Bioactive Compounds of Softwood Bark as Potential Agents against Human Diseases Include the SARS-CoV-2 Virus

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Abstract: In recent years, significant progress has been achieved in developing natural drugs derived from medicinal plants. Multiple in-vitro screening studies reported that some naturally occurring compounds could possess inhibitory activity against various human viruses. The presented work describes significant biological activities of the main class of secondary metabolites such as phenolic compounds and terpenes located in industrially important tree species Norway spruce (Picea Abies) and Scots pine (Pinus Sylvestris). Phytochemicals show promising in vitro antiviral and cytotoxic activities, making them an attractive starting material for new development in various pharmaceutical products. They have the potential to effectively protect human health against cardiovascular diseases, diabetes mellitus, and as therapeutic agents against the SARS-CoV-2 virus.

Keywords: tree bark; phenolic compounds; human diseases; SARS-CoV-2.

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1. Introduction

The advantages of wood biomass include its renewability, biodegradability, low cost, easy availability, and rich source of high-value chemical compounds. Presently, the bark of softwood is a low-value by-product in the forest industry. According to the Food and Agriculture Organization of the United Nations, the global annual contribution of tree logs is 3,591,142,000 m³. Thus, the production of tree bark per year is estimated at 359,114,200 m³ [1–3]. Tree biomass represents a valuable raw material to obtain natural, structurally complex, bioactive compounds - extractives. Extractives are natural components of plants composed of a wide range of phytochemicals with diverse chemical structures. They have significant colloidal, chemical, physicochemical, and biological properties. Phytochemicals obtained from plant-based materials have recently been of considerable interest in the scientific sphere. It is due to numerous epidemiological studies indicating their health benefits such as antiviral, antioxidant, cytotoxic, and anti-inflammatory properties [4-6]. The work by Jablonsky et al. [7] summarized the properties of 237 compounds extracted from tree bark. Compounds have been described regarding their biological activities such as cytotoxic (25 identified phytochemicals), antioxidant (26 phytochemicals), antibacterial (42 phytochemicals), anti-
inflammatory (10 phytochemicals), antimutagenic (5 phytochemicals), pharmacokinetic (5 phytochemicals), and inhibiting (22 phytochemicals).

In the presented work, bark mainly from industrially momentous tree species like Norway spruce (*Picea abies*) and Scots Pine (*Pinus Sylvestris*) are described. The focus was on the health benefits of phytochemicals found in extracts isolated from wood biomass. Phytochemicals such as a phenolic compound with capable antioxidant activity and stilbene-based compounds have excellent opportunities for medical applications, including antiviral and antibacterial activities, e.g., phenolic compounds have been shown to protect nerve cells, and stilbene-based compounds such as resveratrol may help prevent the SARS-CoV-2 virus by disrupting the spike protein of the virus.

2. Materials

2.1. Bark compounds.

The content and spectrum of extractives in tree bark vary depending on the type of tree and can reach up to 40% of extractives per dry bark. Extractives define a large group of low molecular weight predominantly organic compounds, which form a multicomponent mixture of several chemical groups of substances of lipophilic and hydrophilic character. Lipophilic components include chemical groups such as fatty acids, terpenes (mono-, sesqui-, and triterpenes), and sterols, while the hydrophilic component includes a large group of aromatic phenolic compounds such as flavonoids and tannins. Stilbene glycosides are an interesting group of phenolic compounds found in the bark of Norway spruce (*Picea Abies*). The specific composition of extractives in a tree is controlled genetically and depends on external conditions such as climatic and soil conditions, location, tree age, tree species, and others [1,2,8]. The authors of Ånäs et al. [9] and Krogell et al. [2] indicate a significant difference in the composition between the inner and outer bark of Norway spruce (*Picea Abies*). The number of lipophilic components in the outer bark of Norway spruce is up to two times higher than the amount present in the inner bark [2]. Table 1 shows a significant difference in the proportion of extractives depending on the tree species for Norway spruce (*Picea Abies*) and Scots pine (*Pinus Sylvestris*) in individual parts of the tree. [9].

