ERURJ **2023, 2, 1, 177-209**
(Review)

A review on bioactive metabolites and great biological effects of Cranberry

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Received: 28th January 2023 , Revised: 30th January 2023, Accepted: 30th January 2023
DOI:10.21608/ERURJ.2023.190174.1009

ABSTRACT

The Cranberry (Genus *Vaccinium*) is characterized by its high content of acids, sugars, and antioxidants. Some of the latter have been studied for their potential action against the adhesion of bacteria and many microorganisms to the mucous membranes of the body. The effect observed is "mechanical" and not "bactericidal", so there is no risk of developing resistance phenomena. Cranberry and its juice were thus the first plant extracts in the world used to prevent the adhesion of Escherichia coli bacteria on the uro-epithelial cells lining the genitourinary tract and treat recurrent cystitis. It prevents stomach ulcers through prevention the attachment of Helicobacter Pylori bacteria to the stomach wall. Cranberry is used against dental plaque due to its anti-adhesion effect and has positive repercussions on the formation of dental plaque and gum inflammation. Cranberry products, made from the North American cranberry, have long been thought to be effective in helping prevent urinary tract infections (is one of the most common infections in women, requiring antibiotic treatment.). The American cranberry, which is mainly consumed in the form of cranberry juice (CJ), is regarded as a promising functional food for the prevention of chronic diseases such as cancer, heart diseases, type 2

diabetes, and oral diseases. The phenolic compounds found in cranberry, like catechin and epicatechins, Flavonoids, Anthocyanins, phenolic acid, flavan-3-ol, flavonol glycoside, polyphenols, proanthocyanidins B-type, and other phenolic compounds are contributed to the reduction of oxidative stress.

Keywords: Cranberry; Urinary Tract Infections; anthocyanidins

1. Introduction

The Cranberry (genus Vaccinium) is native to the swamps and bogs of North America. It belongs to the Heather family (Ericaceae), which is a very widespread family of about 125 genes and about 3500 species. Members of the family occur from polar regions to the tropics in both hemispheres. the plant (cranberry) has been traditionally used by the Indians for many purposes. In the past 25 years, research on cranberry components and cranberry products and clinical trials on urinary tract infections have continued to accelerate. nutritional alternatives like cranberry products to maintain health and reduce reliance on antibiotics may offer a solution.

Cranberries are a member of the heather family and are related to blueberries, bilberries, and lingonberries. are a group of evergreen dwarf shrubs or trailing vines in the subgenus *Oxycoccus* of the genus Vaccinium. In Britain, cranberry may refer to the native species *Vaccinium oxycoccos*, while in North America, cranberry may refer to Vaccinium macrocarpon. *Vaccinium oxycoccos* is cultivated in central and northern Europe, while Vaccinium macrocarpon is cultivated throughout the northern United States, Canada and This is the most commonly grown species but other types are not found in nature. Due to their very sharp and sour taste, cranberries are rarely eaten raw. In fact, they’re most often consumed as juice, which is normally sweetened and blended with other fruit juices. Other cranberry-based products include sauces, dried cranberries, and powders and extracts used in supplements [1-4]. Cranberries are rich in various healthy vitamins and plant compounds. Cranberry fruits are polyphenol-rich fruits such as anthocyanins proanthocyanidins (tannin), flavonol, flavonoids, phenolic acid, organic acids, and triterpenoids. They have been shown to exert multiple biological activities, for example, antibacterial, anti-inflammatory, antiadhesive, neuroprotective, anticancer, antifungal, antiviral, antioxidant, blood pressure regulation, chronic disease (kidney disease, heart disease, oral disease, type 2 diabetes). Many people consider cranberries to be a superfood due to their high

nutrient and antioxidant content. Research has linked the nutrients in cranberries to a lower risk of urinary tract infection (UTI), the prevention of certain types of cancer, improved immune function, and decreased blood pressure. [3-6]. Historically, Native Americans used cranberries as a treatment for bladder and kidney diseases, while early settlers from England used them to treat poor appetite, stomach complaints, blood disorders, and scurvy, and their juice was said to offer a variety of benefits for women (postmenopausal health and premenstrual syndrome (PMS) symptoms). Because of the antibacterial properties of cranberries, they're sometimes used in mouthwash. Previous research found that mouthwash containing cranberry extract reduced the presence of the *Streptococcus mutans* bacteria more significantly than a placebo. Streptococcus mutans are acid-producing bacteria that can colonize the surface of teeth and cause damage [4-8].

The review aims to shed light on recent studies on cranberries, including their nutrition facts and health benefits.

2. Bioactive metabolites in cranberry

2.1. Phenolic compounds

Several classes of phenolic compounds were observed in cranberry. They were classified into Flavonoids, Anthocyanins, phenolic acid, glucoside, flavan-3-ol, flavonol glycoside, polyphenols, proanthocyanidins B-type, organic acids, Mineral composition, considering each metabolite name, molecular formula, occurrence, geographical origins, extraction, and analytical method [5, 6, 11, 13, 16-18].

2.1.1. Flavonoids

Flavonols

Several flavonoids' compounds were detected and classified into myricetin-3-galactoside, quercetin-3-galactoside, quercetin-3-αL-arabinopyranoside, quercetin-3-α-L-arabinofuranoside, quercetin-3-rhamnoside and quercetin-3-O-pentoside (from 10.1 to 11.8%). Similar results were obtained by Oszmiański et al. and White et al. [3] [8]. Different methods of analysis were s used as UPLC-DAD, UPLC/MS, (LC-MS/MS), NP-HPLC profile, HPLC-UV, UPLC-MS/MS, **Table 1**, [3] [1] [4] [5].

Anthocyanins

Several Anthocyanins compounds were detected and classified into cyanidin-3-O-galactoside, cyanidin-3-O-glucoside, cyanidin- 3-O-arabinoside, peonidin-3-O-galactoside, and peonidin-3-O- arabinoside were analyzed by HPLC--diode array detector (DAD), UPLC-photodiode array detection, LC–Q-TOF–HPLC- MS and MS/MS as a method of analysis [7] [8] [1] [6] [1].

Flavan-3-ols and procyanidins

The most important groups of phytochemical compounds in cranberry fruit are polyphenolic compounds, strong antioxidant properties, and the ability to relieve chronic diseases and influence their sensory properties. The differences in the content of bioactive compounds depend on many factors such as the stage of maturity. The concentrations of polymer procyanidins (the major group of favan-3-ols) were heterogeneous and depended on the maturity of fruits, and they declined remarkably during fruit cv. 'Pilgrim', 'Stevens', and 'Ben Lear' ripening, by around 9.4, 15.2, and 19.0%, respectively, from the immature stage to the commercially mature stage. Similar results were obtained by Oszmiański et al. for cranberry cultivars 'Pilgrim', 'Ben Lear', and 'Stevens'. In addition, the content of favan-3-ol monomers [(+) catechin and (−) epicatechin] increased slightly during ripening from the immature stage to the commercially mature stage in cv. 'Pilgrim' (25%), and reduced in CVS. 'Stevens' and 'Bel Lear' (2.0 and 36.8%, respectively) [8] [3].

Cranberry fruit extract which is found in North America and France contains proanthocyanidins A-type and B-type which are extracted by 80 mL methanol and Shake at 200 rpm for 30 min or 6 mL 70% methanol, centrifugation and filtered through 0.45 μm PVDF using electrophoretic/LC or UV-Vis spectrophotometer [3] [11].

2.1.2. Phenolic acids

In cranberry, we detect several phenolic acid compounds which have been cautioned to be accountable for many health benefits and classify into dihydroxybenzoic acid, p-hydroxy benzoic acid, coumaric acid, sinapic acid, Chlorogenic acid, Benzoic acid, p-coumaric acid, caffeic acid, ellagic acid, syringic acid, ferulic acid, vanillic acid, gallic acid, and ascorbic acid which have a lot of biological activity and was observed that it can extract by 400 mL of boiling water, frozen

at -84°C, lyophilized under 5 mm-Hg or 400 mL of boiling water, frozen at -84°C, lyophilized under 5 mm-Hg pressure or 5 mL 70% methanol by 45 min sonication you can read more as shown in **Table 1**. Different methods of analysis used as HPLC with UV & MS and other methods are mentioned in **Table 1**, but HPLC column isolates separation is extraordinarily based upon mobile phase gradient ratios and pH, in addition to column flow rate, however, only a few investigators have characterized those parameters of their published isolation methods [3] [2] [10] [7].

