CPQ Nutrition (2018) 3:1
Review Article

Plants of Genus *Rubus* as a Source of Pharmaceuticals

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Received: 28 September 2018

Published: 22 December 2018

Keywords: *Rubus Species; Phenolics; Blackberry*

Abstract

In this review, we summarize the compilation of the constituents isolated from the genus *Rubus* over the past decades, also considering the botanical classification and ethno-pharmacology of *Rubus* plants, as well as the biological activities and pharmacological applications of both distinct phytochemicals and medicinally active plant materials (formulations, extracts, etc.) are discussed in detail.

Introduction

The genus *Rubus* (raspberry, blackberry) of the Rosaceae family, a large group of tropical trees consisting of ca. 700 different species, is well-known as a rich and valuable source of bioactive anthocyanins and phenolic compounds. Plants of this genus have applications in indigenous medicines.

Botanical Classification

The genus *Rubus* is worldwide, but absent from deserts and most well represented in the northern hemisphere, naturally occurring in temperate climates [1].

It is found in the temperate regions of America, Asia and South Africa. *Rubus niveus* is native from Indian to southeastern Asia, the Philippines and Indonesia [2]. Some are cultivated in numerous varieties as industrial plants for the quality of nutritious and tasty fruits. The important cultivated species are the European red raspberry (*Rubus idaeus* ssp. *Vulgatus*), the North American red raspberry *(Rubus strigosus),* the eastern North American black raspberry *(Rubus occidentalis)* and the hybrid Andean blackberry *(Rubus glaucus, Rubus adenotrichus).*

Of the many varieties of *Rubus* species such as, *R. imperialis, Rubus rosaefolius, Rubus chingii, Rubus glaucus* and *Rubus adenotrichus, Rubus sanctus, Rubus suavissimus, Rubus pileatus, Rubus pileatus, Rubus fruticosus, Rubus coreanus, Rubus rosaefolius* (Rosaceae), *Rubus brasilensis, Rubus sanctus, Rubus ulmifolius, Rubus chlorotic mottle, Rubus pungens, Rubus* caucasicus L, *Rubus ulmifolius, Rubus laciniatus* Willd, *Rubus aleaefolius* poir and *Rubus allegheniensis* only ten are used commercially. Currently, in Poland, ten varieties of raspberry and two of blackberry were introduced to official Register [3].

The most widely reported species are the *Rubus allegheniensis, Rubus glaucus* and *Rubus adenotrichus* (black berry). *Rubus fructicosus* is the most common European species and *Rubus canadensis* is a common North American species.

Caneberries are *Rubus* species that grow on a leafy cane and produce multiple small fruits such as raspberries and blackberries. Grown in temperate regions, caneberries are prevalent throughout the Northwestern United States. The processing of caneberry fruit for juices and puree typically removes the seed as a byproduct. The development of a value-added use of seeds could expand the market for caneberry products and increase grower profit margins.

The blackberry, genus *Rubus*, consists of a variable and complex group of plants and grows widely throughout the world, especially in the temperate parts of the northern hemisphere. The fruit is eaten fresh or as one of many processed products, *e.g.,* jams, jellies, and pastry fillings. Ellagitannins and free ellagic acid were the main phenolics detected in all five caneberry species and were approximately 3-fold more abundant in the blackberries and the boysenberry than in the raspberries. The black mulberry (Morus nigra) is a dioecious tree native to western Asia. Blackberries grow in wet areas across the United States and Europe. Several species of blackberry exist.

Rubus rosifolius is a red raspberry that is native to Eastern China and is distributed in the Caribbean, Hawaii, Australia and Asia [4]. Also called the West Indian raspberry, it is one of the many fruit-bearing plant species in Jamaica that is under utilized, being known and eaten by only a minority of the populace.

Investigations of other *Rubus* species have been conducted in the last twenty-five years, and have shown possible application for a wide range of indications, including bacterial infections, anxiety, pain and inflammation.

