

 **ElderCraft®**

European Black Elderberry Extract



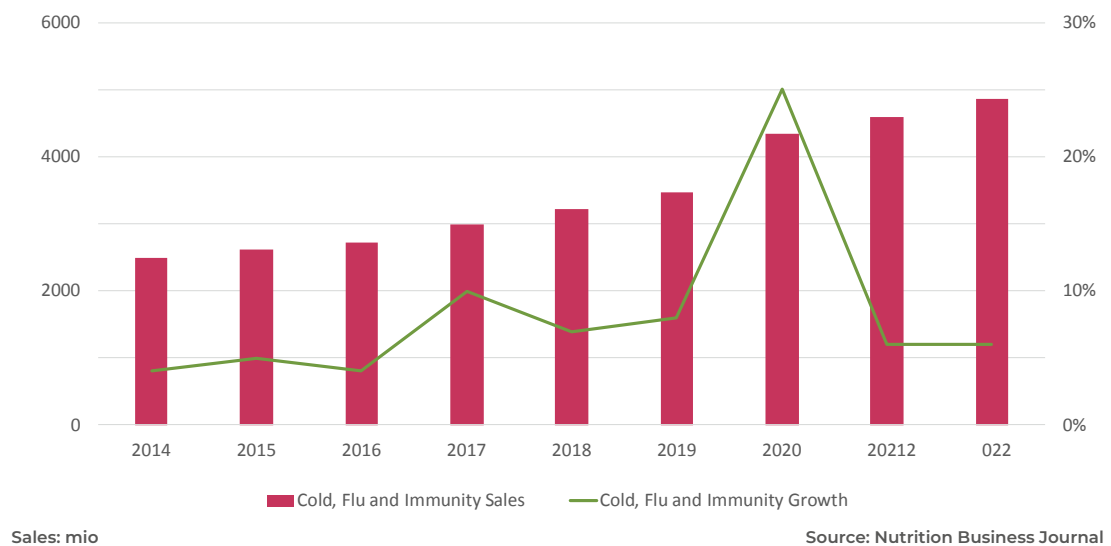
Health through  
Nature



**European Black Elderberry for immune support:** Combining the appeal of traditional medicine with proven clinical evidence

# 01 Introduction

Consumers cited immune health as a top reason for taking supplements well before the emergence of COVID-19. Yet, while sources such as the 2019 Council for Responsible Nutrition consumer survey show immune health was already front of mind for supplement buyers, the coronavirus pandemic has further intensified interest in the category. US sales growth, which has averaged high single digits in recent years, is predicted to jump to 25% in 2020 as consumers focus on improving immune health to stave off the coronavirus (Fig. 1).



**Fig. 1:** Immunity supplement sales and growth, USA

The herbs and botanicals market is poised to benefit from the trend as consumers seek out products with well-established links to immune health. Nutrition Business Journal predicts the market will grow at a near-double-digit CAGR in the coming years to be worth \$12.4 billion by 2022.

Black elderberry supplements are a big beneficiary of rising consumer demand for immune health products. Sales increased 15.5% in 2018 (ABC market report) and online analyses suggest they will jump again in 2020.



As COVID-19 spread in the spring, real-time analysis showed elderberry featured in 20% of the top products in Amazon's Vitamin and Dietary Supplements category. Google Trends data provides further evidence, revealing spikes in searches for elderberry that surpassed those for Tamiflu<sup>®</sup>, a prescription-only antiviral drug.

Consumer interest in elderberries reflects their position at the intersection of traditional medicine and modern science. In recent years, researchers have validated the traditional use of the European black elderberry by running clinical trials that position the ingredient as an effective way to help relieve cold and flu symptoms and reduce illness duration.

In formulating supplements that build on the research, companies may want to consider the effect variables including the type of plant, extraction methods, and ingredient traceability have on their products.

