Antiviral and healing potential of *Sambucus nigra* extracts

Michalina Bartak1, Agata Lange2, Anna Słońska1, Joanna Cymerys*1

**Abstract:** Nowadays, the application of alternative methods instead of clinical treatment creates a new possibility to prevent the development of diseases. Medicinal plants such as *Sambucus nigra* have been well known due to their extraordinary properties. The similarity to synthetic substances makes it potentially dependable; however, a high concentration of cyanogenic glycosides may exert detrimental consequences. It has been documented that *Sambucus nigra* extracts are used against both human and animal viruses, like influenza A and B viruses, human immunodeficiency virus (HIV), dengue virus (DENV-2), human herpesvirus type 1 (HSV-1) and human coronavirus NL63 (HCoV-NL63). Such reports are notably valuable especially considering the widespread usage of commercial drugs, which could be ineffective. This review provides insight on recent research on the health properties of plant *Sambucus nigra* as an antiviral medication that may help propose new therapy.

**KeyWords:** *Sambucus nigra*, extracts, antiviral, healing.

**Introduction**

One of the fundamental issues of general biology and present knowledge of the philosophy of nature is the problem of demarcation of nonliving and living matter. The definition of viruses is similar - they can be categorized as a connection between *morsus et vivus materia*.

Coping with viral diseases using commercial drugs is difficult. They penetrate living cells and alter their metabolism using specific enzymes. It creates a possibility to replicate. The majority of synthetic drugs is precisely directed against the replication process. The main difficulty of antiviral cure is a high potential of getting synthetic substances resistance.

What is more, our knowledge of healing with antiviral drugs is not up to the standard level yet. As a result, finding alternative treatment methods became common. Using plants as medicine have long been known. Nowadays, there is a widespread increase in using natural pharmaceutics, which is defined as a less expensive source of healing. Worldwide estimates prove that 70-80% of people rely on natural medicine because of its sufficient actions in healthcare. However, the topic of plant medicine is not flawless. Sometimes it may come from access to plants' material, including proper living conditions and some other dependencies.

This study is aimed to better understand the health properties of plant *Sambucus nigra* as an antiviral medication that may help propose new therapy.

*Sambucus nigra*

*Sambucus nigra* L. is a part of Adoxaceae family (following Integrated Taxonomic Information System) in the northern hemisphere, especially in Europe, Northern America, and Western Asia. There are three subspecies of *Sambucus nigra* L.: *S. nigra* L. ssp. nigra, *S. nigra* L. ssp. canadensis, *S. nigra* L. ssp. Cerulean.

*Sambucus nigra* is a 7-10 meters high bush or rarely a small tree with a small white flower gathered in cyme (Figure. 1). The flowering season falls in June and July, but it usually happens in its third or fourth year. The leaves with total length in 30 cm are accumulated in 5-7 pair. Both flowers and leaves (during rubbing) have a specific aroma, which can be found as an unpleasant taste. The elders' fruits are firstly green and elongated, but during ripening, they become roundish black and shiny berrylike drupes. Each drupe contains 3-5 seeds inside. The seeds' maturation is connected with the mean October temperature, which is required to be approximately 7°C.

Black elder prefers soil based on nitrogen and calcium compounds. Despite its predilection for alkaline soil, it is also able to grow on a different type of soil even with a pH ranging between 4.2 and 8.0.

**Constituents**

*Sambucus nigra*’s chemical composition is associated with plenty of factors - climate and manner of agriculture alike. Both extracts from fruits and flowers have shown a high possibility of reducing viral infections symptoms.

Crucial constituents of black elder are RIPS (ribosomal inactivating proteins), which (beside lectins) are part of *S. nigra* agglutinins (SNAs). RIPs found in *S. nigra* fruits aim for specific cells or substances which many pathogens bind. They show higher potential than RIPS from other plants. Other antiviral substances present in black elders are peptic polysaccharides through their availability to activate Macrophages.
The main substances are present in Table 1.

**Flowers**

The flowers’ extract is full of bioactive flavonoids and phenolic acids. Through the Schmitzer et al. study, there were identified major flavonoids: flavonol glycosides rutin, kaempferol-3-rutinoside, and isorhamnetin-3-rutinoside.

Listed substances constitute 90% of total flavonoid concentration in elderflowers. In the case of phenolic acids, 70% of them were 5-cafeoylquinic acid and 1,5-di-cafeoylquinic. Using products from the black elder as medicine is supported by its electrochemical activity, which comparable to 21g ascorbic acid per kg dry flowers.