Traditional Applications of *Rubus* Species

A number of plants of this genus are used as traditional herbal medicines, such as being a anti-gastropathic and anti-rheumatic, antinociceptive, anti-inflammatory, anxiolytic, antigiardial activity, antiinflammatory activities, antiviral, antiangiogenic, antinociceptive, antioxidant activities, skin-Irritant activities, analgesic activity, Inhibits bone-resorbing mediators, antigiardial activity, spermatorrhea, enuresis, asthma and allergic diseases, diarrhoea, anxiety.

Species of the genus *Rubus* are widely distributed in the People's Republic of China, and many of them have been used in traditional Chinese medicine as antibacterial, antiinflammatory and antitumor agents, and for the treatment of various diseases such as arthritis, dysentery, enteritis and rheumatism.

The genus *Rubus* consists of many species that are employed in various countries of the world to treat these diseases, especially diabetes [5]. The modern pharmacology research of genus *Rubus* has further revealed many activities, such as antitumor-Promoting and cytotoxic activities, anti-HIV activities, chemopreventive effects, anti-rheumatic, hyaluronidase inhibitory activity, antiviral, antitumor-promoting, antimalarial, antibacterial, as well as cytotoxic activity. Recently, the oxygen radical absorbance capacity, total phenolic content, and total anthocyanin of fruits of blackberry were reported and the consumption of blackberry is expected to be associated with low incidences of various human diseases caused by active oxygen species and free radicals. Chemical and pharmacological studies have confirmed that some of these plants produce active principles that exert hypoglycemic activity, antibacterial effects against Gram-positive bacteria, and anti-allergic activities against allergic rhinitis, atopic dermatitis and asthma.

Investigations of other *Rubus* species have been conducted in the last twenty-five years, and have shown possible application for a wide range of indications, including bacterial infections, anxiety, pain and inflammation.

Tea made from the leaves of *R. idaeus* has been used as a folk medicine to treat wounds, diarrhoea, colic pain, as a uterine relaxant and other applications. Literature survey showed that among the most commonly cited herbs for morning sickness were raspberry leaves [6]. Some recently performed studies provided more comprehensive evidence on the properties assigned to raspberry leaves by the folk medicine practices [7]. Many women consume raspberry leaf herb during their pregnancies in the belief that it shortens labor and makes labor "easier" [8,9]. *Rubus* species have been used in traditional medicine for their many medicinal properties [10].

Blackberry leaves have been used for their astringent, antidiarrhoeic, hypoglycemic activities and as an anti-inflammatory agent for the mucous membrane of the oral cavity and throat [11,12]. Raspberry leaves (R. *idaeus* L.) have been commonly used to treat a variety of ailments including diseases of the alimentary canal, air-passage, heart and the cardiovascular system. However, they are best known for their health benefits in treating fever, influenza, diabetes, menstrual pain, diarrhea and colic pain. The leaves of raspberry may also be applied externally as antibacterial, anti-inflammatory, sudorific, diuretic and choleretic agents [13]. Raspberry leaf extract has been reported to have relaxant effect, particularly on uterine muscles [14,15,7].

Pharmacological studies have confirmed that some of these plants produce active principles that exert hypoglycemic activity, antibacterial effects against Gram-positive bacteria, and anti-allergic activity against allergic rhinitis, atopic dermatitis and asthma [16].

In the search for biologically active compounds, one of the most frequently documented species of the genus is the *R. idaeus,* the leaves of which have been used traditionally as a uterine relaxant and stimulant during confinement, for the treatment of diarrhoea and similar enteric disorders and as an astringent.

Rubus imperialis Chum. Schl. grows abundantly in the south of Brazil, being known as "amorabranca", "amora-do-mato," or "amora-brava". It is used in traditional medicine as a remedy to treat diabetes. However, no reports have been found regarding its pharmacological and phytochemical investigation. The Andean blackberries are native from Mexico to Ecuador and are widely cultivated in South America for their edible fruits, which are eaten fresh or consumed as juice, syrup, or desserts.