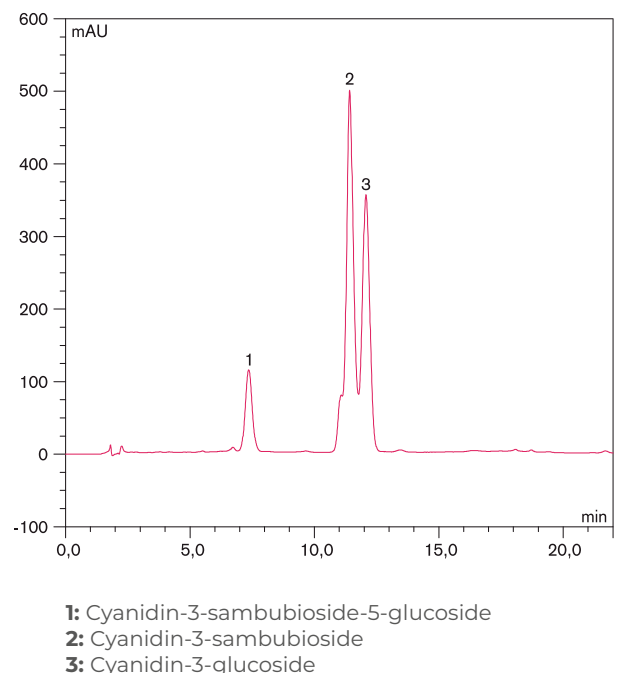
This whitepaper explains why European black elderberry extract a powerful solution for immune support formulations is and provides guidance to help manufacturers choose the right extract with confidence.

## 02 Introducing *Sambucus nigra*, the European Black Elderberry

**European black elderberry (*Sambucus nigra*, variety ‘Haschberg’) is a bushy shrub that can become a tree up to 10 meters tall, with strongly fragrant, cream-white flowers and small violet-black, globular fruit. Highly regarded as a European folk-medicine for relieving symptoms of colds and flu, today it can be found in a number of food supplements worldwide.**

European black elderberries are especially rich in anthocyanins, water-soluble pigments that give fruit red, violet, and purple colors and are known for their antioxidant effects. With 1374 mg per 100 g, black elderberries are among the top three fruits for anthocyanin content, second only to black chokeberries.

In addition to immunologically active polysaccharides, the three main biologically active anthocyanins in the European black elderberry are Cyanidin-3-sambubioside, Cyanidin-3-glucoside, and Cyanidin-3-sambubioside-5-glucoside. These three components appear in a unique and distinctive ratio which can be visualized using HPLC fingerprinting methods (Fig. 2). The unique profile can be used to confirm the authenticity of the extract or the finished product. In addition to anthocyanins, extracts of elderberry contain a variety of polyphenols, including flavonoids like proanthocyanidins, chlorogenic acids, and flavonols such as rutin, quercetin, kaempferol, and isorhamnetin.

