Review paper
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NUTRACEUTICALS AS PHENOLIC BIOACTIVE COMPOUNDS ANALYSIS OF SOFTWOOD BARK AND THEIR POSSIBILITIES OF INDUSTRY APPLICATIONS

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Abstract

Softwoods have a numerically large group of economically important renewable plants. Waste processing of trees mainly bark, needles are reasonable extent not recovered. The waste contains relatively high levels of phenolic compounds. Phenolic compounds are one of the main components that have a high potential in various fields of food, pharmacy, and other industries. This review focuses on the main uses of softwood bark and overviews the extraction and analytical methods used to determine phenolic bioactive compounds in this matrix.

At this time, various extraction techniques are used to obtain secondary metabolites from bark mainly bioactive phenolic compounds. The amount of bioactive compounds derived from the matrix affects the: extraction conditions, choice of the solvent, particle size, content of the water and, in particular, the extraction method. Amount and nature of the isolated compounds greatly depend on the isolation; the isolation is possible to use different methods: extraction in a Soxhlet apparatus, Soxtec extraction, accelerated solvent extraction, ultrasound-assisted, supercritical fluid extraction, pressurized liquid extraction, and microwave-assisted extraction. According to literature were selected nutraceuticals phenolic compounds (isolated from softwood bark): Astringin; Catechin; Epicatechin; Ellagic acid; Ferulic acid; Gallic acid; Hydroxymataairesinol; isolariciresinol; Isorhapontigenin; Isorhapontin,lariciresinol; Lariciresinol-9-p-coumarate; Methylthymol;p-Coumaric acid; Piceatannol; Piceid; Podocarpic acid; Quercetin; Resveratrol; Sesquipinsapol B; Sinapic acid; Tannic acid; Taxifolin; Vanillic acid; Vladinol D.

From this viewpoint, it is important to collect information on pharmacokinetic properties of the nutraceutical phenolic substances isolated from bark according to published papers. Pharmacokinetics properties of phenolic bioactive substances extracted by different techniques such as: molecular weight, logP, AlogP, H-bond acceptor, H-bond donor, total polar surface area, atom molar refractivity, number of rotatable bond, number of atom, rotatable bond count, number of rigid bond, number of atom ring, and number of Hydrogen Bond were calculated by DruLito (Drug LiknessTool).

***Key words**: Nutraceuticals, Bioactive compounds, Phenolic, Bark.*

1. Introduction

Valorisation is a key principle of the biorefinery approach, and full valorisation of lignocellulosics should bring both economic and environmental benefits [1, 2]. A great amount of research in the last decades has been focused on the extraction of bioactive compounds from different types of biomass or bio-waste, especially, of polyphenolic bioactive substances, which

can be used for the production of nutraceuticals. These compounds represent the main group of secondary metabolites in phytomass.

While the bark is a rich source of bioactive compounds, which can find application in the field of food additives, cosmetics and pharmacological or agricultural products, millions of tons of bark are mainly burned or landfilled every year. The various ranges of bioactive nutrients present in natural products, such as bark, roots and needles, play a vital role in the prevention and cure of various diseases.

2. Softwood bark phenolic bioactive compounds and their possibilities for industry applications

2.1 Polyphenolic compounds in bark

Bark is a source of compounds soluble in different non-polar and polar solvents, such as: fats, saturated and unsaturated fatty acids, resins, resin acids, waxes, phenolic and polyphenolic compounds, stilbens, flavonoids, terpenoids, alkaloids and ligands. Bioactive substances show: antioxidant, antimycotic, cytotoxic, antiviral, antitumor, antimalarial, insecticidal, antimutagenic, tumorigenic, pharmacokinetic activities and other properties. The substances present in softwood bark extracts [3 - 15] and their physical properties were discussed in a recently published study by Jablonsky *et al.*, 2017 [16]. Most of these substances may be used as fine chemicals and some have already been used for pharmacological purposes. The extracts isolated from softwood barks contain hundreds of natural products [16], some of which have: cytotoxic (25 identified substances), antioxidant (26 substances), fungicidal (20 substances) and antibacterial (42 substances) effects. In addition, some of these substances are repellents (9 substances) and antifeedants (2 substances), others may cause growth inhibition (8 substances), increase the activity of pheromones or act themselves as pheromones (10).