Pharmacological studies on the Rosaceae have shown that the genus *Rubus* may be an important source of active principles [17,18]. Few of them have already been described as the glycosides obtained from the *Rubus suaissimus* [19] and the xiloglucans, from the *Rubus fruticosus. Rubus brasiliensis* is a rich source of folk medicine used commonly in the Brazilian south and southeast regions.

Chemical Constituents

The chemical constituents of *Rubus* species were classified into four groups, anthocyanin, flavonoids, caffeoyl esters, phenolic compounds (ellagitanins), triterpenoids and some other compounds.

Cyanidin 3-glycosides

A literature survey of the genus *Rubus* revealed the isolation of these natural products, including 1-caffeoylxylose, cyanidin 3-glycosides [20].

Acids

Hydroxycinnamic acids, 9,10-dihydro-1, 2, 3, 4, 6, 7, 8-heptahydroxy-10-oxo-9-anthracene acetic acid, 9, 10-dihydro-1, 2, 3, 4, 6, 7, 8-heptahydroxy-10-oxo-9-anthracene acetic acid [20].

Di-p-coumaroyl putrescine, 13,16-dihydroxy-19-kauranoic acid [21,19]

Saturated and unsaturated fatty acids, 3, 19-dihydroxy-12-ursene-24, 28-dioic acid [22, 23], 2,19-dihydroxy-3-oxo-1,12-ursadien-28-oic acid [24], 3, 7-dihydroxy-12-ursen-28-oic acid [25], ellagic acid, INN [26], 10, 11-epoxyguaiane [27,28], 2, 3, 4, 6-bis (hexahydroxydiphenoyl) glucose [29,30].

Since 1900 more than 100 chemical constituents have been isolated from the genus *Rubus*. The major isolated compounds are triterpene glucosyl ester, triterpene methylglucosides, anthocyanins, phenolics (mainly ellagitannins), D-glucosyl ester, ellagitannins, flavonoids, tannins and ellagic acid. leukoanthocyanidins, triterpenoid saponin dimers, caffeoyl esters (3, 6-di-*O*-caffeoyl-(alpha/beta)-glucose and 1-*O*-caffeoyl-beta-xylose), pentacyclic triterpenoids and their glucosides (coreanoside F1, suavissimoside, niga-ichigoside F1 and -F2) and methylglucosides, hitherto unknown natural tannin, 2, 3-*O*-hexahydroxydiphenoyl-4, 6-*O*-sanguisorboyl-(alpha/beta) glucose, lupeol acetate, corosolic acid, oleanic acid, 2α-hydroxy oleanolic acid, sitosterol, hydroxycinnamic acids, quercetin 3-glucuronide was the typical flavonol glycoside.

Quercetin and kaempferol, caffeic, chlorogenic acids, saturated and unsaturated fatty acids, ursane and oleanane triterpenes, flavonoid glycosides, triterpene glucosyl ester, triterpenoid glycoside dimers, rubupungenosides A and B. *Rubus* species is a rich source of gallic acid, ellagic acid, flavonoids and tannins. The dominant antioxidants could be classified as anthocyanins, ellagitannins, and proanthocyanidin-like tannins, phenolics (mainly ellagitannins), catechins, rubitic acid, a new triterpene acid, pentacyclic triterpenoid glycosyl esters, diosphenol-type triterpene fupenzic acid, kaurane-type diterpene glycosides named suaviosides gallic acid, xiloglucans, from the *Rubus fruticosus, Rubus brasiliensis,* glycosides, Triterpene Glucosyl Ester, Triterpenoid glycoside dimers, rubupungenosides A and B.

Phenolic Compounds

Phenolics are the major components of this genus. The most abundant phenolic compounds in all parts of the blackberry shoot were leukoanthocyanidins, which accounted for approximately 50% of all compounds of this class. Anthocyanins are widely distributed in fruits and vegetables and exhibit potent antioxidant capacity.

