



Please note: The following presentation summaries from the **First International Symposium on ELDERBERRY** held June 9-14, 2013 and hosted at Stoney Creek Inn, Columbia, MO by the University of Missouri. The first half of each entry quotes directly from the printed presentation abstracts provided by the authors in bold font. My personal evaluation of potential present and future relevance to elderberry growers and consumers of elder fruit and flower products follow each quotation in regular font.

Of course, in both cases a large amount of information has been left out due to my editorial objectives of reporting concise statements of key learnings. My selection of what was important represents my own experiential bias without intentional critique of anyone's research. Also, I could not physically attend all presentations; therefore, some presentations will have more commentary due my including information derived from the questions and answers that occurred after each presentation. The full presentations will be publish in a special edition of *Acta Horticulturae*, hopefully by the middle of 2014.

Pharmacological and Clinical Effects of Elderberry Fruit

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In traditional German medicine, the dried ripe or fresh berries of *Sambucus nigra* were used for the treatment of constipation, to increase diuresis, as a diaphoretic in upper respiratory tract infections, for the alleviation of low back and/or neuropathic pain, headache and toothache. In the meantime, there are data on the antibacterial, anti-inflammatory, analgesic and anti-proliferative effects available, but these need further support...The active principle of elderberry, a mixture of procyanidins, anthocyanins and phenolic acids, has a potent antioxidative effect that may be useful for the treatment of the metabolic syndrome (hyperlipidemia, diabetes, hypertonus) associated with obesity...

This paper presents a good list of the traditional uses of elderberry in addressing health issues, as well as some of elderberry's indicated treatment potential from modern research. The author goes on to indicate the need for confirmation by "more rigorous" studies.

Also mentioned were the similar, slightly more potent antioxidant benefits of aronia, which has been researched more. Aronia berries ripen at the same time unlike elderberry, though aronia fruit is significantly more bitter than elderberry, making it harder to consume directly.

The presenter noted that elderberry has three times the antioxidant levels of currants. Furthermore, elderberry seems to act against heliobacter bacteria, and its rich amounts of Vitamin C protect elderberry's active health principle – make it more effective. This fact recommends elderberry juice as a good mixer with other juices or teas rich in Vitamin C.

Usefulness of Elderberry Fruit as Functional Food

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Pharmacological and clinical studies indicate that products from elderberry fruit are useful for the treatment of diseases and the maintenance of health. This, however, requires an adequate

daily dose of the active principle of elderberry fruit. Dose-finding studies have not yet been carried out for the different indications. Most promising are elderberry products for viral infections and diseases associated with oxidative stress including arteriosclerosis, diabetes, hyperlipidemia, cancer, etc. Temperature, oxygen, and light are destroying active principle in elderberry juice. This has to be taken into consideration when preparing elderberry functional food. Addition of vitamin C may help to protect from oxidative degradation. The starting material has to be free of leaves and stems because these contain toxic lectins causing intoxications (acute gastrointestinal and neurologic symptoms). Unlike intoxications with solanin, elderberry intoxications had a benign outcome so far...

The presenter's comments included references to 15th century Swiss monks preparation of elderberry by added oil, honey, vinegar and ethanol, as ethanol concentrates the elderberry's active principle. The presenter admitted that science does not know all of elderberry's active principles and that their accurate measurement is difficult. Current methods tend to over or under estimate antioxidants, for example.

In clinical application of the presenter's summary of indications, in the case of elderberry fruit products she leans toward an error of overdosing vs. underdosing, since the potential negative consequences are minimal. In other words, elderberry juice tends to purge the digestive system, and people typically stop ingesting it when that happens, so that the potential detrimental consequences of consuming too much elderberry is unlikely. In any case, all known overdoses, or intoxications, have been benign, long-term neutral/harmless.

Elderberry Juice Prevents Prostate Cancer *In Vitro* and in an *In Vivo* Mouse Model

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Anti-cancer botanical compounds are proposed to suppress tumor growth by disrupting signaling pathways which are involved with cancer cell growth. Here we investigate the potential for elderberry juice (*Sambucus nigra* L. subsp. *canadensis* (L) Bolli) to inhibit Gli/hedgehog (Gli/Hh) signaling, a pathway previously found to be important for the growth of many cancers, including prostate cancer...