2.2. Organic acids

Several organic acids compounds were detected and classified into citric acid, malic acid, and quinic acid [9] [1] [8] observed in **Table 1**.

2.3. Triterpenoids

Several triterpenoids compounds were detected being classified into ursolic acid, and oleanolic acid which is extracted by 150 mL of ethanol, filtered, then 150 mL of fresh ethanol or dissolved in 600 μL of a DMSO-d6 spiked with standard DSS and other methods as mentioned in **Table 1**. They were analyzed by different techniques such as NMR and multivariate analysis and HPLC. **Table 1** illustrates more about methods of analysis [1] [8].

2.4. Monosaccharides

Monosaccharides are classified into glucose, galactose, xylose, arabinose, rhamnose, and mannose found in cranberry fruit, supplement, and pomace which is extracted by 5 ml 70% methanol or by dichloromethane using HPLC/NMR, GC/MS respectively. polysaccharides from alcohol insoluble solids using anion exchange chromatography [12] [13] [14] [9] [16].

2.5. Mineral composition

In berry and leaf, we found a lot of mineral composition such as nitrogen, magnesium, calcium, Iron, copper, zinc, boron, sulfur, and potassium extracted by HNO3 vapors and re-dissolved in HCl solution or 60mL polyethylene bottles and pre-rinsed (0.45 μm) cellulose membrane filter using colorimetry or atomic [15].

Table 1. Bioactive metabolites described in cranberry:

Compound	Molecular formula	Occurrence	Geographical origin	Extraction procedure	Method of analysis	Reference
Flavonoids						
Quercetin	$C_{15}H_{10}O_7$	Fruit	North America	Ethanol 96%, acetonitrile, methanol	UPLC-DAD	4
				5 ml 70% methanol, centrifugation and filtered through 0.45 μm filter	UPLC/MS	3
				400 ml of boiling water, frozen at -84°c, lyophilized under 5 mm-Hg pressure	(LC-MS/MS)	2
Quercetin-3-galactoside	$C_{21}H_{20}O_{12}$	Fruit	North America	Ethanol 96%, acetonitrile, methanol	UPLC-DAD	4
Quercetin-3-αl-arabinopyranoside,	$C_{20}H_{18}O_{11}$	Fruit	North America	Ethanol 96%, acetonitrile, methanol	UPLC-DAD	4
Quercetin-3-α-l-arabinofuranoside	$C_{20}H_{18}O_{11}$	Fruit	North America	Ethanol 96%, acetonitrile, methanol	UPLC-DAD	4
Quercetin-3-rhamnoside	$C_{21}H_{20}O_{11}$	Fruit	North America	Ethanol 96%, acetonitrile, methanol	UPLC-DAD	4
Myricetin	$C_{15}H_{10}O_8$	Fruit	North America	Ethanol 96%, acetonitrile, methanol	UPLC-DAD	4
				5 ml 70% methanol, centrifugation and filtered through 0.45 μm filter	UPLC/MS	3
Myricetin-3-galactoside	$C_{21}H_{20}O_{13}$	Fruit	North America	Ethanol 96%, acetonitrile, methanol	UPLC-DAD	4
Procyanidin a2	$C_{30}H_{24}O_{12}$	Fruit	North America	24.5:75:0.5 (v/v/v) water/acetone/acetic acid	BL-DMAC method by prior et al	1

				Diluted in methanol-water (4.5:5.5, v/v)	UPLC-MS/MS	5
				CH_2Cl_2-ethyl acetate-formic acid (6:10:1, v/v/v)	NP-HPLC profile	5
				Ethanol-dichloromethane (1:4, v/v) then filtered	HPLC-UV	5
Procyanidin C1	$C_{45}H_{38}O_{18}$	Fruit	North America	Diluted in methanol-water (4.5:5.5, v/v)	UPLC-MS/MS	5
Proanthocyanidins A-type	$C_{31}H_{28}O_{12}$	Rueil Malmaison	France	80 ml methanol and shake at 200 rpm for 30 min.	UV-VIS spectrophotometer	11
Proanthocyanidins B-type	$C_{31}H_{28}O_{13}$	Rueil Malmaison	France	80 ml methanol and shake at 200 rpm for 30 min.	UV-VIS spectrophotometer	
Cyanidin chloride	$C_{15}H_{11}ClO_6$	Fruit	North America	Ethanol water (7:3, v/v) then centrifuge	Butanol HCl assay	5
Anthocyanins						
Cyanidin-3-O-galactoside	$C_{21}H_{21}O_{11}$	Fruit	North America	Waters 515 HPLC pumps, waters 996 photodiode array detector. Wavelength 520 nm	HPLC--diode array detector (DAD)	1
				Isaak et.al. The method with 10 ml of methanol containing 1% formic acid	UPLC-photodiode array detection	6
				Methanol, acetone, and ethyl acetate	HPLC analysis	7
				10 ml of a mixture containing HPLC-grade methanol (30 ml/100 ml)	LC–Q-TOF–HPLC- MS and MS/MS	8
				150 ml of ethanol, filtered, then 150 ml of fresh ethanol	HPLC	1

Cyanidin-3-o-glucoside	$C_{21}H_{21}O_{11}$	Fruit	North America	Waters 515 HPLC pumps, waters 996 photodiode array detector. Wavelength 520 nm.	HPLC--diode array detector (DAD)	1
				Methanol, acetone, and ethyl acetate	HPLC analysis	7
				Isaak et.al. The method with 10 ml of methanol containing 1% formic acid	UPLC-photodiode array detection	6
Cyanidin-3-o-arabinoside	$C_{20}H_{19}O_{10}$	Fruit	North America	Waters 515 HPLC pumps, waters 996 photodiode array detector. Wavelength 520 nm.	HPLC--diode array detector (DAD)	1
				Isaak et.al. The method with 10 ml of methanol containing 1% formic acid	UPLC-photodiode array detection	6
Peonidin-3-o-galactoside	$C_{22}H_{23}O_{11}$	Fruit	North America	Waters 515 HPLC pumps, waters 996 photodiode array detector. Wavelength 520 nm.	HPLC--diode array detector (DAD)	1
				Isaak et.al. The method with 10 ml of methanol containing 1% formic acid	UPLC-photodiode array detection	6
			Poland	10 ml of a mixture containing HPLC-grade methanol (30 ml/100 ml)	LC–Q-TOF–HPLC- MS and MS/MS	8
Peonidin-3-o-arabinoside.	$C_{21}H_{21}O_{10}$	Fruit	North America	Waters 515 HPLC pumps, waters 996 photodiode array detector. Wavelength 520 nm.	HPLC--diode array detector (DAD)	1
				Isaak et.al. The method with 10 ml of methanol containing 1% formic acid	UPLC-photodiode array detection	6