Analysis of Phenolic Compounds in Two Blackberry Species (Rubus glaucus and Rubus adenotrichus) by High-Performance Liquid Chromatography with Diode Array Detection and Electrospray Ion Trap Mass Spectrometry

Blackberries are currently promoted as being a rich source of polyphenols, which are compounds of interest because of their antioxidant activity as radical scavengers and possible beneficial roles in human health, such as reducing the risk of cancer, cardiovascular disease, and other pathologies. Phenolic compounds include several classes such as hydroxybenzoic acids, hydroxycinnamic acids and flavonoids. The major phenolic compounds in berries are hydrolyzable tannins (gallo and ellagitannins) and anthocyanins, hydroxycinnamic acids, flavonols, flavan-3-ols, including proanthocyanidins being present in lower amounts. Major anthocyanins in red raspberry have been identified as cyanidin and pelargonidin glycosylated with rutinose and sophorose, whereas cyanidin 3-glucoside and pelargonidin 3-glucoside were predominant in strawberry. Blackberry anthocyanins have been well-characterized and are only cyanidin-based compounds. Ellagitannins and ellagic acid derivatives were detected in *Rubus* species, but amounts reported were closely dependent on the analytical conditions. Hydroxycinnamic acids are detected as glycosides and as esters with sugars or quinic acid. Flavan-3- ols are found as monomers as well as structural units in proanthocyanidin chains [31].

Further Study on the 1, 4-a-Transglucosylation of Rubusoside, a Sweet Steviol-Bisglucoside from Rubus suavissimus Kazuhiro Ohtani

Rubusoside (D-glucosyl ester of 13-*O*-D-glucosyl-steviol), which is the major sweet principle of leaves of *Rubus suavissimus* S. Lee, was subjected to 1, 4-a-transglucosylation by the cyclodextringlucanotransferase-starch system. The tri- and tetra-glucosylated products were isolated together with the mono- and di-glucosylated products. A prominent increase in intensity of the sweetness was observed for the compounds which were di- and tri-glucosylated at the 13-*O*-glucosyl moiety. This result further substantiated the structure-sweetness relationship for 1, 4-a-glucosylated compounds of steviol-glycosides. For protection of the 19-COO-glucosyl moiety against glucosylation by the CGTase system, the 4-hydroxyl group of the 19-COO-glucosyl moiety was o-galactosylated by the J-galactosidase-lactose system. This galactosylated compound was subjected to a regio-selective glucosylation of the 13-*O*-glucosyl moiety by the CGTase system, which was followed by enzymic elimination of the galactosyl group to furnish an exclusive preparation of the improved sweeteners [27].

Identification and Quantification of Phenolic Compounds in Beries of Fragaria and Rubus species (Family Rosaceae)

High-performance liquid chromatography combined with diode array and electrospray ionization mass spectrometric detection was used to study soluble and insoluble forms of phenolic compounds in strawberries, raspberries, arctic bramble, and cloudberries. Hydroxycinnamic acids were present as free forms in cloudberries and mainly as sugar esters in the other berries. Quercetin 3-glucuronide was the typical flavonol glycoside in all of the berries studied. The composition of the predominant anthocyanins can be used to distinguish the studied red *Rubus* species from each other since cyanidin was glycosylated typically with 3-sophorose in cultivated red raspberry, with 3-sophorose and 3-glucose in wild red raspberry, and with 3-rutinose in arctic bramble. Ellagic acid was present as free and glycosylated forms and as ellagitannins of varying degrees of polymerization. Comparable levels of ellagitannins were obtained by the analysis of soluble ellagitannins as gallic acid equivalents and by the analysis of ellagic acid equivalents released by acid hydrolysis of the extracts [29].

Two new and four known polyphenolics obtained as new cell-cycle inhibitors from *Rubus aleaefolius* poir. Two polyphenolics, rubuphenol and sanguiin H-2 ethyl ester, were isolated together with ellagic acid, ethyl gallate, 1, 2, 3, 4, 6-penta-*O*-galloyl-beta-D-glucopyranose and 1, 2, 3, 6-tetra-*O*-galloyl-beta-D-glucopyranose as new cell-cycle inhibitors from *Rubus aleaefolius*. All compounds inhibited the cell cycle progression of tsFT210 cells at the G0/G1 phase with the MIC values of 14.6 microM (rubuphenol), 22.1 microM (sanguiin H-2 ethyl ester), 10.3 microM (ellagic acid), 7.8 microM (ethyl gallate), 7.9 microM (1, 2, 3, 4, 6-penta-*O*-galloyl-beta-D-glucopyranose) and 6.6 microM (1, 2, 3, 6-tetra-*O*-galloyl-beta-D-glucopyranose) [32].

