Chapter

Red Wine and Yacon as a Source of Bioactive Compounds with Antidiabetic and Antioxidant Potential

Mariia Nagalievska, Mariya Sabadashka and Nataliia Sybirna

Abstract

Phytochemicals derived from different plants are promising therapeutic agents. Herbal compounds can be used under diseases, etiological causes of which are alterations of carbohydrate, protein, and lipid metabolisms, along with increased oxidative stress and chronic low-grade inflammation. Potential sources of biologically active substances may be grape wine, rich in phenolic compounds. Well-studied examples of polyphenols are phenolic acids, catechins, anthocyanins, and flavonoids, etc. Another source of biologically active compounds is yacon (*Smallanthus sonchifolius* Poepp. & Endl.). The aboveground part of yacon is rich in phenolic compounds and terpenes. Main biologically active substances from tuberous roots of yacon are fructooligosaccharides and phenolic compounds. The section will be devoted to the analysis of hypoglycemic and antioxidant effects, and molecular targets of the complex of biologically active substances derived from red wine and yacon.

Keywords: polyphenols, phenolic compounds, flavonoids, fructooligosaccharides, red wine, yacon, diabetes mellitus, antioxidant

1. Introduction

1.1 Red wine as a source of bioactive compounds with antidiabetic and antioxidant potential

Plant foods contain vitamins, phytosterols, sulfur compounds, carotenoids and organic acids that are healthy for human. However, the most effective protective agents are phenolic compounds that are secondary metabolites found in fruits, vegetables, and cereals. It is known that 100 g of apples, pears and cherries fruit contain 200–300 mg of polyphenols [1–4]. Grapes are rich in phenols. 10% of the total phenolic compounds of grapes are contained in the pulp, 60–65% in the seeds, and 20–35% in the peel. The content of phenolic compounds in grapes depends on the plant variety, climatic and other geographical conditions, as well as the degree of maturity [5]. These healthy components are stored in drinks made from grapes. When grape wine is produced, almost 63% of all phenolic substances from grape

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seeds and berry peel are extracted into wine. So provided that the optimal dose is consumed, wine can be considered one of the most effective natural remedies.

It is important that in the process of obtaining wort (fermentation) and maturation of wine, phenolic compounds undergo structural changes, which determines characteristics of the drink. The most intense reactions during the maturation of wine are the polymerization and oxidation of catechins. The products of these reactions give a pleasant taste and golden-brown color of different intensity of wine, so that aged wines are easy to distinguish from young [6, 7].

Another group of substances that are extracted into wine during fermentation is procyanidins. Procyanidins are contained mainly in grape seeds, so they are virtually absent in grape juice. Initially, the wort contains a small amount of procyanidins, as these substances started to extract from the seeds during fermentation when the alcohol content is 6%. As the alcohol concentration increases during fermentation, procyanidins are extracted into the wine. Young wine rich in procyanidins has a tart taste. In the aging process procyanidins react with each other and form longer polymers - condensed tannins. As the wine ages, these chains become very long and difficult to dissolve, so they precipitate [6–8].

Because grape peel and seeds float on the surface, the more often they are immersed in the fermenting wort, the process of extraction of procyanidins better proceed. After fermentation, many wines also insist on the pomance to enhance the color, taste and extract the tannins. Therefore, the highest content of procyanidins and tannins is characteristic of wines that have been infused for three weeks or more. Thus, the consumption of grapes, grape juice and wine has different effects on the body [6].

Numerous researchers pay much attention to the study of the effects of red wine consumption on the organism since the discovery of the "French paradox". Although the father of medicine Hippocrates emphasized the benefits of "moderate wine consumption" [9]. As a result of large-scale studies involving almost 300 thousand people, it was shown that the consumption of 150–400 ml of dry red wine daily significantly reduces the risk of cardiovascular and neurological pathologies, diabetes, many types of cancer, and dysfunction of gastrointestinal tract. These positive effects are associated with the action of grape wine polyphenols [10]. Despite this, the molecular mechanisms of the protective action of wine remain insufficiently studied.

The pharmacological, medical, and biochemical properties of phenols are widely studied. Antioxidant, vasodilating, anti-oncological, anti-inflammatory, immunostimulatory, anti-allergic, antiviral and estrogenic effects are shown. Wine polyphenols inhibit phospholipase A2, cyclooxygenase, lipoxygenase, glutathione reductase, and xanthine oxidase, and chelate metal ions [9, 11–16]. *In vitro* wine polyphenols scavenge free radicals, including superoxide anion radical ($O_2^{\bullet -}$), hydroxide radical ($OH^{\bullet}$), and inhibit lipid peroxidation [9, 12, 17, 18].

In cells incubated with phenols, the expression of genes encoding proteins involved in antioxidant detoxification is induced. These genes are regulated by a specific enhancer, the antioxidant response element (ARE). Red wine polyphenols can alter Nitric oxide synthase (NOS) activity due to the effect on cellular concentration of Ca^{2+} and the phosphorylation of key proteins of the phosphatidylinositol-3′ kinase/Akt pathway after short incubation with cells. After long-term incubation, polyphenols alter NOS activity by regulating the expression of the genes of the constitutive isoforms of NOS enzyme [12, 17, 19, 20].

In vivo studies are less convincing; some indicate the effect of wine on the antioxidant system of blood cells and the oxidation of low-density lipoproteins [17, 21, 22].

Most dietary polyphenols are absorbed in the intestine by passive transport, intensively metabolized in the small and large intestine and liver, where they are converted into metabolites with higher antioxidant and estrogenic activity.