Phenolic acid						
Dihydroxybenzoic acid	$C_7H_6O_4$	Supplement	North America	5 ml 70% methanol by 45 mins sonication	UHPLC-HRMS	3
P-hydroxy benzoic acid	$C_7H_6O_3$	Fruit	North America	400 ml of boiling water, frozen at -84°c, lyophilized under 5 mm-Hg pressure	(LC-MS/MS)	2
Hydroxybenzoic acid glucoside	$C_{13}H_{16}O_8$	Supplement	North America	5 ml 70% methanol by 45 mins sonication	UHPLC-HRMS	3
Coumaric acid	$C_9H_8O_3$	Supplement	North America	5 ml 70% methanol by 45 mins sonication	UHPLC-HRMS	3
Sinapic acid	$C_{11}H_{12}O_5$	Supplement	North America	5 ml 70% methanol by 45 mins sonication	UHPLC-HRMS	3
Chlorogenic acid	$C_{16}H_{18}O_9$	Supplement	North America	5 ml 70% methanol by 45 mins sonication	UHPLC-HRMS	3
Benzoic acid	$C_7H_6O_2$		Finland, Sweden, Russia	Methanol: water (50:50, v/v) followed by acetone: water (70:30, v/v)	HPLC with UV & MS	10
		Supplement	North America	5 ml 70% methanol by 45 mins sonication	UHPLC-HRMS	3
P-coumaric acid	$C_9H_8O_3$	Fruit	Europe	Methanol: water (50:50, v/v) followed by acetone: water (70:30, v/v)	HPLC with UV & MS	10
			North America	400 ml of boiling water, frozen at -84°c, lyophilized under 5 mm-Hg pressure	(LC-MS/MS)	2
Caffeic acid glucoside	$C_{15}H_{18}O_9$	Supplement	North America	5 ml 70% methanol by 45 mins sonication	UHPLC-HRMS	
Caffeic acid	$C_9H_8O_4$	Fruit	North America	400 ml of boiling water, frozen at -84°c,	(LC-MS/MS)	2

				lyophilized under 5 mm-Hg pressure		
Ellagic acid	$C_{14}H_6O_8$	Fruit	North America	400 ml of boiling water, frozen at -84°c, lyophilized under 5 mm-Hg pressure	(LC-MS/MS)	2
Syringic acid	$C_9H_{10}O_5$	Fruit	North America	400 ml of boiling water, frozen at -84°c, lyophilized under 5 mm-Hg pressure	(LC-MS/MS)	2
Ferulic acid	$C_{10}H_{10}O_4$		Finland, Sweden, Russia	Methanol: water (50:50, v/v) followed by acetone: water (70:30, v/v)	HPLC with UV & MS	10
		Fruit	North America	400 ml of boiling water, frozen at -84°c, lyophilized under 5 mm-Hg pressure	(LC-MS/MS)	
Vanillic acid	$C_8H_8O_4$	Cranberry juice	Madison, USA	Methanol, acetone, and ethyl acetate	HPLC analysis	7
Gallic acid	$C_7H_6O_5$	Cranberry juice	Madison, USA	Methanol, acetone, and ethyl acetate	HPLC analysis	7
Glucoside						3
Flavan-3-ol						3
Epicatechin	$C_{15}H_{14}O_6$	Supplement	North America	5 ml 70% methanol by 45 mins sonication	UHPLC-HRMS	8
		Fruit	Poland	10 ml of a mixture containing HPLC-grade methanol (30 ml/100 ml)	LC–Q-TOF–HPLC- MS and MS/MS	8
Epicatechin-glucoside	$C_{21}H_{24}O_{11}$	Supplement	North America	5 ml 70% methanol by 45 mins sonication	UHPLC-HRMS	3
Procyanidins	$C_{30}H_{26}O_{13}$	Fruit	Poland	10 ml of a mixture containing HPLC-grade	LC–Q-TOF–HPLC- MS and MS/MS	8

				methanol (30 ml/100 ml)		
(+) catechin	$C_{15}H_{14}O_6$	Fruit	Poland	10 ml of a mixture containing HPLC-grade methanol (30 ml/100 ml)	LC–Q-TOF–HPLC- MS and MS/MS	
Flavonol glycoside						3
Laricitrin-3-galactoside	$C_{22}H_{22}O_{13}$	Supplement	North America	5 ml 70% methanol by 45 mins sonication	UHPLC-HRMS	3
Quercetin-3-xyloside	$C_{20}H_{18}O_{11}$	Supplement	North America	5 ml 70% methanol by 45 mins sonication	UHPLC-HRMS	8
Quercetin-3-o-galactoside	$C_{27}H_{30}O_{17}$	Fruit (cv ben lear)	Poland	10 ml of a mixture containing HPLC-grade methanol (30 ml/100 ml)	LC–Q-TOF–HPLC- MS and MS/MS	8
Myricetin-3-o-galactoside	$C_{21}H_{20}O_{13}$	Fruit (cv ben lear)	Poland	10 ml of a mixture containing HPLC-grade methanol (30 ml/100 ml)	LC–Q-TOF–HPLC- MS and MS/MS	8
Quercetin-3-o-pentoside	$C_{25}H_{26}O_{15}$	Fruit (cv ben lear)	Poland	10 ml of a mixture containing HPLC-grade methanol (30 ml/100 ml)	LC–Q-TOF–HPLC- MS and MS/MS	
Menotropin						3
Coumaroyl-monotropein	$C_{25}H_{28}O_{13}$	Supplement	North America	5 ml 70% methanol by 45 mins sonication	UHPLC-HRMS	
Proanthocyanidins	$C_{31}H_{28}O_{12}$	Fruit	North America	6 ml 70% methanol, centrifugation and filtered through 0.45 μm filter	Electrophoretic/LC	11
Organic acids						
Citric acid	$C_6H_8O_7$	Fruit	North America	Dissolved in 600 μl of a DMSO-d6 spiked with standard dss	NMR and multivariate analysis	1
Malic acid	$C_4H_6O_5$	Fruit	North America	Dissolved in 600 μl of a DMSO-d6 spiked with standard dss	NMR and multivariate analysis	1

Quinic acid	$C_7H_{12}O_6$	Fruit	North America	Dissolved in 600 µl of a DMSO-d6 spiked with standard dss	NMR and multivariate analysis	1
Butyric acid	$C_4H_8O_2$	Cranberry pomace	North American	95% ethanol at 13.8% (w/v)	Done using GraphPad prism version 8.4.2 and Microsoft Excel	9
Propionic acid	$C_3H_6O_2$	Cranberry pomace	North American	95% ethanol at 13.8% (w/v)	Done using GraphPad prism version 8.4.2 and Microsoft Excel	9
Ferulic acid	$C_{10}H_{10}O_4$	Cranberry pomace	North American	95% ethanol at 13.8% (w/v)	Done using GraphPad prism version 8.4.2 and Microsoft Excel	9
Triterpenoids						
Ursolic acid	$C_{30}H_{48}O_3$	Fruit	North America	Dissolved in 600 µl of a DMSO-d6 spiked with standard dss	NMR and multivariate analysis	1
				150 ml of ethanol, filtered, then 150 ml of fresh ethanol	HPLC	1
			Poland	10 ml of a mixture containing HPLC-grade methanol (30 ml/100 ml)	LC–Q-TOF–HPLC- MS and MS/MS	8
Oleanolic acid	$C_{30}H_{48}O_3$	Fruit	North America	Dissolved in 600 µl of a DMSO-d6 spiked with standard dss	NMR and multivariate analysis	1
				150 ml of ethanol, filtered, then 150 ml of fresh ethanol	HPLC	1
			Poland	10 ml of a mixture containing HPLC-grade methanol (30 ml/100 ml)	LC–Q-TOF–HPLC- MS and MS/MS	8
Ascorbic acid	$C_6H_8O_6$	Fruit	North America	400 ml of boiling water, frozen at -84°c,	(LC-MS/MS)	2

				lyophilized under 5 mm-Hg pressure		
Monosaccharide acetate						13
Arabinose	$C_5H_{10}O_5$	Cranberry fruit	North America	Dichloromethane	GC/MS	12
		Cranberry pomace		Polysaccharides from alcohol insoluble solids	Anion exchange chromatography using an akta purifier	14
		Supplement		5 ml 70% methanol	HPLC AND HNMR	13
L-arabinose	$C_5H_{10}O_5$	Cranberry pomace	North American	From the Ch and da extracts	HPAEC / ICS 3000 Chromatograph	9
Glucose	$C_6H_{12}O_6$	Cranberry fruit	North American	Dichloromethane	GC/MS	12
		Plant cell wall	Pomace	Mixture of extracts obtained by microwave assist alkaline extraction and anhydrous ethanol, after 45 hrs., the mixture was centrifuged for 25 min the precipitates were collected and freeze-dried	Microwave-assisted extraction	16
		Supplement	North American	5 ml 70% methanol	HPLC and HNMR	13
D-glucose	$C_6H_{12}O_6$	Cranberry pomace	North American	From the Ch and da extracts	HPAEC / ICS 3000 Chromatograph	9
Xylose	$C_6H_{12}O_6$	Cranberry fruit	North America	Dichloromethane	GC/MS	12
		Supplement		5 ml 70% methanol	HPLC and HNMR	13
Galactose	$C_6H_{12}O_6$	Cranberry fruit	North America	Dichloromethane	GC/MS	