Ellagic Acid

Ellagic acid is a phenolic compound which scientists have proven contributes to significant inhibition of colon, esophageal, liver, lung, tongue, and skin cancers. Ellagic acid is present in raspberries in three different forms: as ellagitannins, in which hexahydroxydiphenic acid forms esters with a sugar as free ellagic acid and as ellagic acid glycosides.

Ellagic acid is present in raspberries in three different forms, as ellagitannins, in which hexahydroxydiphenic acid forms esters with a sugar as free ellagic acid and as ellagic acid glycosides. Ellagitannins are a major class of phenolics largely responsible for the astringent and antioxidant properties of raspberries and blackberries.

The Crystal and Molecular Structure of Ellagic Acid Dihydrate: A Dietary Anti-Cancer Agent

Ellagic acid inhibits the carcinogenic properties of a variety of chemical compounds including benzo[a] pyrene-7, 8-diol-9,10-epoxide, aflatoxin B, N-methyl-N-nitrosourea, 3-methylcholanthrene and 7,12-dimethylbenz [a] anthracene. Its activity and anti-cancer properties are compared with those of a similar naturally occurring compound, quercetin [33].

Aromatic Ketone: (Anti-obese Action of Raspberry ketone)

Raspberry ketone 4-(4-hydroxyphenyl butan-2-one) is a major aromatic compound of red raspberry *(Rubus idaeus)*. The structure of raspberry ketone is similar to the structures of capsaicin and synephrine, compounds known to exert anti-obese actions and alter the lipid metabolism. A study was performed to clarify whether raspberry ketone helps prevent obesity and activate lipid metabolism in rodents. To test the effect on obesity, these *in vivo* experiments designed, mice were fed a high-fat diet including 0.5, 1, or 2% of raspberry ketone for 10 weeks; 2) mice were given a high-fat diet for 6 weeks and subsequently fed the same high-fat diet containing 1% raspberry ketone for the next 5 weeks. Raspberry ketone prevented the high-fat-diet-induced elevations in body weight and the weights of the liver and visceral adipose tissues (epididymal, retroperitoneal, and mesenteric). Raspberry ketone also decreased these weights and hepatic triacylglycerol content after they had been increased by a high-fat diet. Raspberry ketone significantly increased norepinephrine-induced lipolysis associated with the translocation of hormone-sensitive lipase from the cytosol to lipid droplets in rat epididymal fat cells. Raspberry ketone prevents and improves obesity and fatty liver. These effects appear to stem from the action of raspberry ketone in altering the lipid metabolism, or more specifically, in increasing norepinephrine-induced lipolysis in white adipocytes [34].

Impact of Growing Environment on Chickasaw Blackberry (Rubus L.) Aroma Evaluated by Gas Chromatography Olfactometry Dilution Analysis

Gas chromatography-olfactometry was performed on each aroma extract of Chickasaw blackberry *(Rubus L.)* fraction, to identify aroma active compounds. Aroma extraction dilution analysis was employed to characterize the aroma profile of Chickasaw blackberries from two growing regions of the United States. Comparative Aroma extraction dilution analysis showed that the berries grown in the two regions had similar aroma compositions; however, those odorants had various aroma impacts in each region. The compounds with high flavor dilution factors in Oregon's Chickasaw were ethyl butanoate, linalool, methional, trans, cis-2, 6-nonadienal, cis-1,5-octadien-3-one, and 2, 5-dimethyl-4-hydroxy-3 (2H)-furanone, whereas in the Chickasaw grown in Arkansas, they were ethyl butanoate, linalool, methional, ethyl 2-methylbutanoate, beta-damascenone and geraniol [35].