|          | Norway spruce (*Picea Abies*) | References | Scots pine (*Pinus Sylvestris*) | References |
|----------|-------------------------------|------------|--------------------------------|------------|
| Bark     | 23.5 - 28.3 %                 | [10], [11] | 16 - 25.9 %                    | [10,12,13] |
| Inner Bark | 17.3 - 38.7 %                 | [10], [12] | 15.4 - 41.9 %                  | [10,12,13] |
| Outer Bark | 19.1 - 43.3 %                 | [10], [11] | 16.4 - 20.8 %                  | [10,12,13] |
| Stemwood | 1 - 4.5 %                     | [13–15]    | 1 - 6.8 %                      | [15,17]    |
| Sapwood  | 1.7 - 2.7 %                   | [17], [18] | 3.1 %                          | [16,17]    |
| Heartwood | 1.1 - 1.8 %                   | [17], [18] | 5.1 - 5.35 %                   | [17, 19]   |

3. Discussion

3.1. Extractives as human health protecting agents.

Clinical studies have shown that phenolic compounds significantly prevent many chronic diseases due to their antioxidant effect [20 - 22]. Several assays assessed antioxidant activity scavenging superoxide and free hydroxyl radicals or determining the DNA strand’s oxidative destruction [23]. The antioxidant activity of phenolic compounds is stimulated

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primarily by their reducing properties, and thus they can act as donors of hydrogen atoms and electrons [20]. Beyond antioxidant activity, phenols have been shown to protect nerve cells in vitro by inhibiting the formation of the plaques [24] that characterize Alzheimer’s brain pathology. Phenolic compounds can inhibit the growth of several types of microorganisms, including yeasts and bacteria [25,26], and possess gastroprotective, anticarcinogenic, antimicrobial antifungal [27,28], antibacterial, antiseptic [29], hepatoprotective, cardioprotective, antidiabetic effects [30]. The work of Vainio-Kaila et al. [31] confirmed the antibacterial properties of the Scots pine (Pinus Sylvestris) extract against gram-negative Escherichia coli. Gram-positive bacteria Staphylococcus aureus was sensitive to extracts of Norway spruce (Picea Abies) and Scots pine (Pinus Sylvestris). The work corresponds to the results of the work of Ignat et al. [32], where they determined higher amounts of catechin and vanillic acid (71.9 mg / 100 g dry bark) in ethanolic extract of spruce bark by high-performance liquid chromatography, while gallic acid (10.2 mg / 100 g dry bark) and quercetin (1.39 mg / 100 g dry bark) were present in lower concentrations. The results demonstrate the antibacterial effect of the ethanol extract on gram-positive Staphylococcus aureus and gram-negative bacteria such as Pseudomonas aeruginosa and Escherichia coli. Pietarerin et al. [21] demonstrate higher ability to suppress lipid peroxidation from spruce bark extracts (Picea Abies) IC50 = 49 µg / l compared to extracts from Jack pine (Pinus banksiana) IC50 = 143 µg / l and overhanging Silver birch (Betula pendula) IC50 = 81 µg / l. The bark of Norway spruce contains several stilbene glycosides, lignans, flavonoids, and tannins [33, 34] Stilbene glycosides like piceid (2-[3-Hydroxy-5-[(E)-2-(4-hydroxyphenyl)ethenyl]phenoxy]-6-(hydroxymethyl)oxane-3,4,5-triol), isorhapontin (3, 4’, 5-trihydroxy-3’-methoxystilbene 3-O-ß-D-glucoside) and astringin (3, 3’, 4’, 5-tetrahydroxystilbene 3-O-ß-D-glucoside), and their corresponding aglycones resveratrol, isorhapontigenin, and piceatannol are the main phenolics present in the wood and bark of Picea species. The work by Jyske et al. [8] estimated the total yields of stilbene glucosides in Norway spruce. A younger tree’s bark yielded 27 g of astringin, 18 g of isorhapontin, and 5 g of piceid, while the values for the older trees were significantly higher 618 g of astringin, 324 g isorhapontin, and 90 g of piceid. Resveratrol (3,5,4’-trihydroxystilbene) is one of the most studied natural products due to its beneficial effects on health. Besides antioxidant effects, anti-aging, anti-cancer, anti-inflammatory, neuroprotective, and cardioprotective effects have been found [35,36]. Resveratrol enhances antibacterial activity against the gram-positive human pathogenic bacteria Bacillus cereus, Staphylococcus aureus, Enterococcus faecalis, and gram-negative bacteria Escherichia coli, Salmonella typhimurium, Arcobacter cryaerophilus [37].