Sulfated, glucuronidated, and methylated polyphenols were found in blood plasma. Moreover, a large part of polyphenols undergo hydrolysis and degradation under the action of intestinal microflora to simple phenolic compounds [12, 14, 16, 21, 23]. Metabolites of polyphenols circulate in the blood in a protein-bound form, in particular with albumin, which plays an important role in regulating the bioavailability of polyphenols. The affinity of polyphenols to albumin varies depending on their chemical structure. Albumin binding determines the rate at which metabolites are delivered to cells and tissues or excreted. The accumulation of polyphenols in tissues is the most important stage of polyphenol metabolism because it preserves the necessary concentration for the biological effects of polyphenols. Polyphenols easily penetrate tissues, especially the intestines and liver. Polyphenols excretion and their derivatives occur in urine and bile. In this case, large conjugated metabolites are more likely to be excreted in the bile, while small conjugates, such as monosulfate, are preferably excreted in the urine. The amount of metabolites excreted in the urine correlates with the maximum concentration in plasma [24].

1.2 Composition of phenols in grape wine

Phenols include more than 8000 natural compounds. Their molecule contains phenol (aromatic ring with at least one hydroxyl group). Phenols are classified into polyphenols and simple phenols, depending on the number of phenolic rings in their molecules. Simple phenols include phenolic acids. The group of polyphenols, i.e. phenols that contain at least two phenolic rings, includes flavonoids, stilbenes, and tannins (containing three or more phenolic rings) [11, 13–16, 18, 24].

Flavonoids are a large group of low molecular weight polyphenolic compounds. According to the degree of oxidation of the pyranose ring, hydroxylation of the nucleus and properties of the substituent at the third Carbon atom, flavonoids are divided into subclasses: flavones, isoflavones, flavanols (catechins), flavonols, flavanones, anthocyanins and proanthocyanidins [11, 14, 24–26].

Flavonoids have a vasodilating effect. They cause vascular smooth muscle relaxation, probably mediated by inhibition of protein kinase C or decreased Ca^{2+} uptake by cells [14].

Flavan-3-ols, in particular (−) - epicatechins, (+) - catechins, gallates, and products of their methylation, decarboxylation, and dehydroxylation, as well as quercetin (3,5,7,3′,4′-pentahydroxyflavone), activate antioxidant enzymes. Herewith, quercetin is effective at lower concentrations (5–20 μM) than catechins (500 μM - 1 mM) [27].

Catechins affect cell apoptosis by altering the expression of antiapoptotic or proapoptotic genes. Epicatechins inhibit apoptosis by activating genes of Bcl family proteins and inhibiting caspase-6 activity and Bax, Bad, and Mdm2 gene expression. These compounds also ensure cell survival by activating protein kinase C. It should be noted that at low concentrations flavan-3-ols have an antiapoptotic effect, and at high concentrations (50–500 mM) they promote cell death by the mechanism of apoptosis [28].

Grape wine anthocyanins (malvidin, delphinidin, peonidin, petunidin, and cyanidin) are most often identified in the glycosylated form. It has long been thought that glycosylation is the only pathway for anthocyanin metabolism, but glucuronides and sulfates of these polyphenols have recently been identified [2]. Plasma concentrations of anthocyanins are too low to capture reactive oxygen species (ROS) and reactive nitrogen species (RNS). But anthocyanins are potent antioxidants because they can affect NO content and its stable metabolites. Consumption of 16–500 μM of anthocyanins reduces NO production by more than 50%, mainly due to inhibition of inducible NOS. In this case, anthocyanins do not

cause cytotoxicity [3]. Like other flavonoids, anthocyanins and anthocyanidins poses antioxidant properties. Anthocyanins act as donors of electron or to transfer a hydrogen atom of hydroxyl groups to free radicals [29]. Isolated anthocyanins and a suspension of flavonoids enriched with anthocyanins prevent the disruption of DNA molecule, the development of hormone-dependent pathologies (affect estrogen secretion), regulate immune response by preventing excessive production of cytokines [30]. Anthocyanins exhibit also an anti-inflammatory activity by inhibiting transcription factor NF-κβ. The content of several NF-κβ-dependent chemokines, cytokines, and inflammatory mediators decreases in the plasma and monocytes of healthy people after consumption of anthocyanins [30, 31].

In plants are also synthesized other phenols – non-flavonoids (phenolic acids, tannins, and stilbene), which are also present in grapes and wine.

Phenols, which include one functional group of carboxylic acid called phenolic acids. There are two groups of phenolic acids – hydroxycinnamic and hydroxybenzoic acids. To hydroxycinnamic acids belong *p*-coumaric, caffeic, ferulic, caftaric, coutaric, and coumaric acids. The example of hydroxybenzoic acids is gallic acid [11, 14, 21, 24].

Gallic acid (3,4,5-trihydroxybenzoic acid) is the phenol that is best absorbed into cells and exhibits various biological properties [2, 32]. Gallic acid and its derivatives (unconjugated and conjugated 4-O-methylgallic acid, 2-O-methylgallic acid, pyrogallol, 4-O-methylpyrogallol, resorcinol) in a dose-dependent manner inhibit tyrosine kinases, inhibit P-selectin exposure on the surface of blood cells, affect the release of Ca^{2+} into the cytoplasm, free radicals formation and thus modify cellular signaling pathways [33, 34]. Gallic acid and (−) -epicatechins inhibit NO formation by inhibiting the formation of mRNA of iNOS in immunocompetent cells [30].

Hydroxycinnamic acids cause an increase in the activity of cellular antioxidant enzymes (superoxide dismutase, catalase, glutathione peroxidase, and glutathione reductase) by activating the transcription of their genes [5, 35].