Ellagitannins (Concentration and Mean Degree of Polymerization of Rubus Ellagitannins Evaluated by Optimized Acid Methanolysis)

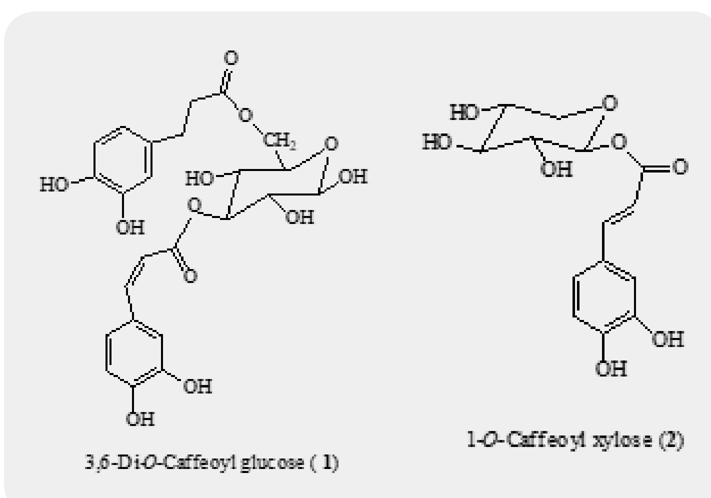
Ellagitannins are a major class of phenolics largely responsible for the astringent and antioxidant properties of raspberries and blackberries. The *Rubus* ellagitannins constitute a complex mixture of monomeric and oligomeric tannins. *Rubus* oligomeric ellagitannins contain, beside the well-known ellagic acid and gallic acid moieties, the sanguisorboyl linking ester group. When exposed to acids or bases, ester bonds are hydrolyzed and the hexahydroxydiphenic acid spontaneously cyclizes into ellagic acid. A new, rapid procedure for the acid hydrolysis of *Rubus* ellagitannins in methanol was developed, which results in maximal yield and enables the quantification of all the major reaction products. Additionally, the method provides the rationale for estimating the mean degree of polymerization of *Rubus* ellagitannins [36].

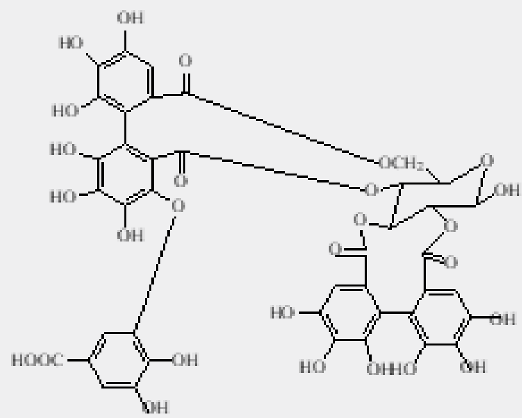
Chemical Composition of Caneberry (Rubus spp.) Seeds and Oils and Their Antioxidant Potential

Processing of caneberry fruit typically removes the seed, and the development of a value-added use of seeds could expand the market for caneberries and the profit margins for growers. An initial step toward the use of the seeds is a characterization of seed and oil. This investigation has described compositional characteristics for seeds of five commonly grown caneberry species, red raspberry, black raspberry, boysenberry, Marion blackberry, and evergreen blackberry. Seeds from all five species had 6-7% protein and 11-18% oil. The oils contained 53-63% linoleic acid, 15- 31% linolenic acid, and 3-8% saturated fatty acids. The two smaller seeded raspberry species had higher percentages of oil, the lowest amounts of saturated fatty acid, and the highest amounts of linolenic acid. Antioxidant capacities were detected both for whole seeds and for cold-pressed oils but did not correlate to total phenolics or tocopherols [37].