**Fruits**

The main products from black elders show the same properties, such as ones used in medical aid. Most of them are anthocyanins that are known for their health-related features.

1 Division of Microbiology, Department of Preclinical Sciences, Institute of Veterinary Medicine, Warsaw University of Life Sciences, Warsaw, Poland.
2 Department of Nanobiotechnology and Experimental Ecology, Institute of Biology, Warsaw University of Life Sciences, Warsaw, Poland.

Corresponding author: jcymerys@op.pl
including antiviral and antibacterial activity, reducing oxidative stress and, as a result – free radicals. Among anthocyanins, cyanidin-3-O-glucoside and cyanidin-3-O-sambubioside were identified. *S. nigra* fruits consist of different variety of sugars with a total content from 68.53 to 104.16 g per kg fresh weight. The central part of this group is occupied by glucose and fructose. Furthermore, organic acids, such as citric and malic acid, are also established in berries. Their concentration in *S. nigra* berries has been observed six times higher than in apples\(^{11}\).

**Application of Sambucus nigra**

There are plenty of purposes of using *S. nigra* even in everyday life, beginning in nutrition. The extracts from fruits are standard in the production of juice, jellies, or wine. However, there are a lot of other properties used in medicine (Figure. 2). Tea from fruits is intended for the treatment of colds and its’ symptoms such as high temperature\(^{11}\). Abundant in tannins and polyphenols extracted from the *S. nigra* shows antioxidant properties, resistance to U.V. radiation, and high biological

| Substance       | Examples                                                                                       | References |
|-----------------|-----------------------------------------------------------------------------------------------|------------|
| Anthocyanins    | cyanidin-3-O-glucoside, cyanidin-3-O-sambubioside                                              | 11,14      |
| Vitamins        | vitamin A-group, B-group, vitamin C, tocopherol                                               | 14         |
| Sugars          | glucose, fructose                                                                            | 11,14      |
| Flavonoids      | quercetin-3-rutinoside (rutin), quercetin-3-glucoside (isoquercitrin), kaempferol-3-rutinoside, isorhamnetin-3-rutinoside, isorhamnetin-3-glucoside | 11,14, 17  |
| Organic acids   | quinic acid-containing caffeic, p-coumaric acid moieties, citric and malic acids             | 11         |

**Figure 1.** *Sambucus nigra* – flowers, berries, and leaves (Source: Amedee Masclef – Atlas des Plantes de France, 1891.

**Table 1.** The most abundant substances in *Sambucus nigra* (Source: as listed in table).
activity, which can be a base of users in cosmetology. What is more, the blackberries are valued in folk medicine. The infusion of blossom is popular for diaphoretic and diuretic properties. The black elder is associated with the immune system; it modulates the production of proinflammatory cytokines such as IL-6, TNF-α. S. nigra extracts are also useful in healing diabetics or obesity. It is related to glucose metabolism in the human organism and insulin uptake. Additionally, S. nigra decreases cholesterol and lipids levels which may cause a weight loss.

Disadvantages of usage Sambucus nigra
As we mentioned in the introduction, using plant extract can have disadvantages. The main disadvantage in the case of S. nigra is the risk of allergenicity. That effect is due to the high amount of cyanogenic glycosides (CGG), which are present in all parts of S. nigra. Among them, sambunigrin and prunasin occur the most frequently (Fig. 3). The content of cyanogenic compounds might have health consequences manifested in poisoning. The mechanism of cyanide’s toxicity relies on inhibition of oxidative phosphorylation caused by cytochrome oxidase, which stops electron transport. As a result, adenosine triphosphate (ATP) synthesis cannot proceed, and cellular respiration has to be halted.

Cyanogenic glycosides may be harmful to animals and humans when implemented between 0.5 and 3.5 mg per kg body weight. It is also known that there exists a possibility to reduce the high level of cyanide during boiling, fermentation, and drying. Despite processing methods that cause a decrease of the cyanide, the human body can only detoxicate it when the low level is present.

What is more, Forster-Waldl et al. in clinical trials showed detection of a protein of 33.2 kDa by IgE in patients’ sera. That is why S. nigra is supposed to contain the allergen Sam n1, which is a representative of RIP (ribosomal inactivating protein).

Antiviral properties of Sambucus nigra extracts
As we described in the introduction, the history of usage of plant extracts is well known. The therapeutic use of plants as a remedy is dated back to 5000 B.C. Nowadays, a significant amount of S. nigra extracts are adopted as homeopathy medicines as well as pharmaceuticals. It is embedded in Slavic and European countries’ culture and history. There are many documented examples of therapeutic use on several human and animal viruses.