		Cranberry pomace		Polysaccharides from alcohol insoluble solids	Anion exchange chromatography using an akta purifier	14
L-rhamnose	$C_6H_{12}O_5$	Cranberry pomace	North American	From the Ch and da extracts	HPAEC / ICS 3000 Chromatograph	9
D-mannose	$C_6H_{12}O_6$	Cranberry pomace	North American	From the Ch and da extracts	HPAEC / ICS 3000 Chromatograph	9
Mineral composition						
N		Berry and leaf	In Latvia.	HNO_3 vapors and re-dissolved in HCl solution	Colorimetry	15
P		Berry and leaf	In Latvia.	HNO_3 vapors and re-dissolved in HCl solution	Colorimetry	15
Ca		Berry and leaf	In Latvia.	HNO_3 vapors and re-dissolved in HCl solution	Atomic absorption spectrophotometer	15
Mg		Berry and leaf	In Latvia.	HNO_3 vapors and re-dissolved in HCl solution	Atomic absorption spectrophotometer	15
Fe		Berry and leaf	In Latvia.	HNO_3 vapors and re-dissolved in HCl solution	Atomic absorption spectrophotometer	15
Cu		Berry and leaf	In Latvia.	HNO_3 vapors and re-dissolved in HCl solution	Atomic absorption spectrophotometer	15
Zn		Berry and leaf	In Latvia.	HNO_3 vapors and re-dissolved in HCl solution	Atomic absorption spectrophotometer	15
Mg		Berry and leaf	In Latvia.	Hno3 vapors and re-dissolved in HCl solution	Atomic absorption spectrophotometer	15
Mo		Berry and leaf	In Latvia.	Hno3 vapors and re-dissolved in HCl solution	Colorimetry	15
B		Berry and leaf	In Latvia.	HNO_3 vapors and re-dissolved in HCl solution	Colorimetry	15
S		Berry and leaf	In Latvia.	HNO_3 vapors and re-dissolved in HCl solution	Turbidimetry	15
K		Berry and leaf	In Latvia.	HNO_3 vapors and re-dissolved in HCl solution	Flame photometer	15

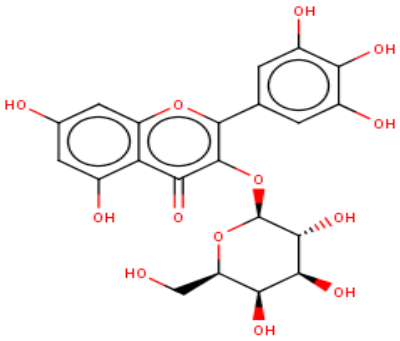
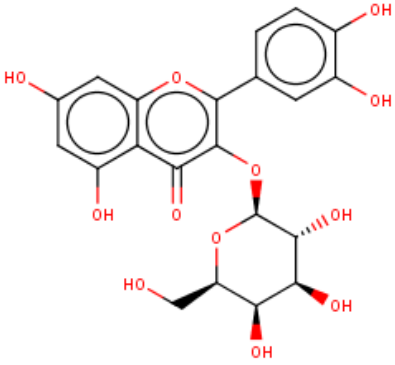
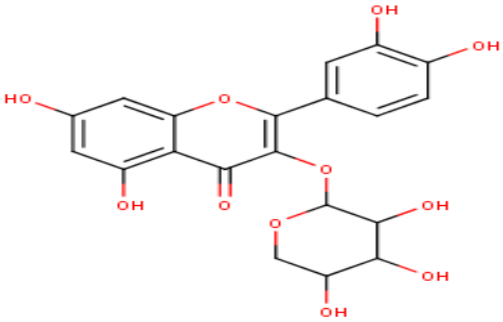
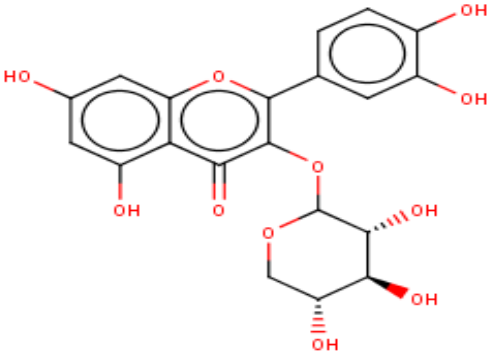
	**Laricitrin 3-O-glucoside**
	**Myricetin 3-galactoside**
	**Quercitin 3-galactoside (Hyperoside)**
	**Quercitrin 3–o-xyloside**

Figure 1. Flavanol-glycosides.

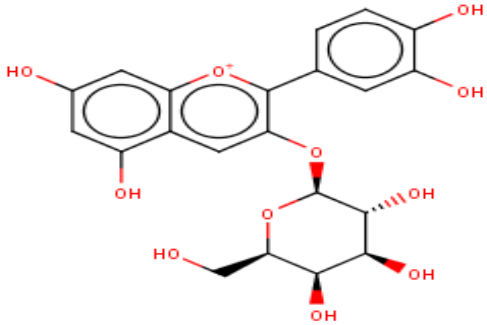
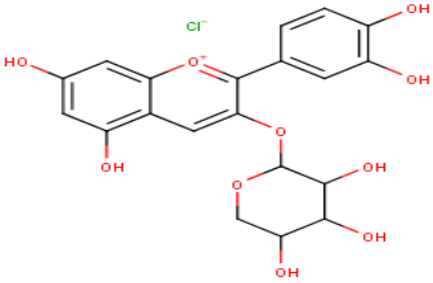
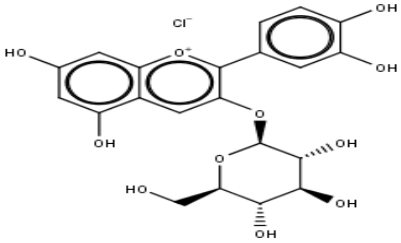
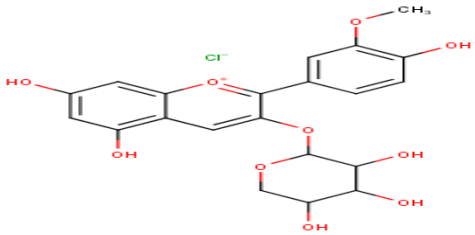
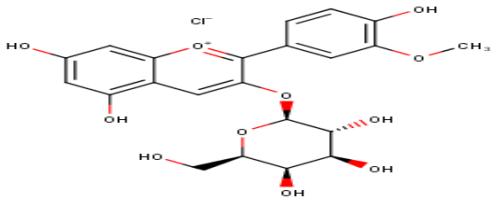
	**Cyanidine 3-O-glactoside**
	**Cyanidine 3-O-arabinose**
	**Cyanidine3-O-glucose**
	**Peonidin 3-arabinoside**
	**Peonidin 3-galactoside**

Figure 2. Anthocyanins.