Caffeoyl Sugar Esters and an Ellagitannin from Rubus sanctus

The new natural caffeoyl esters, 3, 6-di-*O*-caffeoyl-(α/β)- (1) glucose and 1-*O*-caffeoyl-β-xylose (2), together with the hitherto unknown natural tannin, 2, 3-*O*-hexahydroxydiphenoyl-4, 6-*O*-sanguisorboyl-(α/ β)-glucose (3), have been isolated from the aqueous alcohol aerial part extract of *Rubus sanctus* [20].





2,3-O-Hexahydroxy -phenyl-4,6-O-Sorboyl glucose (3)

Diterpenes and their Glycosides

Minor Diterpene Glycosides from Sweet Leaves of Rubus suavissimus

From sweet leaves of *Rubus* suavissimus, 10 new kaurane-type diterpene glycosides named suaviosides were isolated, in addition to the known major sweet glycoside, rubusoside and several known minor glycosides were isolated. Of these minor glycosides, suaviosides B, G, H, I and J taste sweet, and suaviosides C_1, D_2 and F taste bitter, while suaviosides D_1 and E are tasteless [19].

Triterpenes

During previous chemical investigation of *Rubus* species, scientists have reported several pentacyclic triterpenoids and their glucosides and methylglucosides, with a highly oxygenated ring A. Previous studies on bioactivity revealed that these types of pentacyclic triterpenoids and their glycosides from *Rubus* species possess antibacterial and antinociceptive activities.

Two Triterpenoid Dimers from Rubus pungens

Two new triterpenoid saponin dimers, rubupungenosides A (4) and B (6), were isolated in their methylated forms 5 and 7, respectively, from an ethanol extract of the aerial parts of *Rubus* pungens. The structures of 4 and 6 were established on the basis of spectroscopic and chemical methods. (Fig. 1) [38].

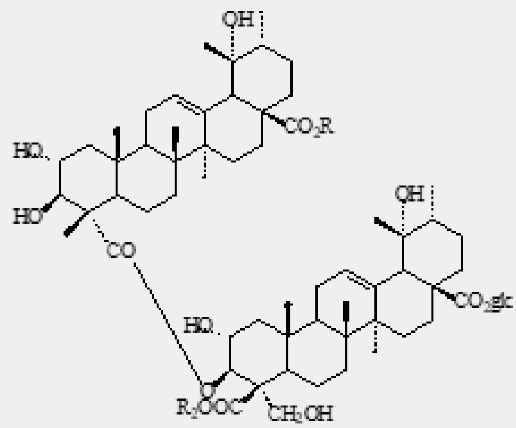


Figure 1: 4 R1 = 6'-*O*-METHYL-b-D-GLUCOPYRANOSYL, R2 = H
5 R1 = 6'-*O*-METHYL-b-D-GLUCOPYRANOSYL, R2 = CH 3
6 R1 = 3'-*O*-METHYL-b-D-GLUCOPYRANOSYL, R2 = H
7 R1 = 3'-*O*- METHYL-b-D-GLUCOPYRANOSYL, R2 = CH 3

These studies describe herein the isolation and structure determination of two novel triterpenoid glycoside dimers, namely, rubupungenosides A (6) and B (7), from the aerial parts of *R. pungens* Camb. var. *oldhamii* Maxim.

Triterpenoids from Rubi Fructus (Bogbunja)

The dried unripe fruits of *Rubus* sp. (Rubi Fructus, Bogbunja) have yielded 13-sitosterol glucoside and four urs-12-en-28-oic acid derivatives, three of which were as their glucosides. They were identified as 23-hydroxytormentic acid (8), rosamultin (9), niga ichigosides F1 (10) and F2 (11) (Fig. 2) [39].