In vitro, measuring the Gli/Hh pathway activity, we observe comparable dose-dependent inhibition of the Gli-reporter activity in Shh light II cells treated with dilutions of either elderberry juice or elderberry pulp extract. Importantly, 100 to 250 fold dilutions of elderberry juice or pulp/pomace extracts are effective at suppressing Gli/Hh signaling by 50%. In vivo, diets containing freeze-dried elderberry juice solids at 3 concentrations (low=0.09%, middle=0.45%, high=2%) were fed to TRAMP mice to determine if elderberry could delay or inhibit prostate cancer progression. [The Middle elderberry diet in mice is the equivalent dose of a 60 kg (132 lb.) human drinking 2 tablespoons of elderberry juice per day.] In comparison with the control group...these 3 concentrations of elderberry in the AIN-93G diet exhibited potent dose dependent inhibition of cancer formation with the Middle and High dose elderberry diets being statistically significant at the $p = 0.03$ and $p = 0.006$ level, respectively. These results support our hypothesis that elderberry juice is capable of preventing prostate cancer. Additional research is warranted on elderberry's mechanism(s) of action in prostate and other cancers that are potentially dependent upon Gli/Hh signaling.

The elderberry juice used in these research experiments was provided by River Hills Harvest Elderberry Producers, LLC. This research supports the practice of consuming small amounts (1-2 tablespoons/day) of elderberry juice on a daily basis as a preventative care immune boost. The indications are positive but not conclusive for human biology. Gli/Hh pathway inhibition is not related to elderberry's dark colored antioxidants.

Bioactive Compounds of Elder (*Sambucus nigra* L.) with Focus on their Potential Anti-diabetic Effects

Lars Porskjaer Christensen, Katherine Bisgaard Christensen, and Xavier Christian Frette. University of Southern Denmark, Denmark.

Preparations of elder (*Sambucus nigra*) are used in traditional medicine as diuretics and to treat colds, influenza, inflammation and diabetes. Elderberries and elderflowers are rich in polyphenols such as phenolic acids, flavonol glycerides, and anthocyanins. Polyphenols are known for their antioxidant activity and are believed to prevent oxidative stress, a condition that may lead to serious diseases such as cancer, cardiovascular diseases, inflammation and type-2 diabetes (T2D). Hence, polyphenols have been pointed out as beneficial agents in both elderflowers and elderberries. Epidemiological investigations tend to confirm the protective effects of polyphenols against cardiovascular diseases and T2D, but the mechanisms by which they exert their protective effects are far from understood...

Extracts of elderflowers have been found to exert insulin-like and insulin-releasing actions *in vitro* and to activate PPAR γ as well as to stimulate insulin-dependent glucose uptake. This indicates that elderflowers may be used in the prevention and/or treatment of insulin resistance...

This research confirmed indirect effects of elderflowers in treatment of insulin and glucose uptake deficiencies. The researchers commented that elderberry polyphenols are bioavailable in the liver, where they incite the development of cytokines. Currently, commercial elderflower preparations sold in North America use European components. Their use is very limited in the USA. For growers of cultivated elder, this research identifies a strong potential market for elderflowers in North America as has been established in Europe due to their effectively potent set of nutrient compounds – especially in the treatment of insulin/glucose uptake health deficiencies in general and Type-2 Diabetes in particular.

Lectins of *Sambucus nigra* as Biologically Active and DNA-protective Substances

Iryna Karpova, Valentyna Lylo, Larysa Macewicz, Kateryna Kotsarenko, Tetiana Ruban, Larysa Palchykovska, and Lyubov Lukash. Ukrainian National Academy of Science, Ukraine.

...The aim of our work is to present a review of own results and literature data concerning DNA-protective potential of *Sambucus nigra* biologically active compounds named lectins, a very large group of universally occurring proteins that recognize and specifically bind to carbohydrates / glycoconjugates...lectins participate in host defense in plants against stress-related conditions, the attack of phytopathogens and phytophagous insects, as well as modulation of immune response, mitogenic stimulation or induction of apoptosis in animals. Antiviral, immunomodulating, antioxidant and insulin-stimulating properties of *S. nigra* fruit and flower extracts have been described in scientific literature. Also, the elderberry lectins were found in roots, leaves, bark, seed and fruits, with SNA-IV being the predominant protein in the juice...