Influenza virus
Influenza viruses, the members of the Orthomyxoviridae family, are enveloped negative-strand RNA viruses with segmented genomes containing seven to eight gene segments. They are divided into three types (A, B, and C), which differ in host range and pathogenicity. Influenza A infects a wide variety of hosts, including birds, swine, horses, humans, and other mammals, and it causes a seasonal epidemic. In humans, the virus causes an acute respiratory disease characterized by the sudden onset of high fever, cough, headache, and inflammation of the upper respiratory tract. Influenza A is classified

Figure 2. The bioactive compounds found in elderberry (own work based on 9).

Figure 3. (A) Chemical structure of Prunasin [(R)-Prunasin], and (B) Sambunigrin [(S)-Prunasin] own elaboration based on PubChem. (Source: https://pubchem.ncbi.nlm.nih.gov/compound/Sambunigrin#section=2D-Structure, https://pubchem.ncbi.nlm.nih.gov/compound/Prunasin#section=Structures).
based on surface glycoproteins: hemagglutinin (H.A.), which binds to host cell sialic acid conjugated glycoproteins and neuraminidase (N.A.), essential for viral release and propagation. There are 16 types of hemagglutinin (H1-H16) and nine types of neuraminidase (NL-N9)77.

Even though S. nigra extract has already been used repeatedly for treating colds and influenza, the antiviral mechanisms of the elderberry extract are still under investigation28,29,30,31. The clinical study presented by Kong28 showed that administration of the elderberry extract to patients presenting flu symptoms significantly relieve influenza-like symptoms within 24 hours from the administration of the first dose. According to recent studies, it can be assumed that flavonoids in elderberry can inhibit the H1N1 influenza virus infection in vitro by binding to the surface of the virus28, S. nigra constituents cause the deactivation of hemagglutinin and thus prevent the virus from entering and replicating in the host cell. The flavonoids in elderberry can also bind to neuraminidase and cause its inactivation; however, confirmation of this hypothesis requires additional research28.

In a recent paper, Ulbericht et al.28, provides the Natural Standard Evidence-Based Validated Grading Rationale™ of the clinical bottom line of S. nigra. The grading scale presents levels from A (strong scientific evidence) to F (strong contrary scientific evidence). Clinical trials on the impact of S. nigra for influenza virus have proven an excellent scientific basis for the use of S. nigra extracts to combat the disease caused by the virus, classifying it on level B (based on the criteria)15.

In monography S. nigra by Throne Research (Biotech & Pharma; USA)9, authors provided the example of Zakay-Rones22 research, in which two randomized, placebo-controlled, double-blind studies, demonstrated the extract (Sambucol) that effectively inhibited influenza A and B strains after 48 hours post-infection symptoms. In the earlier study, 27 individuals experiencing common early flu symptoms were given Sambucol or placebo daily for three days – 2 tablespoons (children) or four tablespoons (adults). Patients were followed for six days, and symptoms were monitored. Serum from all subjects was analyzed for antibodies to influenza type A and B at the initial dose and during the convalescent phase. In the treatment group, significant improvement in flu symptoms was observed in 83.3 percent of subjects within two days after initial dosing, while 91.7 percent of the control group demonstrated improvement after six days. A complete resolution was achieved in the treatment group in 90 percent of patients after 2-3 days, while the placebo group yielded similar results after six days. Of these 27 patients, 23 had laboratory confirmation of influenza type B9. The mechanism is believed to be rendering viruses nonfunctional by staining and coating them. According to a review, in vitro as well as animal research reported that elderberry fruit (Sambucci fructus) affected influenza, other viral infections, and increased antibody titer9.

Other studies have proved that elderberry extract may affect the immune system by enhancing the production of cytokines by monocytes23,24. Torabian et al.35, in their recent research, indicated that the immunomodulatory property of elderberry extracts manifested by increased expression of IL-6, IL-8, and TNF-α.

S. nigra has also inhibiting properties against avian influenza virus H9N2. Research presented by Karimi et al.38, showed antiviral properties of the mixture of Echinacea and elderberry extract on the avian influenza virus. The extracts tested caused a reduction of the load of the virus and thus could be used as a valuable aid to control avian influenza in poultry fields39.

In conclusion, elderberry extract shows multiple modes of therapeutic action against influenza infection, mainly by suppressing viral entry, affecting the post-infection phase, and viral transmission from cell to cell. Further research is still needed to define the antiviral activity of each of the active ingredients contained in the S. nigra. Only then will the treatment be fully effective31.

