blumenthal et al. 2000). Elder may reduce the swelling of mucus membranes and nasal congestion (Ulbricht et al. 2014).

Elder flowers are generally regarded as safe (Ulbricht et al. 2014). No contraindication, warning, or interactions with other medication have been reported (Monographs 2013). Due to limited information on elder flowers, it should not be administered during the pregnancy, and lactation without medical supervision (Organization 2004).

Young children under 2 years old or elder have high mortality rates (Moghadami 2017). Elder berries and elder flowers were well tolerated and safe. The use of elder flowers for treatment of colds, and fu has been confirmed by German commission E (Blumenthal et al. 2000), while the clinical trials confirmed the efficacy of elder berries in treatment of clinical symptoms of fu and common cold (Zakay-Rones et al., 2004; Tiralongo et al. 2016; Kong 2009). Elder berries extract was found to be more effective against influenza A virus than infuenza B type (Zakay-Rones et al. 2004).

Black elderberries for example, are well known to be supportive agents against common cold and flu like symptoms and have been used for centuries (Roxas et al., 2007). Interestingly, a non-travel related clinical trial just revealed that a combination of echinacea herb and root extract supplemented with elderberry (Sambucus nigra L.) can be as effective as the conventional antiviral medicine oseltamivir for the early treatment of influenza (Raus et al., 2015). Elderberries have shown antibacterial (Krawitz et al., 2011) and antiviral activities in in vitro (Roschek et al., 2009). Two clinical trials using a liquid elderberry extract (Sambucol®, Israel) showed a reduction in symptoms and duration of influenza infection (Vlachojannis et al., 2010). A pilot trial with elderberry extract lozenges (Herbal Science, Singapore) also confirmed a beneficial effect on severity and duration of cold and flu like symptoms (Kong, 2009).

In recent times, elderberry has gained popularity in research and the wider community due to its reported antioxidant (Netzel et al., 2005), antidiabetic (Gray et al., 2000), anti-inflammatory and immune-modulating (Badescu et al., 2015), as well as antidepressant (Mahmoudi et al., 2014) properties. The berries are dark violet-black drupes which grow in clusters and owe

their colour to the anthocyanins; a group of phenolic compounds which, amongst flavonoids, are abundant in elderberries and considered the active constituents of the fruits (Mikulic-Petkovsek et al., 2015).

For example, a recent randomised clinical trial showed that supplementation with 1 g of vitamin C daily reduces cold duration by approximately three days (Johnston et al., 2014). Also, echinacea has been reported to reduce severity and cold duration (Jawad et al., 2012 and Karsch-Volk et al., 2015), however more trials report a preventative effect on cold occurrences and re-occurrences rather than a conclusive treatment effect for echinacea (Karsch-Volk et al., 2015 and Schapowal et al., 2015).

Antioxidant polyphenols are present in elderberries (Mikulic-Petkovsek et al., 2015), bioavailable (De Ferrars et al., 2014) and can increase serum antioxidant capacity (Vlachojannis et al., 2010). In a recent randomised clinical trial it was shown that vitamin C supplementation improved physical activity levels in a population with adequate-to-low vitamin C status. The authors related this effect to vitamin C's antioxidant properties since oxidative stress is related to fatigue (Johnston et al., 2014). Dosages recommended by popular elderberry products range from650mg to 1500mg. In the three beneficial influenza trials patients took 60 mL of elderberry syrup (38% extract equivalent to approx. 22.8 mg extract standardised to flavonoids) daily for 5–6 days (Vlachojannis et al., 2010) or lozenges with an equivalent of 700 mg elderberry extract daily for two days with no indication on the anthocyanin content (Roschek et al., 2009). The minimum of anthocyanin doses for the treatment of metabolic syndrome disorders was recently estimated as 110 mg per day and as 3.5 g per day for influenza (Vlachojannis et al., 215).

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