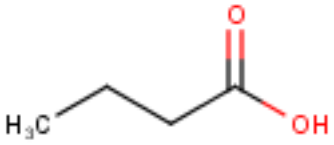
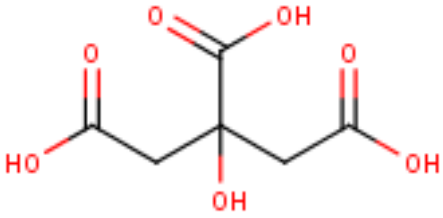
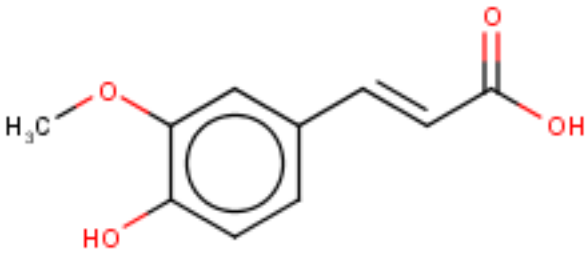
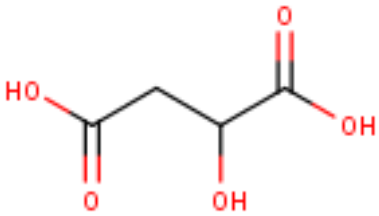
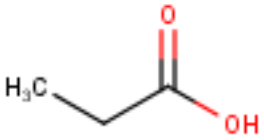
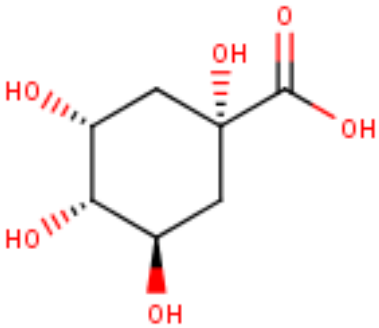
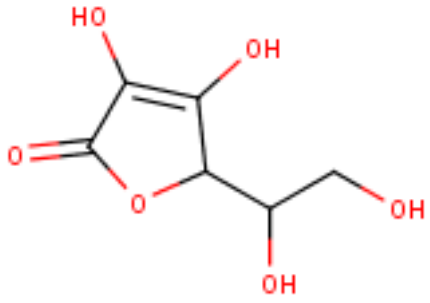
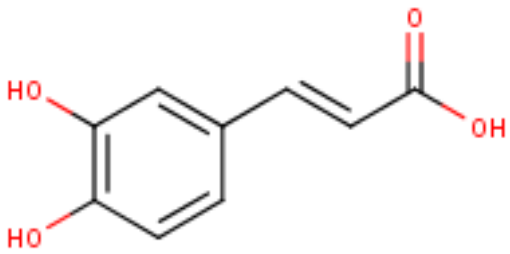
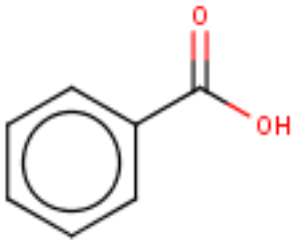
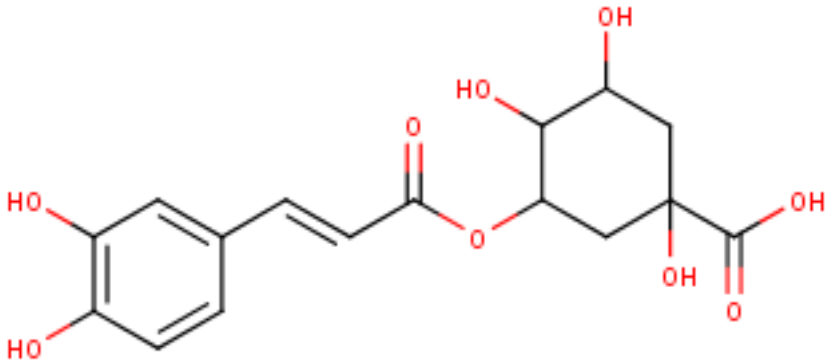
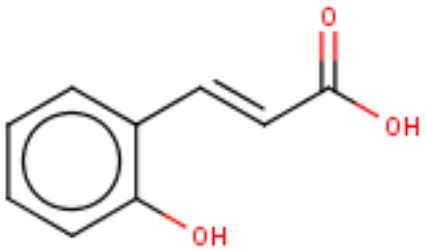
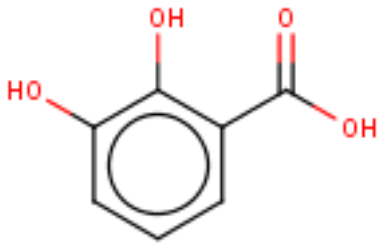
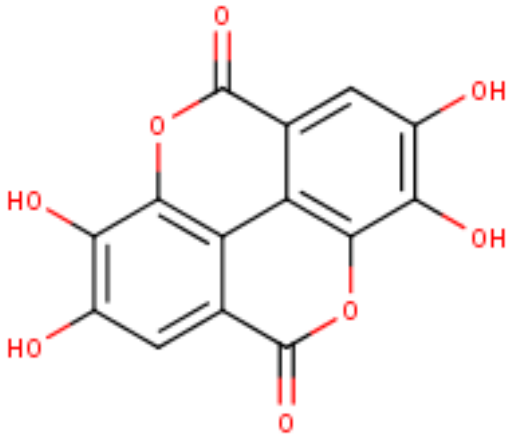
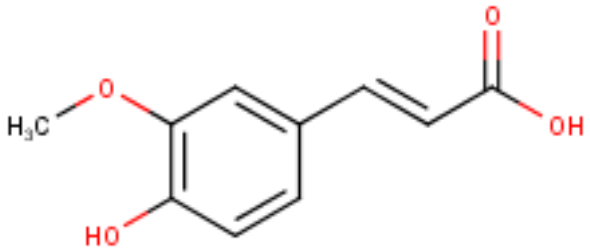
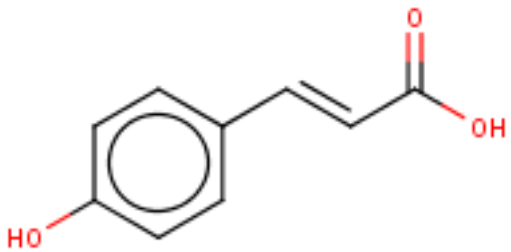
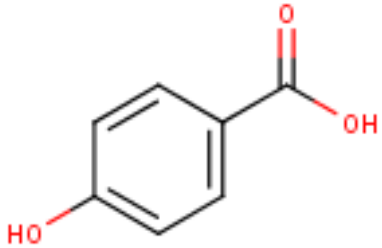
	**Butyric acid**
	**Citric acid**
	**Ferulic acid**
	**Malic acid**
	**Propionic acid**
	**Quinic acid**

Figure 3. Organic acids.

	**Ascorbic acid**
	**Caffeic acid**
	**Benzoic acid**
	**Chlorogenic acid**
	**Coumaric acid**

	**Dihydroxybenzoic acid**
	**Ellagic acid**
	**Ferulic acid**
	**Para coumaric acid**
	**Para hydroxybenzoic acid**

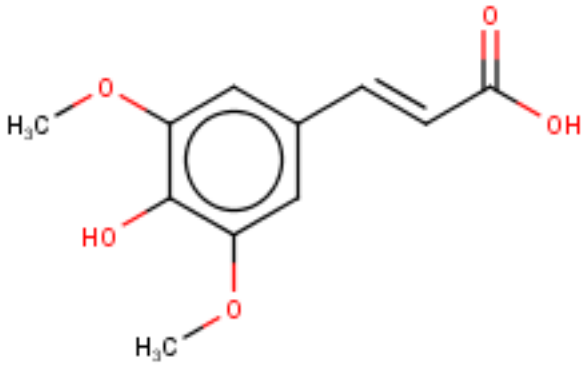
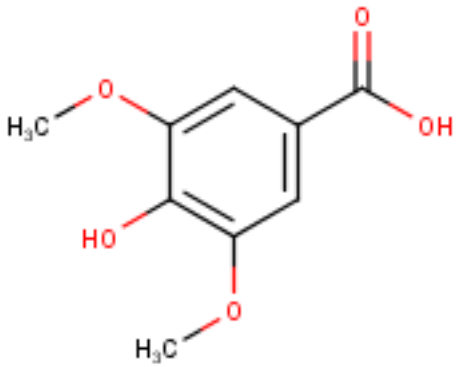
	**Sinapic acid**
	**Syringic acid**

Figure 4. Phenolic acids.