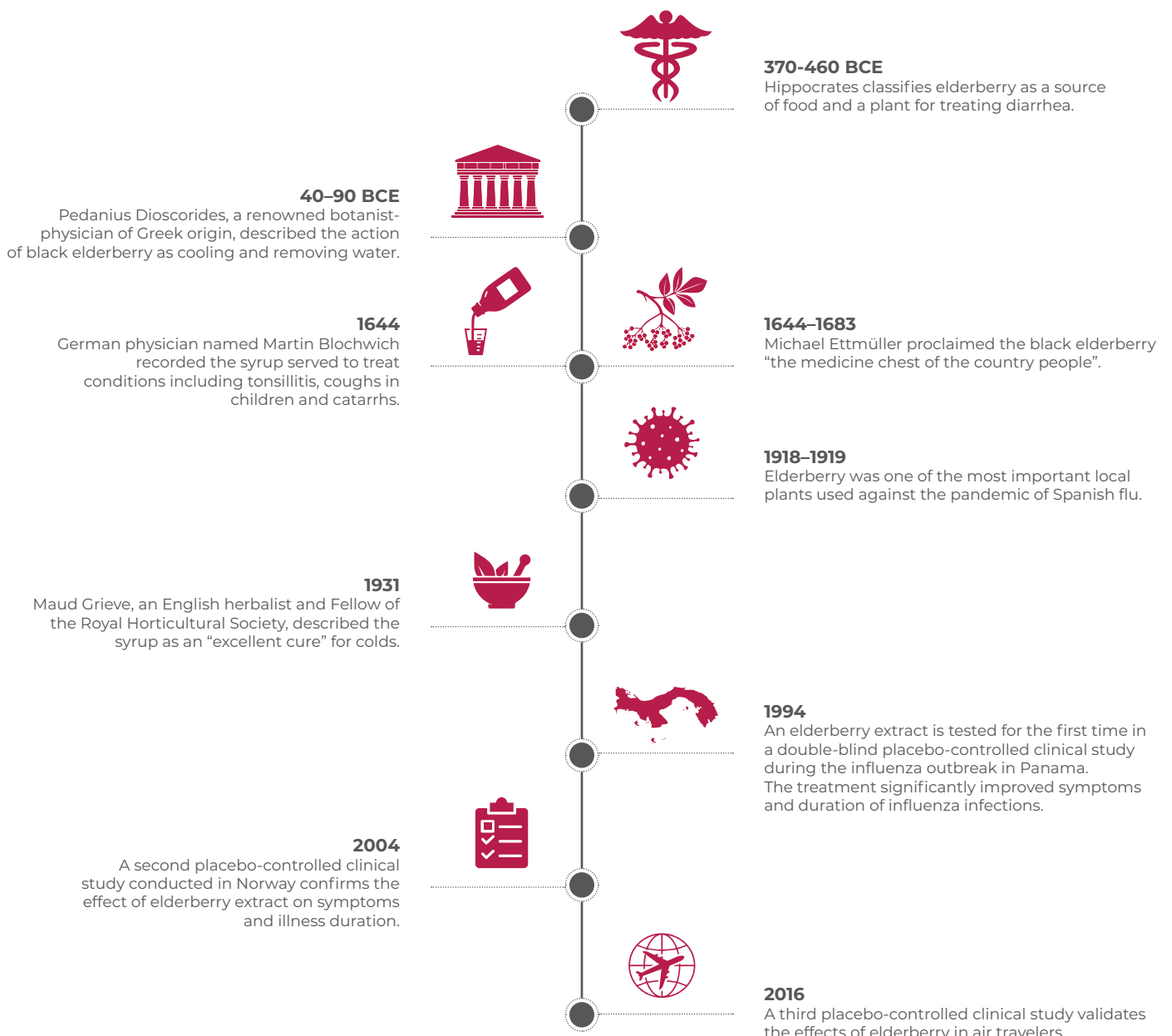


**Fig. 2:** HPLC fingerprint

The European black elderberry, also called *Sambucus nigra* with its variety ‘Haschberg’, is the most studied species of this plant. Its North American counterpart, *Sambucus canadensis* or Canada elderberry, is a different species. The two species have substantial morphological

differences and their fruits show significantly different anthocyanin and polyphenol profiles, raising doubts about whether Canada elderberry delivers the positive health properties seen in clinical trials of its European sibling.

## *Sambucus nigra,* through the ages



## 03 Making the case for elderberry: Human clinical studies

**As of 2020, three independent human clinical trials that tested European black elderberry against upper respiratory infections have been performed and published in peer-reviewed scientific journals. The results are in line with what has been observed for centuries in traditional medicine. A common observation is a reduction in symptoms and a reduction of illness duration.**

### 1 First human clinical study

In a randomized double-blind, placebo-controlled study conducted in Israel in 1993, a syrup containing elderberry extract was shown to reduce the duration of symptoms of upper respiratory tract infections. The tested product was a proprietary syrup formulated with 38% standardized extract of elderberry juice.

The study included 27 patients aged between 5 to 56 years. Infected subjects developed typical symptoms for upper respiratory tract infections, including fever, cough, and inflammation of the mucous membrane of the nose. Syrup or placebo was administered for three days and symptoms were checked for 6 days after onset of the treatment. A clear difference was identified in the persistence of fever as higher temperatures were found to occur for 4 days in the elderberry group and at least 6 days in the placebo group.

After 2 days a complete cure was observed in 40% of patients treated with the elderberry extract, and in 16.7% of patients treated with placebo. For the black elderberry group, the average duration of illness was 2.7 days compared to 4 days in the placebo group.

The authors also tested the extract in vitro and found that dilutions of the extract inhibited the propagation of several strains of type B and type A flu viruses.

1: Sambucol®, Razei Bar Ltd, Jerusalem



## 2 Second human clinical study

A second double-blind, placebo-controlled trial was carried out in the fall and winter of 1999-2000 in Norway and published in 2004. Sixty healthy men and women who had tested positive for influenza type A and B were randomized to receive elderberry syrup or placebo within 48 hours of first symptoms. The syrups were taken 4 times daily for 5 days. Patients were permitted to include paracetamol or aspirin as a rescue medication.