Flavonoids are another important class of phenolic compounds synthesized in trees as bioactive secondary metabolites. They are natural antioxidants capable of quenching hydroxyl and peroxide radicals, having nutraceutical, biological, and clinical effects [38,39]. Flavonoids can be subdivided into different subgroups such as flavanones, flavones, flavonols, flavanols, flavanonols, or catechins, anthocyanins, and chalcones [40]. Of the flavanones, two compounds have been identified in Norway spruce (Picea Abies), namely naringenin and eriodictyol. Naringenin shown in Figure 1 shows strong inhibition against gram-positive bacteria Micrococcus luteus, Staphylococcus aureus, and Staphylococcus epidermidis [41].

Terpenes and terpenoids are divided into mono-terpenes, di-terpenes, sesquiterpenes, and mono-terpenoid, di-terpenoid, sesquiterpenoid, representing a diverse class of extractives in wood biomass. Diterpenoids have antiviral properties against several viruses, such as HIV (Human immunodeficiency virus), hepatitis B virus, dengue fever virus, and herpes simplex
virus. Chen et al. [42] demonstrated the antiviral effect of the diterpenoid sclareolide. The results of the study indicate broad-spectrum effects on infection caused by filoviruses that cause Ebola viral disease. In addition to the antiviral properties, biological studies have also shown the antifungal, antibacterial, anti-inflammatory, and anti-cancer effects of sclareolide. From diterpenes, α-cadinol was identified in work [43] in spruce bark using supercritical extraction using CO₂. α-cadinol is known for its antifungal, hepatoprotective properties with the potential as an effective drug in treating infectious tuberculosis, which in 1900 was one of the three leading causes of death. The triterpenoid gamma-sitosterol also had a high proportion in spruce bark (13.6% and 13.2%). In contrast to beta-sitosterol, which is found in almost all plants, laboratory tests in Balamurugan et al. [44] have shown that gamma-sitosterol has the potential as an antidiabetic, reduces hyperglycemia, and can be used in the treatment of type 2 diabetes (Diabetes Mellitus). Gigante et al. [45] studied the biological effects of the effect of dehydroabietic acid and its derivatives on yeasts, filamentous fungi, and bacteria. Resin acids confirmed a bactericidal effect against Staphylococcus aureus and a fungicidal against Trichophyton mentagrophytes.

![Figure 1. Chemical structure of Naringenin.](image)

Lipophilic compounds such as fatty acids and phytosterols found in conifers reduce the risk of cardiovascular disease. Cardiovascular disease has the highest mortality rate of up to 375,000 people per year in the United States. Research published in the Journal of the American Medical Association has radically changed the understanding of the development of heart disease. The researchers performed a series of nearly 300 autopsies on American victims of the Korean War, with an average age of 22 years. As many as 77% of soldiers had atherosclerosis, the arteries of some soldiers were blocked up to 90% [46]. Phytosterols such as campesterol are effective protection against atherosclerosis, stroke, regulate hormonal disorders and hot flashes [47]. Wiliam C. Roberts, editor-in-chief of the American Journal of Cardiology, argues that the main risk factor for arteriosclerotic plaque is cholesterol, especially elevated LDL cholesterol levels [48]. It is the lipophilic extract compounds that have a favorable effect on the level and ratio of LDL and HDL cholesterol. Of the fatty acids [43], linoleic acid, hexadecanoic acid, methyl behenate, and ethyl oleate were identified in the work [42]. Research [49] suggests reducing the risk of lung, prostate, and breast cancer using linoleic acid, which is currently used to treat eczema and diabetic neuropathy.

3.2. Plant-derived compounds against the SARS-CoV-2 virus.

Phenolic compounds are a significant group of substances that show strong antiviral activity against the SARS-CoV-2 virus, such as quercetin, which also showed antiviral activity in the first type of SARS-CoV PLpro with an IC₅₀ of 8.6 ± 3.2 μM [50]. Scots pine's most common phenolic compounds (Pinus sylvestris) and Norway spruce (Picea Abies) include stilbenes, proanthocyanidins, flavonoids, phenolic acids, and lignans. In common spruce, the main representative of stilbenes is resveratrol, and the main representative of flavanoids is...
myricetin. To a lesser extent, coumaric acid is present in Norway spruce (*Picea Abies*) and in White fir (*Silver Fir Abies*) [51]. The most common phenolic compounds of Scots pine (*P. sylvestris*) include pinosylvin-type stilbenes and flavonol-type and dihydroflavonol-type flavonoids such as quercetin, kaempferol, taxifoline, and their derivatives [52]. Other important phenolic compounds in Scots pine include caffeic, salicylic, ferulic, and gallic acids [53].