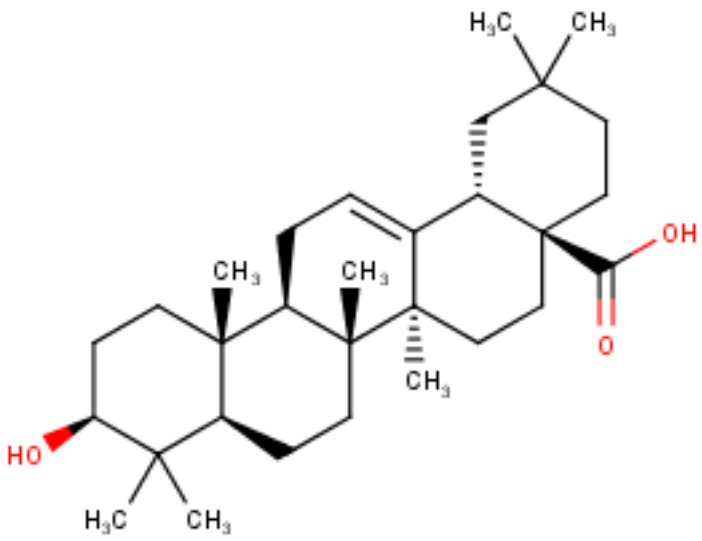
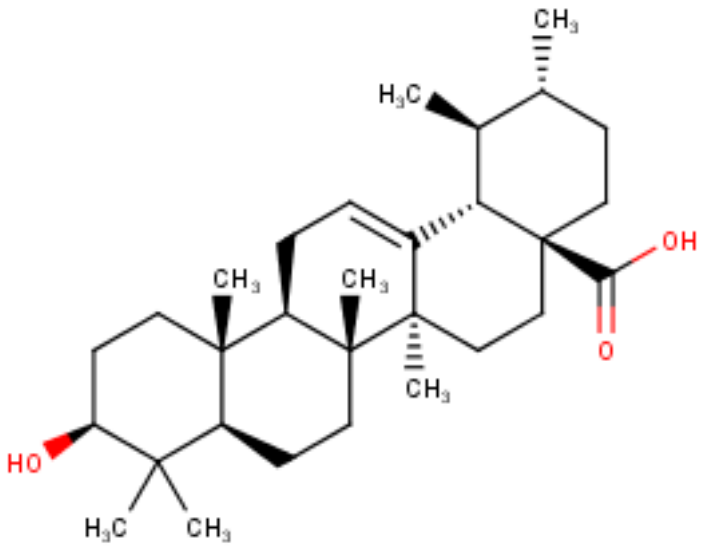
	**Oleanolic acid**
	**Ursolic acid**

Figure 5. Triterpenoids.

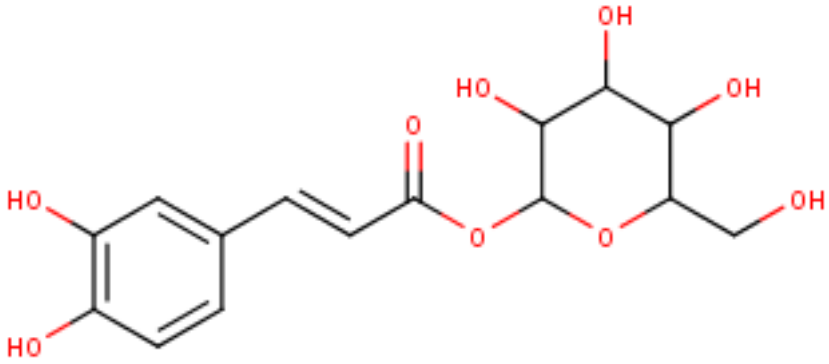
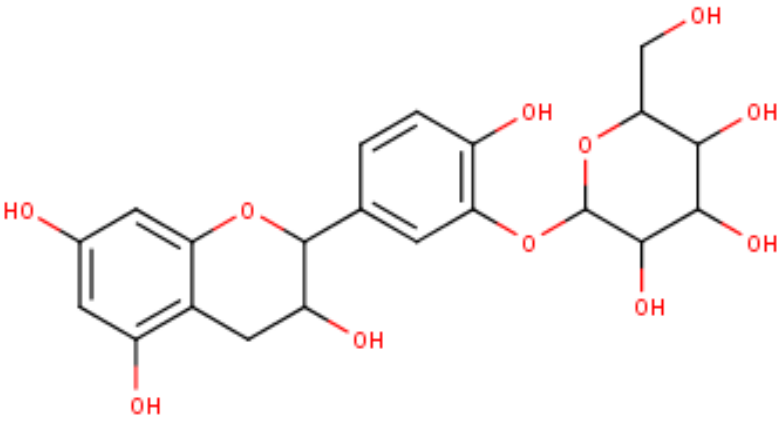
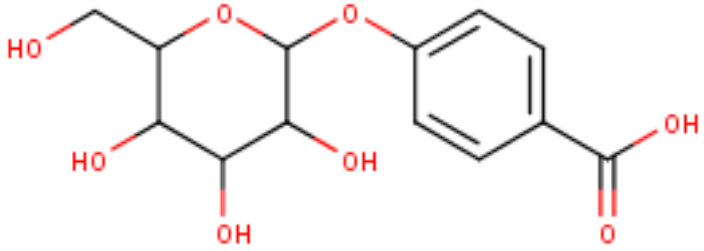
	**Caffeic acid 3-glucoside**
	**Epicatechin 3-glucoside**
	**Hydroxybenzoic acid glucoside**

Figure 6. Glucosides.

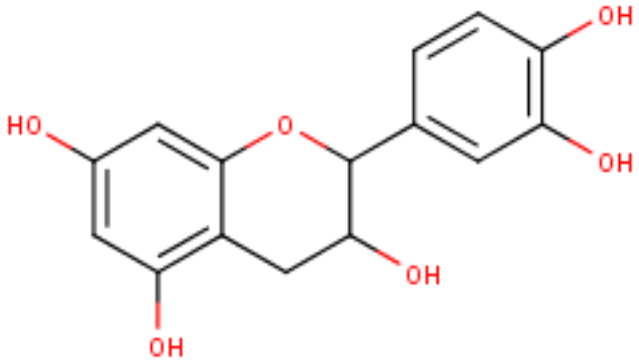
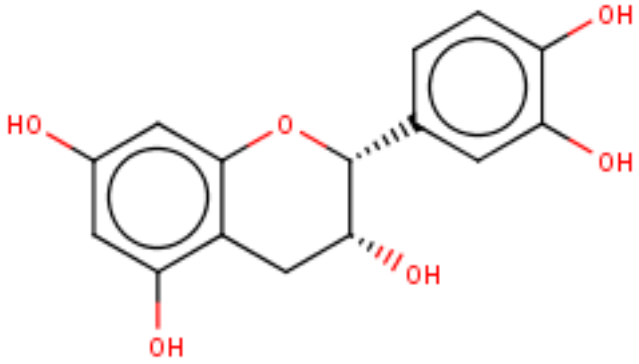
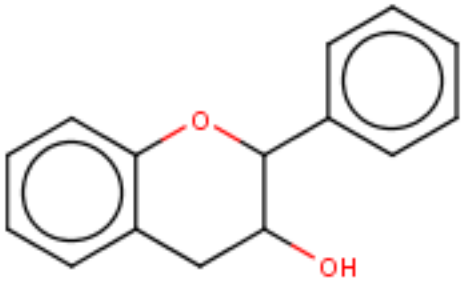
	**Catechin**
	**Epicatechin**
	**Flava-3-ol**

Figure 7. Flavan-3-ols.