Within a few days, patients' scores for symptoms showed remarkable differences. In the black elderberry group, symptoms improved after 3 to 4 days, while in the placebo group it took 7 to 8 days to reach a similar level of improvement. Analysis of individual symptoms showed significant improvements in the elderberry group (Fig. 3). Additionally, a significantly lower percentage of patients in the black elderberry group resorted to rescue medications.

Symptom	Elderberry	Placebo
Aches and pain	9.8	0.5
Quality of sleep	9.5	1.0
Nasal congestion	9.2	0.6
Mucus discharge	9.2	1.0
Frequency of coughing	8.7	0.6

**Fig. 3:** Visual analog scores for symptoms on day 4: Score of 0 for highest symptom severity and score of 10 for complete absence of discomfort.



### 3 Third human clinical study

#### Elderberry as immune support in air travelers

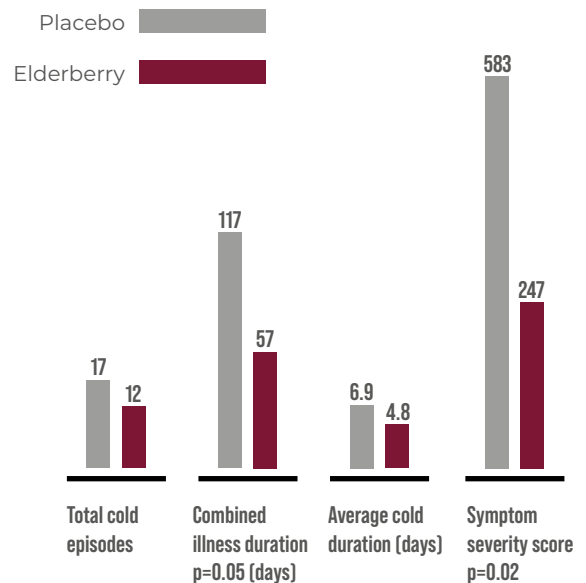
Long-distance flights place substantial burdens on the immune system by exposing travelers to recycled air and depriving them of sleep. As a consequence, up to 20% of passengers on long-haul flights suffer from a cold, fatigue, or illness soon after arrival.

A double-blind, placebo-controlled study performed between April 2013 and December 2014 tested if ElderCraft® European Black Elderberry Extract prevents upper respiratory tract infections in intercontinental air travelers.

The study enrolled 312 economy class passengers from Australia who went on flights lasting for at least seven hours.

Subjects received capsules with 300 mg of the proprietary standardized elderberry extract or a matching placebo for 10 days before and 4 days after the flight. Standardized questionnaires were used to record symptoms of a common cold or flu, mental and physical well-being as well as quality of life.

The study found the elderberry extract had significant benefits to upper respiratory tract health, as compared to placebo.



**Fig. 4:** Summarized study results: ElderCraft® significantly reduced illness duration and symptom severity.

People in the elderberry group suffered 51.3% fewer days with cold symptoms and reported a 57.6% lower symptom severity score, on average.

Additionally, physical health during travel and arrival at destinations significantly declined in the placebo group, while being stable in the ElderCraft® group.



## 04 Fighting influenza: mechanism of action and active constituents

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Human clinical trials have shown a reduction in severity and duration of common cold and flu infections. However, the mode of action is still a topic of discussions within the scientific community. Currently there are three different explanations for possible mode of actions which might act in parallel.

### Mode of action A

#### Flavonoids mask the surface of the virus

In-vitro tests with flu viruses have shown that components present in black elderberry block viral hemagglutination, the mechanism by which flu viruses attach to blood cells.

Interestingly, the extracts of elderberry showed a dose-dependent inhibition of a type A flu virus in mammalian cells. Two flavonoids were found to bind to the virus surface: One a derivative of dihydromyricetin, and the other a derivative of quercetin.

The authors of the study argue that the molecular mode of action could be a result of the flavonoids binding directly to the virus particles, stopping them entering host cells to replicate and thereby effectively preventing an infection. The effective concentration needed to inhibit virus replication was comparable to Tamiflu®, a commonly used prescription drug for treating influenza.