**Human immunodeficiency virus**

Human immunodeficiency virus (HIV) belongs to the Lentivirus genus of the family of Retroviridae. The genome of the virus is composed of two copies of positive-sense single-stranded RNA that codes for the nine genes, including the reverse transcriptase. HIV infects a variety of immune cells such as CD4+ T cells, macrophages, and dendritic cells and causes acquired immunodeficiency syndrome (AIDS)30.

Recent studies indicate that the elderberry extract also has activity against HIV, and it can effectively block the ability of HIV virions to infect host cells37,38. Antiviral effectiveness show flavonoids and A-type proanthocyanidins (PACs) contained in S. nigra extract. These compounds bind to viral envelope glycoproteins, likely to the gp120, and block HIV entry into and infection of host cells likely through the CD4CCR5 receptor system39.

Interestingly in other cases, after application of the boiled extract of Sambucol (with Glucosamine sulfate, chondroitin, and commercial product-Thymate), a decrease of viral particles was observed from 39,000 particles/mL to an undetectable amount in ten days after the administration of a mixture40. Moreover, S. nigra extract (Sambucol) was tested for the potential to inhibit the infectivity of HIV isolates in CD4+ cell lines, peripheral blood lymphocytes, and laboratory HIV strains. S. nigra extract, prepared in two different dilutions, was incubated with the virus before adding to cells. A significant decrease in virus infectivity was observed, and no virus load could be detected after four- or nine-days post-incubation40. Other studies show that the combination of elderberry extract and thymus extract has reduced the viral load in HIV patients. Unfortunately, studies do not sufficiently confirm the effect of this treatment method40.

The identified compounds of elderberry extract, mainly flavonoids, which inhibit HIV infection41, could be a new therapeutic target for HIV-1/AIDS, which shows promise for co-therapy uses with existing HIV-1 antiviral agents.

**Herpes simplex type 1**

Herpes simplex virus type 1 (HSV-1), the member of the Alphaherpesviridae subfamily, causes a contagious infection that affects approximately 1/3 population of the world population. HSV-1 has a double-stranded linear DNA genome that is approximately 152 kbp in length, and it is an etiological agent of orofacial blisters, keratitis, pneumonia, or encephalitis. Following primary infection in the mucosal epithelia, virions migrate to the trigeminal ganglion neurons, where the latent infection is established.

The influence of Sambucol against HSV-1 was examined in the cell line of human diploid fibroblasts. In their research, Morag et al.42 have used four HSV-1 strains – a reference strain, two acyclovir-resistant strains, and a strain isolated from a patient. Complete inhibition of viral replication was observed in all utilized strains, whether the cells were pre-incubated with the extract, simultaneously incubated with extract, or the extract was added 30 minutes after viral adsorption to cells. The complete inhibition of four strains of HSV-1 in vitro by
Elderberry extract warrants further clinical trials in humans. A formula of *S. nigra* (flower extract) in combination with *Hypericum perforatum* and *Saponaria officinalis* was also found to inhibit the replication of HSV-1 via\(^{39}\). Among the described flavonoids of *S. nigra*, the kaempferol and quercetin show the most promising activity against HSV-1\(^{43}\).

**Dengue virus**

Another virus that is claimed to be cured with *S. nigra* extract is the dengue virus. Dengue virus (DENV) is a single positive-stranded RNA virus, which belongs to the family *Flaviviridae* and genus *Flavivirus*. DENV is a mosquito-borne, and it causes a wide range of clinical manifestations, from mild fever to potentially fatal dengue shock syndrome\(^{44}\). Effective anti-dengue therapeutic drugs, as well as protective vaccines, have still not been developed\(^{45}\).

The antiviral effect of various flavonoids obtained from various plants on the dengue virus has already been repeatedly confirmed\(^{44,45,46}\). *S. nigra* methanolic extracts apart from flavonoids also contain alkaloids and small amounts of coumarins which exhibit anti-DENV-2 activity. In their research, Castillo-Maldonado et al.\(^{45}\) revealed that methanolic extracts of leaves and flowers of *S. nigra* have anti-DENV-2 properties when added to Vero and BHK-21 cell lines. The best results were obtained when DENV-2 was pre-incubated with the extracts for 1 hour and then added to the cell cultures. They additionally confirmed this result by analyzing the synthesis of NS-1 and the extent of intracellular DENV-2\(^{46}\).