The family of stilbenes includes resveratrol, pterostilbene, and piceatannol, which are characterized by the presence of a double bond connecting phenolic rings [14, 24]. Resveratrol has anti-infectious, antioxidant, cardioprotective, anti-proliferative, and pro-apoptotic activities. It induces apoptosis by activating signaling pathways mediated by phosphorylation of p53 proteins, protein kinase C, MAPK or through the death receptor Fas/CD95/APO-1 [36].

Tannins are polymer compounds, divided into two groups (condensed and hydrolyzed). Condensed tannins are polymeric flavonoids. Hydrolyzed tannins include gallotannins, that are gallic acid polymers, and similar in structure esterified compounds [14]. These plant polyphenols are powerful antioxidants that protect against free radical damage and, as a result, reduce the risk of skin cancer and premature aging [15].

It is known that the consumption of white or red wine causes various effects. The reason for this is the differences in the quantity and quality of polyphenols in different varieties of grape wines. The bioavailability of phenolic compounds also plays a crucial role [18]. For example, data on the absorption and the kinetics of disproportion of quercetin indicate that a glass of red wine is a much poorer source of this compound than a cup of black tea and onions [37].

It should be taken into account that excessive consumption of wine has a toxic effect on the body. Using concentrated preparations of natural polyphenol complex of grape wine can be promising, as it will allow to obtaining the required useful dose of phenolic compounds and reduce wine consumption.

Today, a large number of methods to obtain a concentrate of phenolic compounds of grape wine have been developed. The technique of lyophilization, which consists in drying polyphenolic compounds in a vacuum with pre-freezing of wine,

is most often uses in the industry. The method of isolating polyphenols through a column and their subsequent drying by spraying is quite common. Although these methods prevent the loss of phenolic compounds, however, the obtained dry preparations are poorly soluble in water, which reduces their value [38]. To obtain a polyphenol concentrate, we chose the method of evaporation of dry red grape wine, in the optimal conditions for the preservation of polyphenolic compounds present in the raw material. Obtained concentrate contained also monomeric polyphenols, which were found in wine [39].

The following substances were detected in the obtained concentrate: anthocyanins (malvidin, delphinidin, peonidin, petunidin, cyanidin), flavones (quercetin, quercitin-3-O-glycoside), flavan-3-ols ((+)-catechins, (−)-epicatechins), phenolic acids (gallic, caftaric, coutaric, syringic). This spectrum of polyphenols probably determines the antioxidant and antidiabetic properties of the obtained concentrate [40, 41].

1.3 Antidiabetic action of red wine polyphenols

Chronic hyperglycemia in diabetes mellitus causes chronic inflammation, which are accompanied by relapses and are difficult to treat. Diabetes mellitus causes damage, dysfunction, or insufficiency of various organs and systems, including eyes, kidneys, nervous system, heart, and blood vessels.

In recent years, there has been growing evidence that plant polyphenols, due to their biological properties, can be an unique dietary supplement and additional treatment for various aspects of diabetes. Natural polyphenols are potential multifunctional agents that reduce the risk of developing diabetes and diabetic complications [42]. Red wine polyphenols significantly increase the sensitivity of peripheral tissue cells to insulin in diabetes [25].

Decreased insulin secretion in diabetes is often combined with reduced sensitivity to this hormone in peripheral tissues. The lower sensitivity of tissues to insulin can be diagnosed using a glucose tolerance test. It allows to obtain information about the dynamics and degree of assimilation of carbohydrates and identify possible violations of this process [43, 44].

When administered polyphenol complex to animals with diabetes mellitus during 14 days, fasting blood glucose was 9.8 mmol/l (in control this index was 4.9 mmol/l). 15 min after *per os* glucose administration, the level of glucose was increased and reached a maximum after 60 minutes (13.9 mmol/l). The concentration of glucose in the blood was 1.5 times lower than the values at the same time point in animals with diabetes [45].

Hypoglycemic effects of polyphenolic compounds may be associated with inhibition of carbohydrate digestion. Polyphenols inhibit α-amylase and α-glucosidase activity, slowing glucose absorption in intestine, stimulate insulin secretion, and protect pancreatic β-cells against glucose toxicity. Polyphenols can inhibit the release of glucose by liver cells by affecting hepatic glucose homeostasis, in particular glycolysis, glycogenesis, and gluconeogenesis, which are impaired under diabetes mellitus. Polyphenols also activate insulin receptors or stimulate glucose uptake into insulin-sensitive tissues [46–48]. In addition, some polyphenols, including resveratrol and quercetin, contribute to the preservation of the integrity of pancreatic β-cells in rats with streptozotocin-induced diabetes against oxidative stress damage, thus help maintain normal insulin levels [48].

During carbohydrates metabolism glucose, fructose, or glucose-6-phosphate can non-enzymatically bound to proteins, including hemoglobin. This is a glycation reaction, the essence of which is the non-enzymatic addition of free aldehyde groups to free amino groups of proteins. Under hyperglycemia, excessive glycation

is observed. The structure and function of glycated proteins change, which leads to cell damage and various diabetic complications [49, 50].

Glycated hemoglobin (HbA1c) reflects the average glucose level for the previous 2–3 months and is one of the reliable diagnostic criteria for diabetes [51]. Accordingly, this indicator has become one of the main standard methods for assessing the level of glycemia and the effectiveness of its correction, as well as the most important way of long-term metabolic control over the course of diabetes [52].

It was found that the content of glycated hemoglobin increases in the blood of rats with diabetes mellitus compared with control. In the condition of polyphenolic complex concentrate administration to animals with diabetes, we observed the normalization of glycated hemoglobin content [53]. The decrease in the level of glycated hemoglobin under the administration of polyphenolic complex to animals with diabetes mellitus indicates a stable long-term hypoglycemic effect of the studied concentrate.