The recovery of the extractive compounds present in bark is affected by: temperature, time, and pressure of the extraction agent used (depending on the nature of the extraction agent used - polar, non-polar), the choice of the solvent, the particle size, the content of water. An important parameter is how the matrix was adjusted due to the fact that it can to some extent influence the quantity and quality of the product (extract). Moreover, the amount and nature of the extracted compounds greatly depend on the separation methods used, such as: Soxhlet extraction [17], Soxtec extraction, accelerated solvent extraction, ultrasound-assisted extraction [18], supercritical fluid extraction [19], pressurized liquid extraction [20], microwave-assisted extraction [21], pressurized solvent extraction and enhanced solvent extraction [22]. According to a paper published by Jablonsky *et al.*, [16], the following polyphenolic compounds with nutraceutical potential were isolated from softwood bark: astringin; catechin; epicatechin; ellagic acid; ferulic acid; gallic acid; hydroxymatairesinol; isolariciresinol; isorhapontigenin; isorhapontin, lariciresinol; lariciresinol-9-p-coumarate; methylthymol; p-coumaric acid; piceatannol; piceid; podocarpic acid; quercetin; resveratrol; sesquipinsapol B; sinapic acid; tannic acid; taxifolin; vanillic acid; vladinol D.

2.2 Pharmacokinetic properties of nutraceuticals

In the literature, a large number of studies can be found on the structure and activity of natural compounds, however, only a few papers related to the pharmacokinetic characteristics of compounds isolated from bark extracts have been noted. Phytochemicals/nutraceuticals act in different ways in the human body to prevent or treat various ailments [23, 24]. The pharmacokinetic properties of nutraceuticals as bioactive polyphenolic substances extracted from softwood bark include: molecular weight (MW), partition coefficient (logP), octanol-water partition coefficient (AlogP), H-bond acceptor (HBA), H-bond donor (HBD), total polar surface area (TPSA), atom molar refractivity (AMR), number of rotatable bonds (nRB), rotatable bond count (RC), number of rigid bonds (nRigidB), and nHB (number of Hydrogen Bonds). The properties and their values can be calculated by the Drug Likeness Tool (DruLiTo) techniques [25]. The values obtained for the physicochemical properties of the compounds under study are listed in Table 1.

In our study, we chose 25 natural polyphenolic compounds identified in the extract of softwood bark, which have a remarkable antioxidant property or an inhibition effect, and act mainly by scavenging free radical species [26]. A key factor for accelerating the process of drug discovery and development is the estimation of molecular transport [27]. Traditionally, the calculated values of the octanol/water partition coefficient have been used for this purpose. The Lipinski criteria (Ro5) are widely used by medicinal chemists to predict not only the absorption of compounds, as Lipinski originally intended, but also the overall drug-likeness, to reduce the number of entries that satisfy the majority (90%) of orally absorbed substances [28, 29]. The conditions of the filters are as follows: MW ≤ 500, LogP ≤ 5, number of HBD ≤ 5, and number of HBA ≤ 10. No more than one violation is tolerated. However, Ro5 does not predict whether a compound is pharmacologically active. Another very helpful parameter for the prediction of absorption is the total polar surface area. This parameter is easy to understand and, most importantly, provides good correlation with experimental transport data [27, 28]. TPSA checks the bioavailability

Table 1 Drug-likeness descriptors calculated by DruLiTo application

Compound	Mw	logP	AlogP	HBA	HBD	TPSA	AMR	nRB	nAtom	RC	nRigidB	nHB
Astringin	406.13	0.879	-1.46	9	7	160.07	108.91	5	51	3	26	16
Catechin	290.08	0.852	-0.936	6	5	110.38	81.07	1	35	3	22	11
Epicatechin	290.08	0.852	-0.936	6	5	110.38	81.07	1	35	3	22	11
Ellagic acid	302.01	1.366	-1.304	8	4	133.52	74.69	0	28	4	25	12
Ferulic acid	194.06	0.78	0.267	4	2	66.76	55.45	3	24	1	11	6
Gallic acid	170.02	0.964	-0.721	5	4	97.99	41.77	1	18	1	11	9
Hydroxymatairesinol	374.14	0.751	-0.428	7	3	105.45	104.11	6	49	3	23	10
Isolariciresinol	360.16	0.231	-1.093	6	4	99.38	103.39	5	50	3	23	10
Isorhapontigenin	258.09	2.077	0.695	4	3	69.92	81.25	3	33	2	17	7
Isorhapontin	420.14	0.771	-1.395	9	6	149.07	113.95	6	54	3	26	15
Lariciresinol	360.16	1.062	-0.64	6	3	88.38	103.34	6	50	3	22	9
Lariciresinol-9-p-coumarate	506.19	1.802	0.282	8	4	125.68	148.7	9	67	4	31	12
Methylthymol	164.12	2.808	1.728	1	0	9.23	54.93	2	28	1	10	1
p-Coumaric acid	164.05	0.751	0.766	3	2	57.53	48.8	2	20	1	10	5
Piceatannol	244.07	2.185	0.631	4	4	80.92	76.21	2	30	2	17	8
Piceid	390.13	0.742	-0.897	8	6	139.84	107.31	5	50	3	25	14
Podocarpic acid	274.16	3.16	0.778	3	2	57.53	79.32	1	42	3	21	5
Quercetin	302.04	1.834	-1.244	7	5	127.45	83.44	1	32	3	23	12
Resveratrol	228.08	2.048	1.194	3	3	60.69	74.61	2	29	2	16	6
Sesquipinsapol B	540.24	0.812	-1.468	9	5	138.07	155.22	12	75	4	30	14
Sinapic acid	224.07	1.2	-0.231	5	2	75.99	62.09	4	28	1	12	7
Tannic acid	1700.17	9.537	-5.356	46	25	777.98	420.15	31	174	11	101	71
Taxifolin	304.06	0.803	-1.369	7	5	127.45	81.47	1	34	3	23	12
Vanillic acid	168.04	0.508	-0.094	4	2	66.76	45.2	2	20	1	10	6
Vladinol D	374.14	0.314	-1.064	7	3	105.45	104.75	6	49	3	23	10