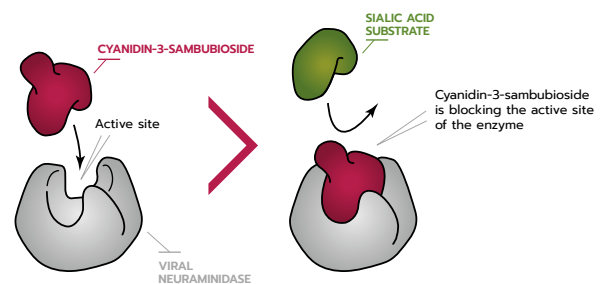
**Mode of action B**

**Neuraminidase Inhibition by anthocyanins**

Neuraminidase is an enzyme located on the surface of influenza viruses that enables viruses to be released from their host cell soon after successful replication. During this final stage of virus replication, the release from the host cell needs a cleavage of a sugar bond. Neuraminidases cleave this bond between the virus and host cell, effectively releasing the virus particle into the bloodstream.

An Australian research group working with elderberry extracts and viral neuraminidases discovered Cyanidin-3-Sambubioside (C3Samb) — a major anthocyanin in European black elderberries — can bind to and inhibit the activity of the enzyme neuraminidase of the pandemic type A influenza. The anthocyanin C3Samb reduces the activity of viral neuraminidase by binding to its active center and effectively blocking its ability to cleave the sugar bond between the virus and the host cell (Fig. 5).

This mode of action is effective in suppressing viral replication in-vitro. A common antiviral drug, oseltamivir, has a similar mode of action and is commonly used in the treatment of influenza.



**Fig. 5:** Cyanidin-3-Sambubioside binds to the active site of the viral neuraminidase and inhibits the processing of the sialic acid substrate. Cleavage of sialic acid is needed to the release of the viral particles from the host cells.

Ref: Swaminathan



## Mode of action C

### **Black elderberry polysaccharides as potent immunostimulants**

Herbal polysaccharides are a type of water-soluble dietary fiber known to stimulate complement-fixing and macrophage activity. Polysaccharides are part of the high molecular weight fraction of botanical extracts and consist of long chains of sugar molecules.

The immunostimulatory activity of black elderberry has recently been characterized in a mouse study. The research showed high molecular fractions from elderberry support the mammalian immune system, thereby helping the organism in the fight against viral infections.

Mice were infected with a human type A flu virus and fed with a dried elderberry powder. The results showed significantly enhanced local and systemic immune responses. Influenza virus-specific immunoglobulins A and G — antibody-producing proteins that bind to and immobilize pathogens — increased significantly.

Virus-neutralizing antibodies also increased significantly in a dose-dependent manner, with mice dosed with elderberry having up to 1.8 times higher concentrations of the antibodies than those in the water-treated control.

In an attempt to identify the bioactive components, the researchers fractionated the extract and found that a high molecular weight sub-fraction rich in polysaccharides showed the most overall activity. Interestingly, elderberry had a similar effect as the prescription drug Tamiflu® in reducing the viral yields in lung fluids.

## 05 Extraction methods, a crucial point of differentiation

**Like most botanical extracts, black elderberry extracts can be obtained through alcohol or water extraction. The process used to extract bioactive components affects the quality and composition of the product.**

Alcohol-based methods featuring solvents such as ethanol and methanol are commonly used to extract active components from fruit pomace and skins. However, while these methods efficiently extract anthocyanins from hard-to-access matrices such as skins and stems, they necessitate the use of large amounts of energy to remove the alcoholic fraction.