The work of Mani *et al.* [54] classified myricetin, caffeic acid, and quercetin among promising natural compounds that show inhibition of SARS-CoV-2 infection (Figure 2). These extractive compounds have shown a high ability to bind to the angiotensin-converting enzyme 2 (ACE 2), through which the SARS-CoV-2 virus enters human cells [55,56]. Publication by Nguyen *et al.* [57] confirmed the inhibitory activity of myricetin IC50 43 ± 1 μM, quercetin IC50 93 ± 5 μM, and caffeic acid IC50 197 ± 1 μM against SARS-CoV-2 Mpro.

Several scientific publications [58–61] state that stilbene-based compounds, particularly the chemical compound resveratrol, are a potential natural compound in treating the SARS-CoV-2 virus. In a study by Yang *et al.* [61], the results showed that resveratrol significantly inhibited the SARS-CoV - 2 virus replication with an EC50 (half-maximal effective concentration) of 4.48 μM. And in the study by Nguyen *et al.* [57] demonstrated inhibitory activity for resveratrol of IC50 103 ± 6 against SARS-CoV-2 Mpro. Savariar *et al.* [62] identified several compounds, including myricetin gamma sitosterol, as potential phytochemicals capable of inhibiting the SARS-CoV-2 virus major protease 3CLpro (6LU7). In the scientific publication, Fischer *et al.* [62] identified natural flavonoid compounds, namely (-) - Taxifolin (Figure 3) and rhamnetin, as potential inhibitors of the crystal structure of the main protease the SARS-COV-2 virus.

Taxifolin (5,7,3,4-flavan-on-ol), also known as dihydroquercetin belongs to the flavonoid subclass of flavanons. According to scientific studies, it is present in conifers such as Norway spruce, black spruce, Siberian spruce, Roxburg pine, Himalayan cedar, Chinese yew [64]. From a pharmacological point of view, it acts as a chemopreventive agent, inhibits the growth of ovarian cancer cells, has antiproliferative effects on several cancer cells, and can prevent their growth and spreading by inhibiting fatty acid synthase [64]. Taxifolin has also
shown promising pharmacological effects on microbial infections, oxidative stress, cardiovascular disease, and liver disorders [65,66]. It has significant antioxidant activity and has the potential in the food industry to significantly extend the shelf life of foods such as vegetable oils [67,68]. A scientific study by Weng et al. [69] monitored antiviral activity against HCo-V-NL63 coronavirus. Phenolic components such as caffeic acid (IC50 = 3.54 μM) and coumaric acid (IC50 = 71.48 μM) showed anti-HCoV-NL63 activity. Caffeic acid significantly inhibited HCoV-NL63 replication independent of the cell type and specifically blocked virus attachment [69,70]. In addition, caffeic acid can inhibit other viruses, such as the hepatitis B virus [71].

Infected patients with the SARS-CoV-2 virus show long-term persistent health problems even months after the initial infection. As a result, more than 90 clinical studies have been performed. The effect of commercially available Pycnogenol powder on human immunity support was studied. Pycnogenol is a concentrated natural extract obtained from maritime pine (France). Pycnogenol consists mainly of procyanidins and their monomers such as catechin and epicatechin, as well as phenolic acids. The total amount of procyanidins is 70 ± 5%. The work of Weichmann et al. [72] demonstrated anti-inflammatory, vascular, and endothelial protective effects of Pycnogenol. Because the SARS-CoV-2 virus strongly affects the lining of endothelial cells, Pycnogenol may be beneficial in promoting recovery and mitigating symptoms due to infection.

4. Conclusions

Wood residue-based compounds like stilbene glucoside, terpenes, flavonoids can be used as health-promoting compounds and materials to prevent or treat chronic, cardiovascular, and cancer diseases. Phenolic compounds and terpenes obtained from the bark have potential uses as antiviral agents against diseases such as HIV (Human immunodeficiency virus), hepatitis B virus, dengue fever virus, and herpes simplex virus. Phytochemicals such as quercetin, caffeic acid, or myricetin promise phenolic compounds against the SARS-CoV-2 virus. The bioactive properties of extracts make them attractive materials for the pharmaceutical industry as pharmaceuticals or therapeutic or protective agents. Although the extracts from tree bark show significant biological activity for human health, several in vitro and in vivo studies and further knowledge of the aspects are required.

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Conflicts of Interest

The authors declare no conflict of interest. The funders had no role in the study's design, in the collection, analyses, or interpretation of data, in the writing of the manuscript, or in the decision to publish the results.

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