Legend: MW, molecular weight; logp, partition coefficient; AlogP, octanol-water partition coefficient; TPSA, total polar surface area. AMR, atom molar refractivity; HBD, H-bond donor; HBA, H-bond acceptor; nRB, number of rotatable bonds; nRigidB, number of rigid bonds; RC, rotatable bond count; nHB, number of hydrogen bonds.

of natural substances as per the Veber's rule for good oral bioavailability, the number of rotatable bond ≤ 10, and TPSA ≤ 140 Å [30]. The number of rotatable bonds has been shown to be a very good descriptor of oral biovalability of drugs and has been found very helpful in discriminating between compounds that have oral biovailability of drugs [26]. When using the Ghose filter, the substances should fulfil the following requirements: Mw 160 to 480 g/mol; logP -0.4 to 5.6; Atom-Count 20 to 70 and atom molar refrectivity 40 to130.

In the present investigation, the selected compounds were evaluated by the virtual screening tool DruLito, considering a number of rules and filters (Table 2 and

Table 3). DruLiTo calculations are dependent on various drug-likeness rules, namely: Lipinski's rule, Veber rule, Ghose filter, BBB rule, CMC-50 like rule, and quantitative estimate of drug-likeness (QED). From the entire set of compounds, 19 followed well the Ro5 parameters, while 6 compounds (astringin; isorhapontin; lariciresinol-9-p-coumarate; piceid; sesquipinsapol B and tannic acid) violated more than one the rules. The latter substances can create problems in oral bioavailability.

2.3 Determination of polyphenolic bioactive compounds and their properties

In recent years, in the area of plant use and waste valorisation, research has been intensively underway with regard to the application of various extraction methods. Recent trends in extraction techniques have largely focused on the use of green solvents and new techniques, and last but not least, the research focuses on the use of wastes from various industries, for

Table 2 Drug-likeness Descriptors Calculated by DruLiTo application

Sample	Lipinski´s rule of five	Ghose filter	CMC-50 like rule	Veber's rule	MDDR like rule	BBB likeness rule	Unweighted QED	Weighted QED
Astringin	0	1	0	0	0	0	1	1
Catechin	1	1	0	1	0	0	1	1
Epicatechin	1	1	0	1	0	0	1	1
Ellagic acid	1	1	0	1	0	0	1	1
Ferulic acid	1	1	0	1	0	0	1	1
Gallic acid	1	0	0	1	1	0	1	1
Hydroxymatairesinol	1	1	0	1	0	0	1	1
Isolariciresinol	1	1	0	1	0	0	1	1
Isorhapontigenin	1	1	1	1	0	1	1	1
Isorhapontin	0	1	0	0	1	0	1	1
Lariciresinol	1	1	0	1	1	0	1	1
Lariciresinol-9-p-coumarate	0	0	0	1	1	0	1	1
Methylthymol	1	1	0	1	0	1	1	1
p-Coumaric acid	1	1	0	1	0	0	1	1
Piceatannol	1	1	1	1	0	1	1	1
Piceid	0	1	0	1	0	0	1	1
Podocarpic acid	1	1	1	1	0	0	1	1
Quercetin	1	1	1	1	0	0	1	1
Resveratrol	1	1	0	1	0	1	1	1
Sesquipinsapol B	0	0	0	0	1	0	1	1
Sinapic acid	1	1	0	1	0	0	1	1
Tannic acid	0	0	0	0	1	0	0	0
Taxifolin	1	1	0	1	0	0	1	1
Vanillic acid	1	1	0	1	0	0	1	1
Vladinol D	1	1	0	1	1	0	1	1

Legend: 1 - passed; 0 - not passed.