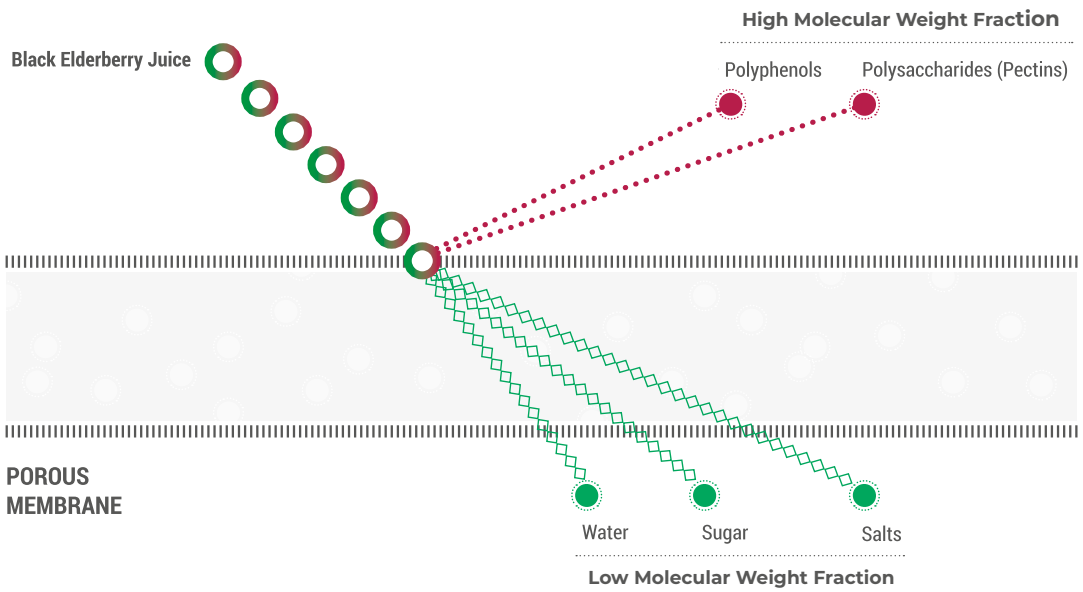
Extracts made by alcoholic solvent extractions have a better solubility in alcohol-based formulations, but, despite the use of energy-intensive mitigating measures, a carryover of solvents to the final product cannot be excluded. On the other hand, water extraction methods are gentle processes and have the advantage of retaining more aroma and taste from the original fruit matrix. Water extracts are more soluble in water-based formulations.

IPRONA Polyphenol Technology (IPT) is a proprietary and particularly gentle extraction process that combines water extraction and ultrafiltration (Fig. 6).

Whole elderberries are pressed into juice, in combination with water extraction of the pomace, followed by IPRONA's proprietary IPT technology (an entirely physical, solvent free, separation, concentration, and enrichment ultra-filtration process).

IPT utilizes specially designed membranes with different pore sizes to separate solids into two streams (fractions) based on the size (molecular weight) of the molecules. The desired larger molecules (including active polyphenols, anthocyanins, and polysaccharides) are concentrated and retained in one direction through the membrane, while smaller molecules (including salts, mono-, and disaccharides) pass through the membrane and are discarded.

In sum, IPRONA's IPT technology enables extraction and purification without resorting to the use of solvents. IPRONA's IPT technology yields highly water-soluble extracts which are uniquely characterized by preserving the original phytonutrient fruit matrix of the whole berry, while retaining the original taste, flavor, and aroma profile of elderberry.



**Fig. 6:** IPRONA Polyphenol Technology

## 06 Supply chain control, from nice-to-have to essential requirement

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**Ingredient traceability is becoming an essential requirement in the nutraceutical industry, and choosing an extract produced with full control of the supply chain can make all the difference when it comes to customer trust and loyalty.**

Companies are under increasing pressure from consumers, governments, NGOs, and other stakeholders to collect and provide more information about their supply chains. More consumers than ever are demanding and expecting a transparent supply chain from the products they buy.

A study at the MIT Sloan School of Management showed consumers may be willing to pay 2% to 10% more for products from companies that provide greater supply chain transparency.

As such, it is becoming increasingly important for nutraceutical companies to collect and validate supply chain related information about the ingredients in their finished products. Failure to guarantee authenticity and origin can lead to increased reputational risk and substantially reduce the company's standing as a trustworthy enterprise.

### **Supply chain transparency from farm to shelf**

The raw material for ElderCraft® European Black Elderberry Extract is grown by more than 500 contracted farmers exclusively for IPRONA in south-east Austria. Soon after harvest the berries are pre-processed locally, then transported to the neighbouring region of northern Italy for the final processing. The integration of the upstream supply chain in the production of ElderCraft® guarantees the highest level of transparency and traceability.

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For further information about ElderCraft®, European Black Elderberry Extract, please visit [www.eldercraft.info](http://www.eldercraft.info) or email us on [extracts@iprona.com](mailto:extracts@iprona.com)



### About IPRONA

With nearly 40 years of experience serving a dynamic, international clientele, IPRONA is the peerless supplier of any fruit-specific ingredients you need to take your business to the next level. Thanks to our passion for fruit and zeal for the latest in innovation, we offer a wide array of fruit concentrates, infusions, extracts as well as tailored pre-mixes and compounds.



### About the author

Dr. Stephan Plattner is Business Development Manager at the Business Unit Extracts at IPRONA. With over 8 years of experience in the international Nutraceutical industry his contribution span from clinical trial developments to new applications and product developments in collaboration with international partners.

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