**Human coronavirus NL63**

Human coronavirus NL63 (HCoV-NL63) is one of the common HCoVs species that occur worldwide. HCoV-NL63 belongs to the genus of *Alphacoronavirus* in the *Coronaviridae* family. The viral genome is positive-sense, single-stranded RNA. HCoV-NL63 infects the upper respiratory tract causing runny nose, cough, and sore throat and also infects the lower respiratory tract (pneumonia, bronchiolitis). Considering this, it is worth noting that unraveling which viruses use cellular factors during replication and viral attachment of Human coronavirus NL63 was additionally confirmed this result by analyzing the synthesis of NS-1 and the extent of intracellular DENV-2\(^{46}\).

**Infectious bronchitis virus**

Infectious bronchitis virus (IBV) is of the species avian *Coronavirus*, which belongs to the family *Coronaviridae*. The viral genome is positive-sense single-stranded RNA\(^{52}\). IBV infects the respiratory tract of chickens and causes the deformation of eggshell, thus causing economic losses to the poultry industry\(^{45}\). Due to the highly recombinant nature of the virus, current vaccination strategies are not sufficient against new infections, and for that reason, new methods defending against IBV are needed. In their work, Chen et al.\(^{54}\) investigated the influence of three plant species: *Rhodiola rosea*, *Nigella sativa*, and *Sambucus nigra* on avian IBV replication. Among these plants, *S. nigra* presented the best results of inhibition in the early step of the infection cycle. More precisely, the results from these experiments revealed that combining pre-V (the only virus was treated before infection) treatment with post-treatment worked together to inhibit IBV replication fully. The pre-C (only cells were treated with extract before infection) treatment was not necessary for full virus inhibition, nor did it impact the viral load of the supernatant. However, it did work synergistically with pre-V treatment to reduce viral load in the cells an additional three orders of magnitude, as compared to pre-V treatment alone. Probably, the bioactive compounds are lectins (Elder bark agglutinin I (SNA-I), Elder bark agglutinin II (SNA-II), *Sambucus nigra* agglutinin III (SNA-III), from *Sambucus nigra* that could bind directly to viral proteins and inhibit infection. What is more, authors suspect that two flavonoids isolated from *Sambucus nigra* fruits (same, which affect influenza: 5,7,3',4'-tetra-O-methylquercetin and 5,7-dihydroxy-4-oxo-2-(3,4,5-trihydroxyphenyl)chroman-3-yl-3,4,5 trihydroxy cyclohexanecarboxylate\(^{55}\) could also have an inhibitory impact on IBV replication\(^{54}\).

**Conclusions**

Ancient knowledge of the antimicrobial properties of various plants’ extracts provides an authoritative source for new antiviral drugs, which can be successfully used instead of synthetic medicine. Because of its chemical composition, *S. nigra* is a plant that finds its contribution in widespread use. *S. nigra* is rich in phenolic acids, flavonoids, catechins, and proanthocyanidins, and these compounds in addition to antiviral properties, they also show anti-cancer, immune-stimulating, antibacterial activity, antioxidant and antidepressant potential. The increasing resistance of viruses to commonly used drugs forces the development of new therapeutic methods that are not based on synthetic chemical compounds. In the present review, we provided insight on recent research on the health properties of plant *S. nigra* is an antiviral medication that may help propose new therapy.

The search for new antiviral therapies is especially important nowadays when humanity is struggling with the SARS-CoV-2 pandemic. Both influenza virus and SARS-CoV-2 have an RNA genome and cause respiratory disease. Moreover, there is preclinical research showing that *S. nigra* inhibits replication and viral attachment of Human coronavirus NL63 (HCoV-NL63), which similar to SARS-CoV-2, belongs to the coronavirus family\(^{44}\). Among the above examples of antiviral applications, most reports refer to the use of *S. nigra* extracts in the treatment of diseases caused by the influenza A and B viruses. This is probably related to the high variability of influenza virus, as a result of which the flu vaccine is reformulated each season for a few specific influenza strains and is usually effective against three or four types of influenza acti-
vitity in the world during that season. Based on evidence that S. nigra could be used in the treatment of influenza, it is tempting to speculate that it could also be applicable in the treatment of COVID-19. However, this hypothesis requires thorough research and confirmation.

The antiviral effect of S. nigra has also been documented against herpes simplex virus, human immunodeficiency virus, dengue virus, or infectious bronchitis virus. The possibility of full-value application of extracts S. nigra is not currently used. Despite this, it is worth noting that it has excellent potential for antiviral use due to its good tolerability and low extraction costs in contrast to synthetic drugs.

**Conflict of interest**

No conflict of interest is declared.

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