Revealed properties to regulate glucose tolerance and reduce the level of glycated hemoglobin justify the possibility of using polyphenolic compounds of wine as a basis for the development of new adjuvant antidiabetic therapeutic agents or to prevent the development of diabetic complications.

1.4 Antioxidant potential of polyphenols of red wine

Due to the peculiarities of the chemical structure, all phenols are able to neutralize the electron of free radicals and form relatively stable phenoxyl radicals and thus stop oxidative chain reactions in cells [24]. Polyphenols can scavenge ROS and RNS, lipoperoxide radicals, and can chelate metal ions such as iron and copper, which play an important role in initiating free radical reactions [15]. Thus, these compounds realize antioxidant and anti-inflammatory activity. There are data in the literature on the ability of some polyphenols to affect cellular signal transduction [30], to modulate the functioning of the endocrine system, and hence the action of hormones on various physiological processes, as these compounds react with metal ions and enzymatic cofactors [11].

It is noted that the obtained concentrate of natural polyphenol complex of red wine showed antioxidant properties, at the level of individual tissues and organs and at the level of the whole organism under low level irradiation and experimental diabetes mellitus [45, 53–55]. The use of polyphenolic complex concentrate helped to prevent the accumulation of lipoperoxidation products, which indicates the powerful antioxidant properties of polyphenolic components of red grape wine. Polyphenols react with ROS and convert them into products with much lower reactivity. It is believed that the most effective protection of the lipid bilayer is provided by more hydrophobic polyphenols. Epicatechin gallate has been shown to be soluble in the membrane lipid bilayer and is a highly effective protector under excessive lipid peroxidation [56, 57].

The level of ROS in the cell is controlled by the endogenous system of antioxidant protection. However, under pathological conditions, the production of ROS increases, and, at the same time, the mechanisms of antioxidant protection are disrupted [58–60]. Polyphenolic compounds cause a decrease of ROS level by normalizing the activities of antioxidant enzymes. The ability to affect the endogenous antioxidant system has a large number of phenolic compounds present in grape wine. In particular, flavan-3-ols, ((−) - epicatechins, (+) - catechins, gallates and products of their methylation, decarboxylation and dehydroxylation), quercetin, hydroxycinnamic acids (caftaric, coutaric and coumaric acids) activate transcription of genes of the enzymes.

It is known that red wine polyphenols increase the antioxidant capacity of plasma and other tissues of animals and humans. This effect is associated with the stimulation of the activity of superoxide dismutase, catalase and glutathione peroxidase and with an increase in the content of both reduced and oxidized glutathione [10, 14, 38, 61].

It was established a decrease of NOS total activity in peripheral blood, leukocytes, aorta and kidneys of rats after low doses irradiation on the background of polyphenolic complex concentrate consumption. The same effect was found in leukocytes, erythrocytes, pancreas and heart of rats with streptozotocin-induced diabetes mellitus [62]. It was detected a lowering in the total content of nitrites and nitrates in the case of X-ray irradiation in peripheral blood, leukocytes, aortic and renal tissues [40, 45, 63–66]. Under conditions of streptozotocin-induced diabetes mellitus, it was observed a significant decrease in the content of nitrite and nitrate in leukocytes, in peritoneal macrophages and in pancreas in the case of polyphenol complex concentrate consumption.

It is known that polyphenolic compounds of grape wine have the ability to capture and neutralize NO and its metabolites. Due to this, polyphenols can also prevent the development of oxidative-nitrative stress.

Grape wine anthocyanins (malvidin, delphinidin, peonidin, petunidin and cyanidin) are potent antioxidant because they can affect NO content. One of the possible mechanisms of polyphenols influence on the level of NO is the regulation of the activity of NO synthases. It is known that phenolic compounds show diverse effects on the activity of various isoforms of the enzyme: they inhibit neuronal NOS (nNOS) and inducible NOS (iNOS) and increase the activity of endothelial NOS (eNOS). In blood cells has been detected inhibition of mRNA translation of iNOS, the synthesis of which is induced by lipopolysaccharides, interleukin-1 or tumor necrosis factor α (TNF-α) [28, 31]. Catechins scavenge NO and peroxynitrite, inhibit the activity of neuronal and inducible NOS by inhibiting the binding of nuclear factor NF-κβ to the NOS gene promoter. For example, catechins activate endothelial NOS in rats aorta by binding to the antioxidant response element (ARE) of the promoter of the eNOS gene [17, 19, 21, 28, 30, 31, 67].

This effect on NOS activity is offset by an increase in Ca^{2+} concentration due to release into the cytoplasm from intracellular depots or a receptor-dependent mechanism, the key event of which is an increase in guanylate cyclase activity in cells. As a result, the activity of eNOS increase, as this isoform of the enzyme is calcium-dependent [12]. A number of authors describe the ability of catechins, anthocyanins, quercetin, and other wine polyphenols to activate eNOS by phosphorylation mediated by activation of the Src/PI3′-kinase/Akt signaling pathway. This mechanism is dependent on the intracellular generation of ROS.

However, much more attention today is paid to the role of peroxynitrite ($ONOO^-$). Peroxynitrite is a powerful prooxidant and cytotoxin, interacting with lipids, DNA and proteins in oxidation, nitration and nitrosylation reactions cause cell damage and cell death [68–73].