***Sambucus nigra* lectins demonstrated the protective and antimutagenic effects against heavy metals (nickel ions) in the soil bacteria *Bacillus subtilis*. Also, it was shown that lectins under study can modulate in a concentration-dependent manner the frequency of mutations and genotoxic activity of alkylating agents in eukaryotic cell cultures...The results obtained give reason to conclude that the protective functions of lectins both in pro- and eukaryotes involve complex mechanisms including components of DNA repair system.**

Ukrainian researchers have investigated various ways to treat the effects of the Chernobyl radiation disaster. Here indications for use in treating the potential genetic damage from heavy metals present in one's body were derived from lab tests with soil bacteria. Some natural healing practices include the use of elderberry fruit and flower extracts in treating an excess of heavy metals in humans, so consumers should check with their medical professional for further guidance if concerned about symptoms possibly related to an excess of heavy metals.

Lectins of *Sambucus nigra* in Regulation of Cellular DNA-protective Mechanisms

Valentyna Lylo, Iryna Karpova, Kateryna Kotsarenko, Larysa Macewicz, Tetiana Ruban, and Lyubov Lukash. Ukrainian National Academy of Science, Ukraine.

Genomes of living organisms are constantly affected by exogenous and endogenous factors, which lead to generating cytotoxic, carcinogenic, and/or mutagenic DNA lesions. However cells possess a number of protective mechanisms directed against DNA damage. The repair enzyme O6-methylguanine-DNA methyltransferase (MGMT) plays a key role in the repair of primary damages of DNA caused by alkylating compounds, which are widely used in industry and medicine. In humans MGMT protects the integrity of the genome, but also contributes to the resistance of tumors to DNA-alkylating chemotherapeutic agents. Therefore, modulation of MGMT expression is a possible strategy to improve the efficiency of cancer therapy and defend normal cells from toxicity of alkylating drugs...

Protective and antimutagenic activity of *S. nigra* lectins against some DNA-damaging factors with different mechanism of action (nickel ions and alkylating agents) have been studied in mammalian cells *in vitro*. Lectins are known to exhibit no enzymatic activity, but can up- and down-regulate the activity of different enzymes and other regulatory proteins such as cytokines...These lectins were shown to be able to affect in concentration-dependent manner the genotoxic activity of damaging agents and to modulate MGMT gene expression at the protein level. The obtained results give us the reason to assume that one of the protective mechanisms of the lectin acting is stimulating DNA repair in a cell, including direct reversal repair with the help of the MGMT enzyme.

In this research, elderberry lectins indirectly enhanced the repair of DNA damage in the lab. The elderberry lectins beneficially affected proteins and enzymes including messaging cytokines. These experiments evidenced “**direct reversal repair**” of damaged DNA in cells. Elder bark lectins may be more effective. Also, this research suggests regular ingestion of elderberry particularly before, and in connection with, chemotherapy sessions in order to protect healthy cells.

Health from the Root to the Flower

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Elderberry (*Sambucus nigra* L.) is one of the oldest medicinal plants. All parts could be usefully applied in phytotherapy. It is usually used as a dried drug, and its healing power is enhanced in a mixture herbs. Leaves are collected before flowering. Flowers with wonderful fragrance are collected from May to June. They are the most famous parts of this species for preparing tea. Young sprouts provide bark for medicinal uses. A toxic substance, sambunigrine, occurs in immature fruits of elderberry, but it is possible to deactivate it by higher temperature. Attention has to be paid in use of extracts from bark and roots of elder. Study of this species is necessary because not all components and their therapeutical effects are known in this modern age.

Toxic proto-cyanides are found in unripe berries of black elder, as noted, as well as in the twigs, leaves, bark and roots. Truly ripe berries are safe, and each person’s sensitivity to sambunigrine varies, as is common with many plants. Thus, the preparation of elderberry products must eliminate stems and unripe berries.

River Hills Harvest Elderberry Producers developed a mechanical de-stemmer operated in water to separate the stems from berries and float off unripe berries, chaff, bits of leaves, stems, etc. Moderate heating is required by the FDA, thus River Hills Harvest brand products are heated to 180 degrees F and kept there for about four minutes. The combination of these two steps provides a good example of how to safely process elderberry fruit products. Elder flowers are either dried or frozen before use as in food, teas or as flower-derived ingredient.

The Effect of Sambucol on the Immune System (Cytokines Production)

Vivian Barak and Madeleine Mumcuoglu. Israeli Cytokine Standardization Laboratory, Hadassah – Hebrew University Medical Center, Jerusalem, Israel.