Table 3. Various filters applied for screening purposes evaluated by DruLiTo application

Selected filters	Total number of molecular filters	Total number of molecules that violated the rule
Lipinski's Rule of Five	19	6
Ghose_Filter	21	4
CMC-50 Like Rule	4	21
Veber's Rule	21	4
MDDR Like Rule	7	18
BBB Likeness Rule	4	21
Unweighted QED	24	1
Weighted QED	24	1
All Selected Filters	0	25

example, bark or food waste. Various methods are used to evaluate the content of substances isolated from plants. Mostly, the content of phenolic substances is determined for various groups, especially polyphenols, tannins, anthocyanins, and flavonoids. Most polyphenolic compounds and their active metabolites have been known as potent antioxidant phytochemicals due to their unique structure. Still, despite the need, there is no standardized methodology for identifying these substances. Each of the methods used has certain drawbacks that relate to the reproducibility of the method and the interference from the various other substances present in the extract. Total polyphenolic compounds may be determined using permanganate titration, colorimetry, the Folin-Denis method and the Folin-Ciocalteu method [31]. Approximately 20 methods are known for the determination of the antioxidant activity of extracts. These methods use different reagents, with a different composition of the reaction mixture, standards and analytical evaluations [32]. The antioxidant activity of bark extracts can be determined by different assays, such as: 2,2-diphenyl-1-picrylhydrazyl (DPPH), 2,2´-azinobis (3-ethyl benzothiazoline 6-sulfonate (ABTS), ferric reducing antioxidant potential (FRAP), oxygen radical absorption capacity (ORAC), hydroxyl radical averting capacity (HORAC), ferric thiocyanate assay (FTC), Trolox equivalent antioxidant capacity (TEAC), cupric reducing antioxidant power (CUPRAC), potassium ferricyanide reducing power (PFRAP) and different types of: HPLC, electrophoresis, fluorimetry, cyclic voltammetry, amperometry, biamperometry and GC/MS [32 - 34]. The absolute values of individual methods for determining the antioxidant activity differ significantly. The work of Prior *et al.*, [35] compares the methods available for the measurement of the antioxidant capacity and evaluates the most important advantages and shortcomings of such methods as TEAC, ORAC and the Folin-Ciocalteu assay. Finally, the authors state that other assays may need to be considered in the future as more is learned about some of the other radical sources and their importance to human biology. Therefore, standard procedures for determining antioxidant properties are still ambiguous, which makes it difficult to compare the results of antioxidant activity obtained by different methods.

3. Conclusions

- The waste material in the forest industry has a specific composition, which does not change significantly, remaining more or less similar. Bark waste is a rich source of natural compounds, which may serve as important substances in the field of nutrition, health and medicine. A possible way to reduce environmental pollution (waste landfilling or burning) is related to the full utilization of the waste potential, considering that this waste contains interesting compounds that can be valorised.

- More recently, research and development efforts have been initiated with the objective of transforming waste bark into value-added and eco-friendly industrial products with large market potentials. Thus, bark can be exploited in two main ways: by using the raw material obtained directly from bark after milling to develop more environmentally friendly products, and by extracting the useful substances present in the bark. These compounds have a wide range of biological activities that make their exploitation extremely interesting, representing an important contribution to the upgrading of these industrial residues.

- Bark flours obtained from different wood species (fir and spruce) have been investigated as additives for making plywood panels [36]. Also, bark has been used as additive in feed for improved feed utilization and animal health. On the other hand, polyphenolic compounds are becoming increasingly interesting for nutritionists, food, cosmetic and medicine industries [37, 38].

- Among the ingredients used in nutraceuticals and in cosmeceuticals, antioxidants, such polyphenols, represent one of the most important classes [38, 39]. Polyphenolic compounds, such as: catechin, epicatechin, taxifolin, piceid and isohapontin, are capable of producing diverse potentially protective effects against chronic and degenerative diseases [16]. For example, quercetin possesses: anti-inflammatory [39], antivirus, anticancer, inhibitory (against platelet aggregation) [40], antioxidant [41], antimicrobial [42], cardioprotection [43], and neuroprotection [44] activities. Also, ellagic acid has shown: antimicrobial, antifungal, inhibitory (against enzyme activity) [45], antioxidant, antibacterial [46], antimalarial [47] and antitumor [48] properties.

- Thus, the exploitation of bark waste by both ways, but as far as this study is concerned, by valorising the bioactive principles it contains, would contribute to a sustainable biorefinery process, which is expected to bring both economic and environmental benefits.

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4. References

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