Modern strategies aimed at limiting the formation of cytotoxins are the use of various herbal compounds with the ability to neutralize RNS *in vitro*, in particular, $ONOO^-$, for example, phenolic compounds of grapes and grape wine [69]. It was shown that polyphenolic compounds from grape wine regulate the intensity of protein nitration processes in leukocytes, aorta and kidney cortical layer of irradiated rats and in erythrocytes of animals with diabetes mellitus [40, 63, 64]. The decrease in the content of 3′-nitrotyrosine-modified proteins may be due to the ability of grape polyphenolic compounds to detoxify NO, $ONOO^-$, and other RNS. Similar effects of grape wine polyphenols on the level of nitrated proteins have been described in the literature [74, 75].

Our results open up prospects for the use of drugs, the main active ingredients of which are phenolic compounds, as adjuncts in complex therapy and prevention of damage to the blood system, cardiovascular and excretory systems caused by ionizing radiation. Drugs of complex action, which will inhibit the development of oxidative-nitrative stress, will be effective treatment of different diseases, including diabetes mellitus and radiation sickness.

2. Yacon as a source of bioactive compounds with antidiabetic and antioxidant potential

Today there is an urgent need for effective drugs for the treatment of metabolic disorders, the etiological cause of which is a violation of the redox status of cells. A successful strategy for finding such substances is to search for them among agents of natural origin due to their lower generation of side effects and the availability in obtaining material.

One of the promising plant is yacon, which has been discovered antidiabetic and antioxidant properties [76].

Yacon (*Smallanthus sonchifolius* (Poepp. and Hendl.) H. Robinson) is also known by its old name *Polymnia sonchifolia* Poepp. & Endl. Such a discrepancy in the classification of this plant is due to the fact that it was described for the first time as *Polymnia sonchifolia* Poepp. by Eduard Friedrich Poeppig in 1845. Afterward in 1978 genus *Smallanthus* (Asteraceae, Heliantheae) was rediscovered by Harold Ernest Robinson, who established the *Smallanthus* gender by separating *Polymnia* [76, 77]. Yacon is known to mankind for centuries, it was found in burial grounds from centuries before the Incas. This plant was represented on textile and ceramics in a littoral archeological deposit Nazca (500–1200 A.C.). 1653 is a year of first written allusion on yacon comes from the chronicler Padre Bernabé Cobo [77]. Until the 1980s, the scientific community paid little attention to yacon. The plant itself originates from the Andean region, from where it spread to New Zealand, Japan, and Brazil. Today it is cultivated in many countries around the world, including Ukraine.

2.1 Phytochemical profile of *Smallanthus sonchifolius* tuberous roots

Yacon is a perennial plant with underground tubers that are grouped in clump. Average tuber weight fluctuates from 100 to 500 g, and rarely reaches more than 1 kg [77]. Yacon root tubers have great nutritional potential due to its sweet taste and lower energy content (619–937 kJ/kg of fresh matter) provided by its 70% water composition [78].

The underground storage organs of yacon accumulate mainly low molecular mass oligomeric (GF2–GF16) inulin-type β(2 → 1) fructans (over 60% on a dry basis). The main *fructooligosaccharides (FOS)* are nystose, 1-kestose, and 1-fructofuranosyl nystose [79, 80]. Storage compounds of yacon tubers are low in glucose content and by the structure are of the inulin type, i.e. β(2 → 1) fructofuranosyl saccharose or fructooligosaccharides [77]. These FOS are mainly represented by oligosaccharides from trisaccharide to decasaccharide with terminal saccharose [81]. FOS derived from yacon are linear fructooligosaccharides containing almost exclusively (2 → 1)-linked β-fructofuranosyl units, with terminal α-glucopyranosyl and β-fructofuranosyl units [82].

β(2 → 1) fructans of the inulin-type are considered to be dietary fiber or the indigestible residues of plant origin due to lack of enzymes in humans body capable to hydrolyze the β(2 → 1) bond in such compounds. Because FOS do not digest in

the human gastrointestinal tract and they transported to the colon they recently been classified as prebiotics. In the colon they undergo fermentation into short-chain fatty acids (acetate, propionate, and butyrate), lactic acid, carbon dioxide, and hydrogen by selected species of gut microbiota, especially *Bifidobacterium* and *Lactobacillus* [77, 82].

FOS except as prebiotics can be used as non-specific immunostimulators. Mechanisms of such effect can be indirect by shifting the composition of the intestinal flora and enhanced production of immunoregulatory short-chain fatty acids. On the other hand, it was suggested that fructooligosaccharides can possess direct effects on the intestinal epithelial cells and immune cells through binding to carbohydrate receptors [82].

S. sonchifolius roots are also rich in *fructose, glucose, sucrose*, amount of which fluctuates during the growing cycle, and harvest [77, 78, 80].

Other important biologically active substances in the composition of yacon root tubers are *phenolic compounds*. The phenols group include chlorogenic acid, protocatechuic acid, p-coumaric acid, ferulic acid, and caffeic acid derivatives [77–79]. Phenolic acids have a high antioxidant potential result from the presence of an aromatic ring, a carboxyl group, and one or more hydroxyl and/or methoxyl groups in the molecule [83]. Yacon tubers have been identified as a source of flavonoids including quercetin and some unidentified flavonoids [77, 84]. Flavonoids can be found only in acid-hydrolyzed yacon tubers and have an influence on lipid peroxidation, acetylcholinesterase, and butyrylcholinesterase [80].

The most abundant *amino acid* in this part of the plant is tryptophan known as a precursor of serotonin and melatonin. This compound eliminates free radicals from the oxidative damage low-density lipoprotein [80]. Chlorogenic acid and tryptophan were identified as two of the major antioxidants of yacon roots [85].