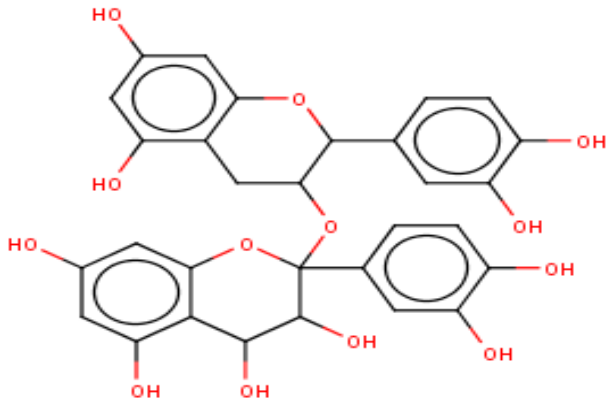
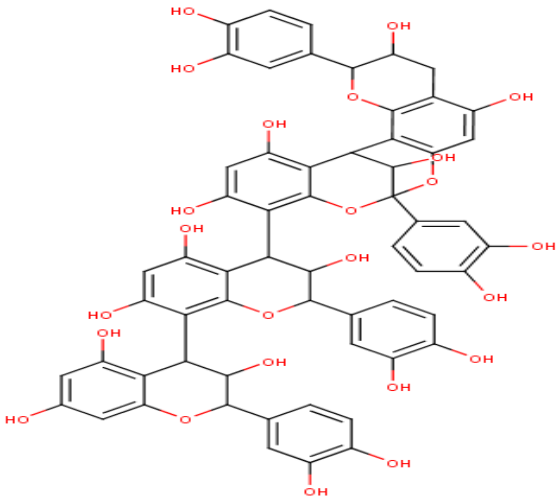
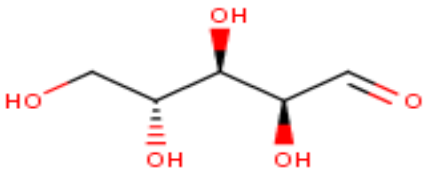
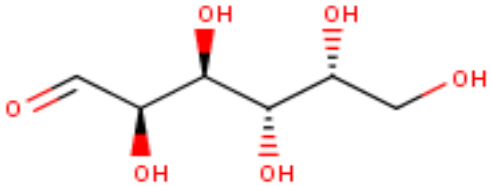
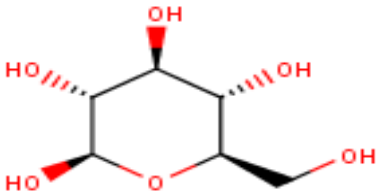
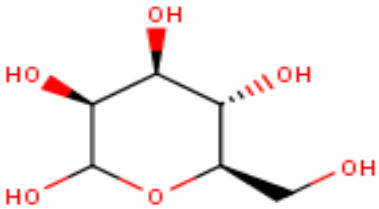
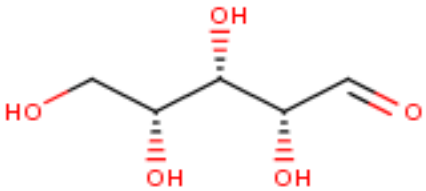
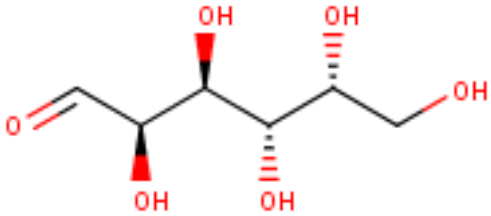
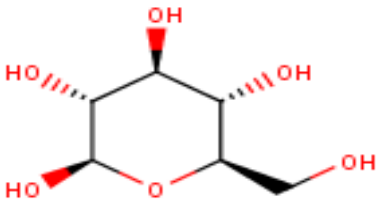
	**Proanthocyanidin**
	**Proanthocyanidin type A**

Figure 8. Polyphenols.

	**Arabinose**
	**D-galactose**
	**D-glucose**
	**D-mannose**
	**D-xylose**
	**L-galactose**
	**L- glucose**

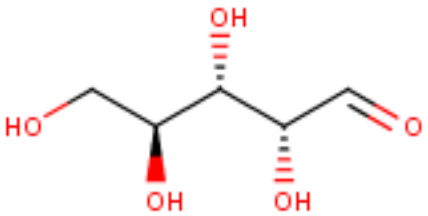
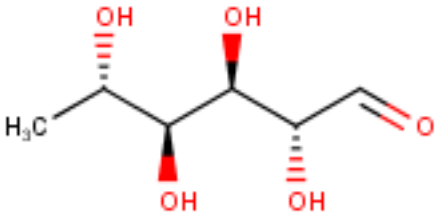
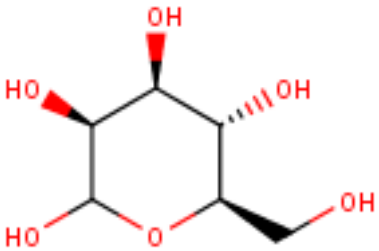
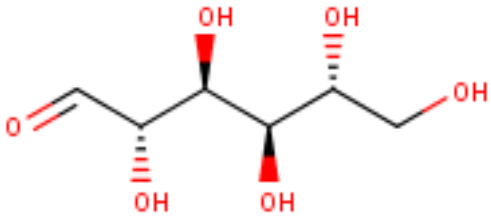
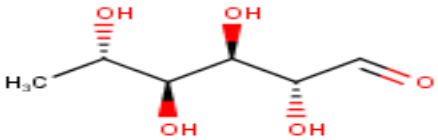
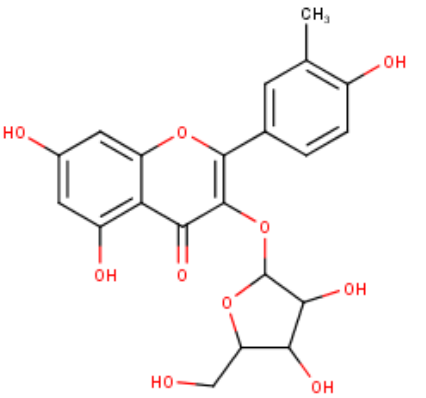
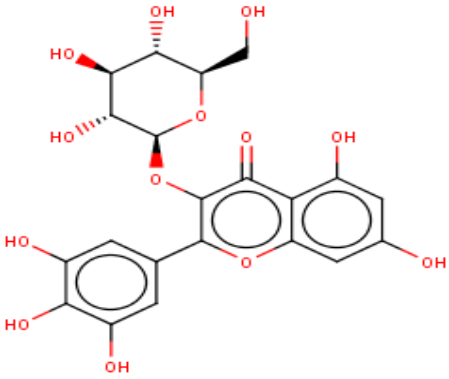
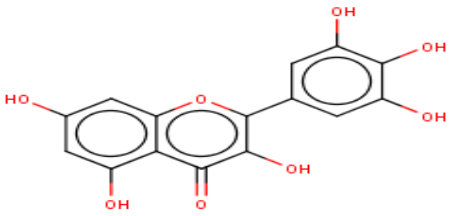
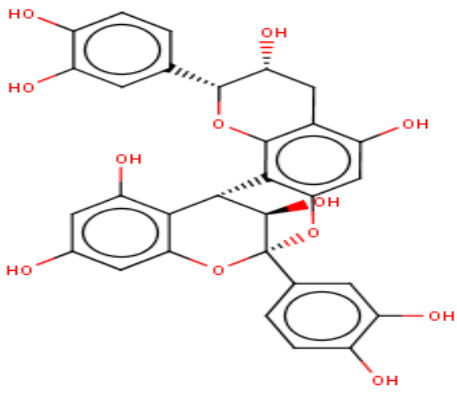
	**L- arabinose**
	**L- rhamnose**
	**Mannose**
	**Mannose**
	**Rhamnose**

Figure 9. Monosaccharides.