Natural remedies, including *Sambucus nigra*, were shown *in vitro* and *in vivo* to have activating effects on the immune system and to possess antiviral properties, as published in former studies. Sambucol products...based on a standardized black elderberry (*Sambucus nigra* L.) extract, were studied in comparison to two other natural products (Protec and Chizukit N) containing Propolis and Echinacea. Those five herbal remedies, which are sold as food additives and believed to have immune enhancing properties, have been evaluated for their effects to stimulate production of cytokines – one of the main components of the immune system activation...Sambucol formulations demonstrated activation of the healthy immune system by increasing inflammatory and anti-inflammatory cytokines production, while the effect of Protec and Chizukit N is much less. Sambucol could therefore have immune-stimulatory properties when administered to patient suffering from influenza or immune depressed cancer / AIDS patients, in conjunction with chemotherapeutic or other treatments.

Sambucol is one of the oldest, and most researched, commercially produced line of European elderberry products. This *in vitro* study demonstrated elderberry's positive effects in stimulating immune response in human lymphocytes at all kinds, including innate and adaptive classes. It improves immune response pathways to T-helper cells, apparently balancing the body's response to infectious agents. The researchers mentioned unpublished findings suggesting elderberry demonstrated very positive aid in cancer treatment by enhancing/activating both immune-protectors and immune-stimulators in conjunction with chemotherapy. Propolis and Echinacea disappointed in most cases stimulating only one type of cytokine.

Clinical Studies on the Effects of Sambucol – a Review

Vivian Barak. Israeli Cytokine Standardization Laboratory, Hadassah – Hebrew University Medical Center, Jerusalem, Israel.

Sambucol, a standardized elderberry extract, was evaluated in several clinical studies:
[Summary omitted here.]

1) A placebo-controlled double blind study was carried out on a group of individuals living in an agricultural community (kibbutz) during an outbreak of an outbreak of influenza B/Panama in 1993. Fever, feeling of improvement, and complete cure were recorded during 6 days. Sera obtained in the acute and convalescence phases were tested for the presence of antibodies to influenza A, B, respiratory syncytial and adenoviruses. Convalescent phases serology showed higher mean hemagglutination inhibition (HI) titers to influenza B in the group treated with Sambucol, than in the control group. A significant improvement of symptoms, including fever, was seen in 93.3% of the cases in the Sambucol treated group within 2 days, where as in the control group 91.7% of the patients showed an improvement within 6 days ($p < 0.001$). A complete cure was achieved 2 to 3 days in nearly 90% of the Sambucol-treated group and within at least 6 days in the placebo group. Considering the efficacy of the extract *in vitro* on all strains of influenza virus tested, the clinical results, its low cost, and absences of side effects, this preparation could offer a possibility for safe treatment for influenza A and B.

2) The efficacy and safety of oral elderberry syrup for treating influenza A and B was tested. Sixty patients suffering from influenza-like symptoms for 48 h or less, were enrolled in this randomized double-blind, placebo-controlled study during the influenza season of 1999-2000 in Norway. Patients received 15 ml elderberry or placebo syrup four times per day for five days, and recorded their symptoms using a visual analogue scale. Symptoms were relieved on average four days earlier and use of rescue medication was significantly less in those receiving elderberry extract, compared with placebo. It was concluded that the Elderberry extract offered an efficient, safe and cost-effective treatment for influenza.

3) The effects of Sambucol treatment on flu like symptoms in chimpanzees were evaluated, and a reduction in those symptoms and the duration of illness was reduced in the treated primates.

Sambucol is one of the oldest, and most researched, commercially produced line of European elderberry products. In case #1, 27 kibbutz patients were used. In case #2, in Oslo, Norway 60 patients (age 18-54 years) suffered from influenza A or B. Patients experienced quick relief of aches, pains and coughs and slept better without the use of painkillers and nasal decongestants. In both cases #1 & #2, patients completely recovered in about 4 days with elderberry versus 8 days without. In case #3, the chimpanzees were housed in the Jerusalem zoo. Barga published this study in **Zoo News** some in 1999. The chimps were given 1 tablespoon of Sambucol per day for the purposes of disease prevention. Blood tests showed that interferon gamma was stimulated as well as the production of macrophages and lymphocytes. The elderberry-taking chimpanzees experienced 5-6 times fewer observable/measurable cold/flu symptoms than the control group.