From yacon tuber have been isolated 4′-hydroxyacetophenone, 4′-hydroxy-3′-(3-methylbutanoyl) acetophenone, 4′-hydroxy-3′-(3-methylbutenyl) acetophenone, and 5-acetyl-2-(1-hydroxy-1-methylethyl) benzofurane which are related antifungal *phytoalexins* that possess antimicrobial activity [77, 80].

Also, *S. sonchifolius* root contains small amounts of *vitamin C and potassium* [80].

2.2 Phytochemical profile of *Smallanthus sonchifolius* leaves

Smallanthus sonchifolius stems can reach 2 m in height are densely foliaged with dark green leaves and covered by violet-colored trichomes. The inflorescence grows at the top of the main stem is small (30 mm in diameter), with a yellow or orange color. The fruits are black, about 2 mm small [77]. Yacon leaves, next to the root tubers, also have a high potential, both in nutritional purposes and in medical practice. It can be consumed as a tea, also can be used as a material for raw and organic extracts [78].

One group of compounds that can play an essential role in antioxidant and antidiabetic properties of yacon leaves is *phenolic compounds*. The compounds were identified as chlorogenic, caffeic, ferulic, gallic, and gentisic acids [77], also protocatechuic, rosmarinic, vanillic and gentisic acids, as well as 3,4- dicaffeoylquinic, 3,5-dicaffeoylquinic and 4,5- dicaffeoylquinic isomers of dicaffeoylquinic acid [86].

S. sonchifolius leaves are rich in flavonoids, such as luteolin 3′,7-O-diglucoside and luteolin 7-O-glucoside together with apigenin and luteolin [86], 5, 7-dihydroxy-4′-methoxyflavonol, 5, 7, 3′-trihydroxy-4′-methoxyflavonol, 5-hydroxy-4′-methoxy-7-O-glycosilflavone and 7,4′-dihydroxy-3,5′-dimethoxyflavone [87]. Presence of polyphenols in yacon leaves predetermine its acrid and astringent flavor and characteristic odor. Due to the high antioxidant capacity of polyphenols these

compounds may play an important role in lowering the risk of cancer, cardiovascular disease, atherosclerosis, and diabetes [80]. It can be concluded that yacon is a very rich source of antioxidants. Regarding the content of phenolics and phenolcarboxylic acids, the yacon parts could be arranged in such an order: rhizomes >leaves > stems > tuberous roots [88]. The fact that not only yacon leaves but also its root part are rich in antioxidants is valuable for search of effective means against hyperglycemia.

Terpenes in yacon leaves determine its antifungal properties. To substances with such properties belong *ent*-kaurenoic acid, and related diterpenoid substances *ent*-kaur-16-en-19-oic acid 15-angeloyloxy ester, 18-angeloyloxy-*ent*-kaur-16-en-19-oic acid and 15-angeloyloxy-*ent*-kauren-19-oic acid 16-epoxide, as well as 4-hydroxystyrene and 3,4-dihydroxystyrene. Antifungal properties also possess melampolide-type sesquiterpene lactones sonchifolin, polymatin, uvedalin, and enhydrin from leaves [77], as well as smallanthaditerpenic acids A, B, C and D [89]. Recently were identified propionate and butyrate analogs of sonchifolin, tiglate analog on C8 of polymatin B, fluctuadin, polymatin C and the aldehyde derivative on C14 of uvedalin. Some of above-mentioned terpenes (sonchifolin, uvedalin, enhydrin, and related compounds fluctuanin, 8β-tigloyloxymelampolid-14-oic acid methyl ester and 8β-methacryloyloxymelampolid- 4-oic acid methyl ester) are also reported to be antibacterial compounds [77, 79, 80]. The main lactone of yacon leaves is enhydrin that has antidiabetic properties, so much so that it was included in a patented anti-diabetic pharmaceutical formulation [90]. Melampolide-type sesquiterpene lactones shown to inhibit NO production in LPS-stimulated murine macrophage RAW 264.7 cells [91]. Sesquiterpene lactones also can regulate the immune response. Enhydrin and uvedalin, inhibit the NF-κB, a transcriptional factor that has a central role in the transcription of the genes related to the inflammatory process [92]. Enhydrin, uvedalin and sonchifolin inhibited cell proliferation and induced apoptosis in cervical cancer cells. Their apoptotic effect is associated with caspase-3/7 activation and NF-κB inhibition [93].

Major unsaturated *fatty acids* found in yacon leaves extracts were gamma-linolenic (ω-6), eicosapentaenoic (ω-3), and linoleic (ω-6) acids. In addition, in this part of the plant were found lauric, myristic, pentadecanoic, palmitic, palmitoleic, margaric, stearic, oleic, arachidic, eicosatrienoic, di-homo-alpha-linolenic, heneicosanoic, behenic, eicosadienoic, and docosahexadienoic acids [94]. Polyunsaturated fatty acids in addition to their anti-inflammatory, vasodilator, antihypertensive, and immunosuppressive effects can cause the reduction of plasma lipids amount and normalize hyperglycemia [95].

Yacon leaves contain a wide range of *essential oils* such as beta-pinene, caryophyllene, y-cadinene, β-phellandrene, β-cubebene, β-caryophyllene and β-bourbonene [86].

2.3 *Smallanthus sonchifolius* antidiabetic potential

The possibilities of innovative technologies in the pharmaceutical industry make it possible to expand the range of search for effective natural substances as a form of additional or substitution therapy of different pathological conditions. Natural substances affect not only carbohydrates but also lipids metabolism, regulate water balance, and normalize the functional state of the kidneys and liver. Herbal preparations support the state of long-term compensation for diabetes mellitus. In folk medicine around the world for the treatment of diabetes, aqueous extracts of yacon are widely used.