	**Quercetin 3-o-α-l-arabinofuranoside**
	**Myricetin-3-galactoside**
	**Myricetin**
	**Procyanidin**

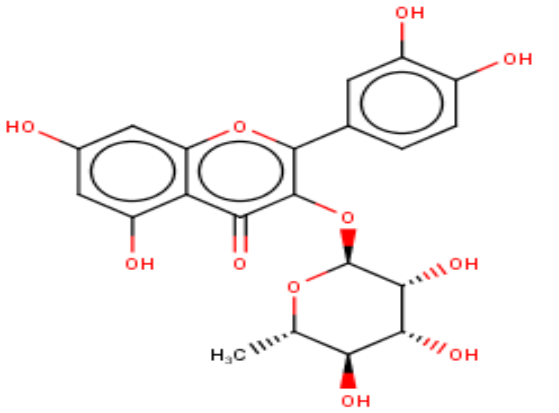
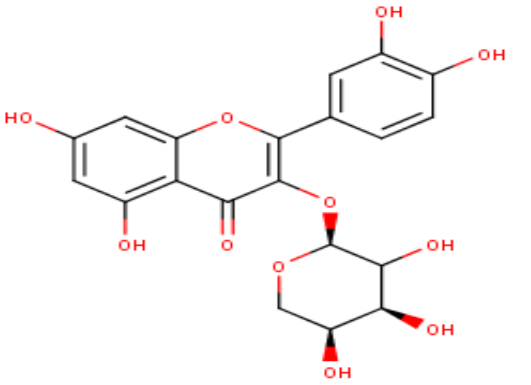
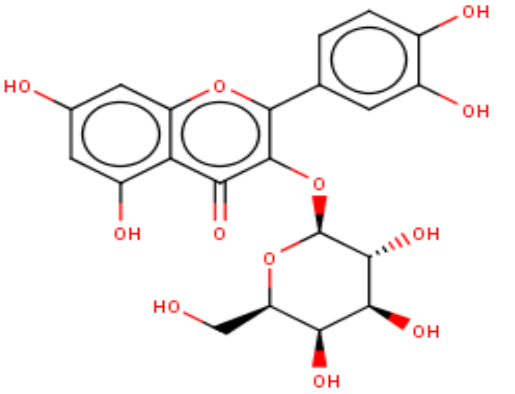
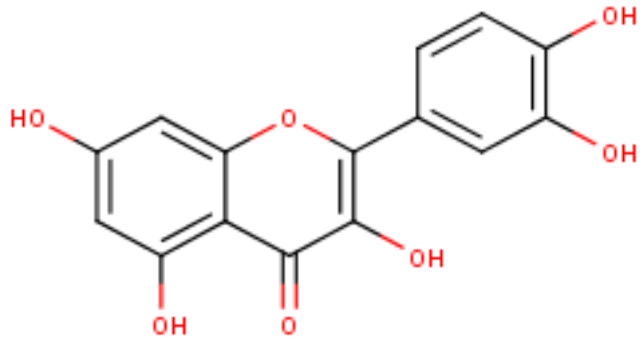
	**Quercetin 3-O-rhamnoside**
	**Quercetin 3-O-α-L-arabinopyranside**
	**Quercetin O-galactoside**
	**Quercetin**

Figure 10. Flavonoids.

3. Biological Effects

3.1. Antimicrobial activity & urinary tract infection

Jeremy Ranfaing [19] isolates 12 UPEC (uropathogenic E.coli) from a patient with cystitis, pyelonephritis, or asymptomatic UTI. A mix of filtered urine has been used for the overnight culture of our strains, extract was obtained by using dried fruit and phosphate-buffered saline. Purified PAC extract was obtained with a concentration of 190 microgram/L combinate with propolis. The result of adding cranberry extract with propolis to bacterial culture is the inhibition of the bacterial biofilm.

3.2. Antifungal properties

Emerenziana Ottaviano et al [20] a study done on isolates from the genitourinary tract (C. albicans) which were stored at 80 °C, were grown overnight in yeast extract peptone dextrose by taking cranberry tablets and collected after 12 hrs. after taken orally and found that high inhibition of biofilm and reduction in yeast cell viability in biofilm.

3.3. Hebatic stellate cell activation and liver fibrosis

Lyian Shi [21] studied rats that were injected intraperitoneally with CCl4 to induce liver fibrosis. Then the injected rats were treated with 5-10 mg /kg CPS through intragastric administration. These effects might be achieved by inhibiting the expression of inflammatory cytokines TGF TGFß / Smad signaling pathway. Therefore, CPS is expected to be an ideal drug to treat liver fibrosis.

3.4. Antiviral activity

Mattia Mirandol [22] did a study in vitro on isolated virus cells from African green monkey kidney cells (HAZV) treated with a dose of 100 microgram/ml of Cranberry fruit extract and showed that Cranberry extract inhibits the early stages of the HAZV replication cycle.

3.5. Antioxidant activity & anti-triglyceridemic effect:

Thamara C. Peixoto [23] injects male rats with HFD-induced obesity producing a high rate of ROS with 200 mg/kg cranberry extract (fruit extract). Then total triglyceride was lowered and

hepatic damage caused by ROS was reduced. Actually, those effects were related to the anthocyanins content of cranberry extract.

3.6. Blood pressure regulation:

Flammer et al. [24] found that Cranberry juice had no long-term effect on vascular function (2× 230 ml daily for 4 months, with a total phenolic content of 1740 g/ml).
Conducted research on multiple species has confirmed repeatedly that flavonoids and polyphenols from Cranberry reduce blood pressure through a reduction in ornithine decarboxylase activity and inhibition of cyclooxygenases.

3.7. Anti-inflammatory activity

Panunzio MF et al. [25] conducted a study with 41 women diagnosed with RA. The control group (n=18) keep their usual diet. The intervention group (n=23) ingested 500ml/d of reduced calories cranberry juice. after 90 d, the intervention group indicated a considerable decrease in DAS28 and anti-CCP levels. The hypothesis of the activity of cranberry juice in the reduction activity of RA was partially confirmed and required more studies to verify this. However, there is proof that quercetin, a flavonoid present in high amount in cranberries, is a great down regulator of the nuclear factor (NF)-kB pathway, and inhibit the activities of cyclooxygenase and lipoxygenase, which are the initiator of the inflammatory response. Also, decreased the expression of inflammatory genes relevant to cardiovascular disease by modifying NF-kB and JAKSTAT3 pathways in cultured cells.

3.8. Neuroprotective activity

Neto [26] reports that cranberry juice extracted from the fruit causes a reduction in cell death(reduction of necrosis), which can treat neurons of rat brain suffering from a stroke. That effect is related to the presence of a combination of anthocyanin & flavonoids in cranberry juice.

3.9. Chronic kidney diseases

Raffaella, et al [27] designed a study on Neutered cats suffering from stage II – III Chronic kidney disease The cats were assigned randomly to receive either a nutraceutical diet (70-85 gm for 6-7 kg) for 90 days according to the Manufacturer directive. All Cats screened veterinary for

90 days. Hematological and Urine analyses, Cranberry improves BUN, serum creatinine, urine color score, AST, and urinary protein concentration in cats affected by Chronic kidney (CKD) administration of nutraceutical diet resulting in an improvement in CKD signs. A further study showed that ALT and AST serum levels began to be higher during the elementary stages (2 and 3) of CKD compared with the later stages (4 and 5) (Sette and Lopes). Similarly, in this study, the nutraceutical diet significantly decreased AST in cats with stage 2 and 3 CKD. These decreases are paralleled with the significant decrease in creatinine observed following nutraceutical diet supplements.

4- Conclusion

Several studies focused on the phytochemical composition of cranberry juice expressing its richness in polyphenolic as flavonoids, anthocyanins, phenolic acid organic acids, triterpenoids, and proanthocyanidins B-type. Besides, cranberry juice possesses several biological activities, for example, antioxidant, anti-triglyceridemic effect, antimicrobial activity, and Blood pressure regulation with remarkable neuroprotective activity and anti-inflammatory properties. Furthermore, cranberry extracts cause a reduction of necrosis, that effect is related to the presence of a combination of anthocyanin & flavonoids in cranberry juice. Furthermore, the phenolic compounds of this berry, which include A-type proanthocyanidins (PACs), possess many bioactivities that can hinder the development of dental caries. In addition, cranberry extract composed primarily of flavonol-type glycosides showed the best antioxidant activity in lipid-containing hydrophilic media as an anti-triglyceridemic effect.

- **Conflict of Interest**

  The Authors declare no conflict of interest.

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