One of the biochemical methods for diagnosing carbohydrate metabolism disorders, in particular, in diabetes mellitus, is a glucose tolerance test. This approach

allows checking the dynamics and degree of glucose absorption in the body and identifying possible violations of this process. The rate of decrease in glucose levels after oral administration depends mainly on the function of the cells of the islets of Langerhans of the pancreas.

Glucose tolerance test is a convenient tool for analyzing not only changes in the efficiency of carbohydrate absorption but also can be a convenient tool for assessing the effectiveness of treatment aimed at reducing postprandial hyperglycemia. This approach is often used to assess the antidiabetic potential of medicinal plants.

A screening study showed that under conditions of glucose load in healthy animals, different parts of the aboveground part (leaves, petioles, stems) of yacon have different hypoglycemic effects. A comparative analysis of the hypoglycemic effect of aqueous extracts of the aboveground part of yacon showed that the highest and longest hypoglycemic effect after single oral administration possesses yacon leaves extract. It should be noted, that in control animals, the hypoglycemic effect was achieved at a dose of 0.07 g per kg of weight of the animal [96]. No such pronounced hypoglycemic effect was found while administering a similar dose of yacon leave extract to animals with experimental diabetes mellitus. However, increasing the dose of the extract to 0.5 g per kg of animal weight led to a significant improvement in the absorption of exogenous glucose by animals with experimental diabetes mellitus [97]. In addition to convincing data on the hypoglycemic effect of the aqueous extract of yacon leaves obtained by the glucose tolerance test, a pronounced hypoglycemic effect of this extract was also demonstrated when administered it to rats with diabetes for 14 days [98]**.** This study confirmed that an effective hypoglycemic effect has an aqueous extract of yacon leaves at a dose of 0.5 g per kg of body weight. When using the extract at this dose, a significant decrease in both plasma glucose and glycosylated hemoglobin was shown [98].

Some authors attribute the hypoglycemic effect of yacon leaves to the presence of a number of biologically active substances, among which polyphenols play an important role [77, 99]. Chlorogenic acid has been shown to inhibit the enzyme glucose-6-phosphatase, thus, affecting the metabolism of carbohydrates (glycolysis, glycogenolysis, and gluconeogenesis). Some studies have shown that polyphenols derived from aqueous extracts of yacon leaves inhibit alpha-amylase and sucrose. They also inhibit glucose transport through gastrointestinal cells by inhibiting the functioning of the sodium glucose co-transporter (S-GLUT-1) [86]. The yacon leaves contain enhydrin, which increases the number of β-cells and the level of insulin mRNA in the pancreatic islets of rats with streptozotocin-induced diabetes [90]. Enhydrin also inhibits α-glucosidase activity, a similar inhibitory effect possesses smallanthaditerpenic acids A, B, C, and D isolated, which are also contained in the leaves of yacon [89, 90].

The uniqueness of yacon as a source of biologically active substances for the treatment of diabetes is that their source can be not only the aboveground part of the plant but also the root tubers. A comparative analysis of the hypoglycemic effect of water extracts of yacon roots in healthy animals in a dose of 0.07 g per kg of weight of the animal suggests that a more pronounced hypoglycemic effect has an extract of yacon root tubers, while the extract of root tubers peels possess much less pronounce effect [96]. However, another study showed that a dose of 0.07 g per kg of body weight of water extract of root tubers is insufficient for hyperglycemia compensation. Only the use of the extract at a dose of 0.5 g per kg leads to significant changes in the dynamics of exogenous glucose uptake under conditions of streptozotocin-induced experimental diabetes mellitus [100]. An additional approach in the creation of drugs based on plant raw materials is their use in the form of suspensions. The advantages of this form of medicines include the production of medicines of prolonged action by regulation of duration of their action by

changing in the size of medicinal raw materials particles, simultaneously usage of soluble and insoluble medicinal substances, allow mask unpleasant taste and smell of medicines. Suspensions prepared by mixing homogeneous powdered root tubers with water (at a dose of 0.5 g per kg) significantly affect the intensity of glucose uptake in animals with experimental diabetes mellitus. Interestingly, the use of surfactants to stabilize the physical properties of the suspension increases its hypoglycemic effect. Comparing all forms of yacon underground part administration, yacon root tubers when they are used in the form of stabilized suspension possesses the best hypoglycemic effect [100, 101]. Long-term use (within 14 days) of the extract and suspensions of yacon root tubers in diabetes has shown a pronounced hypoglycemic effect. The use of water extract in doses 0.07 and 0.5 g per kg of body weight causes a significant reduction of plasma glucose level. However, only the use of the extract in a higher dose caused a significant decrease in the level of glycosylated hemoglobin. Suspensions of yacon root tubers stabilized with surface-active substances of biogenic origin at fourteen days of use also caused a significant decrease in both glucose and glycosylated hemoglobin in diabetic animals. Non-stabilized form of the suspension had a less pronounced hypoglycemic effect. The authors attribute this to the fact that the addition of surfactants to the suspension increases its stability and bioavailability of biologically active substances [98].

The hypoglycemic effect of yacon root tubers is less studied. The sugar-lowering effect of this part of the plant may be due to presence in its composition a high FOS content that can change the kinetics of carbohydrates absorption. As mentioned above FOS do not decompose in the gastrointestinal tract, can absorb a great amount of exogenous glucose. High absorption ability of FOS interferes with glucose transportation into blood, which causes a decrease in the level of blood sugar after meals. The stable decrease in the level of glucose causes normalization of insulin production by pancreatic cells. Intestine microorganisms hydrolyze FOS into smaller fragments and free fructose. Short fragments of FOS molecules facilitate the transportation of glucose into the cell by inserting into the cell membrane [102]. FOS also modulates concentrations of GIP (glucose-dependent insulinotropic polypeptide) and GLP-1 (glucagon-like peptide 1) - peptides that regulate insulin release after meals [103]. Some yacon root tubers' hypoglycemic effect can be attributed to essential amino acid L-tryptophan. It is known that this amino acid normalizes tolerance to carbohydrates and elevates the insulin level. In hepatocytes, L-tryptophan increased activity of glucokinase, hexokinase, and glucose-6-phosphate dehydrogenase that are the key enzymes of the carbohydrate exchange [85].

Hypoglycemic effect of yacon leaves and root tubers is very valuable in the development of antidiabetic medicines in terms of counteracting the harmful effects of hyperglycemia as an etiological cause of chronic diabetic complications.

2.4 *Smallanthus sonchifolius* antioxidant potential

The advantages of yacon as a source for the creation of effective antidiabetic medicine is that it has a high content of antioxidant compounds. Extract of the yacon leaves possesses the free radical scavenging activity and inhibitory effects on lipid peroxidation in rat brain and liver [104, 105]. *S. sonchifolius* leaves extracts show antioxidant activity in 1,1-diphenyl-2-picrylhydrazyl and xanthine/xanthine oxidase superoxide radical scavenging tests [106]. Similar effects perform extracts from yacon tuberous roots [85, 107].

Red blood cells are one of the most suitable models for the investigation of the antioxidant effect of plant material. During their circulatory life span, erythrocytes are continuously exposed to glucose. The glucose concentration in the erythrocyte

cytosol is close to that in the plasma because is ensured by passive transport through GLUT1 (insulin-independent glucose transporter) [108, 109].

Hyperglycemia induced generation of free radicals is a plausible contributing factor of lipid peroxidation the intensity of which is reliably evidenced by the level of thiobarbituric acid reactive substances (TBARS). Water extracts of *S. sonchifolius* leaves in doses of 0.07 and 0.5 g per kg of body weight cause a significant reduction of TBARS in erythrocytes of diabetic rats. Extract in higher concentrations had a more pronounced protective effect on the peroxidation of erythrocyte lipids. The extract causes a similar effect on healthy animals. The development of oxidative stress in diabetes has a destructive effect not only on cell lipids but also significantly damages the structure of proteins. The level of such damage is indicated by protein carbonyl content (PCC). Yacon water extract cause PCC reduction on the condition of diabetes mellitus and such change was not dose-dependent [110].

One of the mechanisms of this antioxidant effect of yacon leaves extract may be its effect on antioxidant enzymes of cells. Indeed, it was established that the administration of yacon extract to diabetic rats (at a dose of 0.07 and 0.5 g/kg) causes increased activity of SOD in a dose-dependent manner. Interestingly, the extract in a lower concentration caused a more pronounced increase in CAT activity compared to its higher dose [110]. An additional mechanism of the antioxidant effect of yacon is its ability to inhibit the synthesis of myeloperoxidase that can cause causes oxidative damage of proteins and DNA [111].

The antioxidant effect of leaves extract may be caused by the presence of phenolic compounds. Chlorogenic and caffeic acid effectively scavenge N_2O_3, organic free radicals, HOCl, $O_2^{\bullet -}$, $OH^{\bullet}$, $ONOO^-$ and peroxyl radical. After the reaction of chlorogenic or caffeic acid with free radicals products that are formed rapidly broken down to the products which are unable to generate more free radicals. Thus, no other antioxidants are necessary for the reduction of such oxidation products [112]. Flavonoids by which leaves of yacon are rich in can reduce enhancement of transition metal oxidation by donating a $H^{\bullet}$ to them, rendering them less prooxidative. In addition, flavones and some flavanones can preferentially bind metals at the 5-hydroxyl and 4-oxo groups [113].

In the condition of diabetes, yacon root tubers in the form of water extract or suspensions cause a significant reduction of TBARS and PCC levels. Water extract of root tuber at a dose of 0.5 g per kg body weight causes a remarkable increase in SOD, CAT, and glutathione peroxidase activities, while in 0.07 g per kg body weight dose its effect was less pronounced. In comparison with the water extract, the suspensions obtained from the powder of yacon root tubers caused a smaller increase in the activity of the antioxidant enzymes of erythrocytes. However, the surfactant-stabilized suspension had a slightly higher antioxidant potential compared to non-stabilized one [110].

The antioxidant potential of the root part of yacon may be due to the high content of FOS. It was confirmed the significant antioxidant activity of inulin [114]. The ability of FOS to enhance the absorption of copper can reduce the deficiency of this element under the conditions of diabetes and as a result, might be one of the reasons for increased SOD activity in diabetes animals that were treated with yacon root tuber extract and suspension [115]. Similar to the leaves, yacon root tubers contain a number of phenolic compounds that have a pronounced antioxidant effect. In addition, yacon roots contain tryptophan, an antioxidant compound that scavenged hydroxyl radicals [116].

Effect of leaves and root tubers on the state of prooxidant-antioxidant balance of red blood cells may predetermine yacon as a promising source of biologically active substances that can be used for treatment and prevention of chronic diseases involving oxidative stress, among which diabetes mellitus is present [110].

Author details

Mariia Nagalievska*, Mariya Sabadashka and Nataliia Sybirna
Department of Biochemistry, Faculty of Biology, Ivan Franko National University of Lviv, Lviv, Ukraine

*Address all correspondence to: khmarija@gmail.com

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