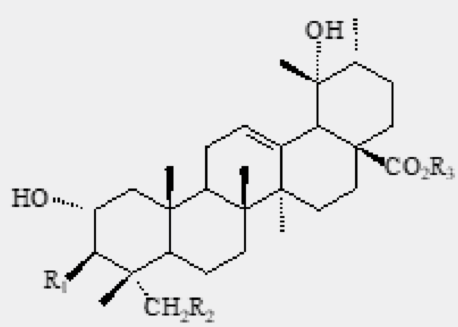
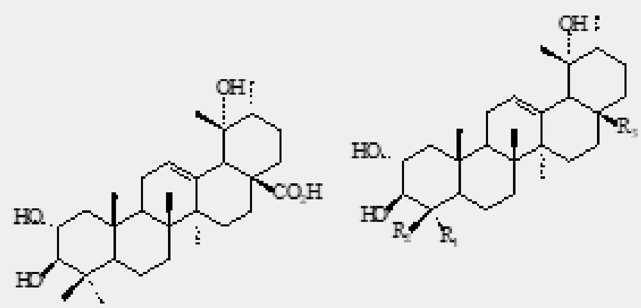


Figure 2: 8 R1 = β-OH R2 = OH R3 = H
9 R1 = β-OH R2 = OH R3 = Glucose
10 R1 = β-OH R2 = OH R3 = Glucose
11 R1 = β-OH R2 = OH R3 = Glucose

Ursolic Acid Analogues: Non-Phenolic Functional Food Components in Jamaican Raspberry Fruits

Phytochemical examination of the ethyl acetate extract of the fruit of *Rubus rosifolius* yielded eight compounds of the 19-α-hydroxyursane type: euscaphic acid (12), 1-b-hydroxyeuscaphic acid (13), hyptatic acid B (14), 19a-hydroxyasiatic acid (15), trachelosperogenin (16), 4-epi-nigaichigoside F1 (17), nigaichigoside F1 (18), and trachelosperoside B-1 (19) [40]. Inhibition of cell proliferation by these compounds were determined by using MCF-7 (breast), SF-268 (CNS), NCI H460 (lung), HCT-116 (colon) and AGS (gastric) human tumour cells. Among the human tumour cell lines assayed, only compounds 14 and 17 displayed significant growth inhibition and was specific to colon tumour cells by 56% and 40%, respectively. These ursolic acid analogues werealso tested for anti-inflammatory activity using *in vitro* cycloxegenase-1 and cycloxegenase-2 enzyme inhibitory assays. Compounds 12, 13 and 14 showed selective cycloxegenase-1 enzyme inhibitory activity (13%, 25% and 35%) at 25lg/ml. In the lipid peroxidation inhibitory assays, compounds 13, 15, 18 and 17 inhibited LPO by 62%, 60%, 53% and 68%, respectively, at 25lg/ml (Fig .3).



12) R=H
13) R=OH

	R1	R2	R3
14)	H	CH2OH	H
15)	CH2OH	H	H
16)	CH2OH	CH2OH	H
17)	H	CH2OH	Glc
18)	CH2OH	H	Glc
19)	CH2OH	CH2OH	Glc

Figure 3: Structures of compounds 12-19.

Studies on Chemical Constituents in Fruit of Rubus chingii

Eleven compounds were isolated from the fruit of *Rubus* chingii as oleanic acid, ursolic acid, maslinic acid, 2 α-hydroxyursolic acid, arjunic acid, hexacosyl p-coumarate, tiliroside, stearic acid, lacceroic acid, beta-sitosterol, daucosterol [41].

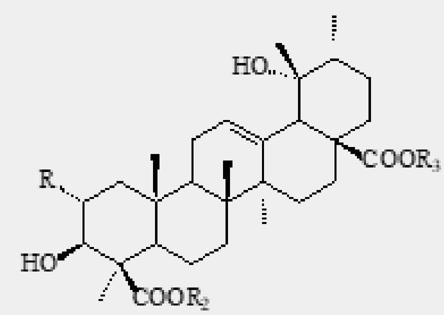
A Triterpene from the Fruits of Rubus chingii

A new diosphenol-type triterpene fupenzic acid, was isolated from the fruits of *Rubus* chingii and characterized as 2,19α-dihydroxy-3-oxo-urs-1,12-dien-28-oic acid [22].

Pentacyclic Triterpenoid Glycosyl Esters from Rubus pileatus

Five pentacyclic triterpenoid glycosyl esters have been isolated from the aerial parts of *Rubus* pileatus. Their structures were elucidated as 3β,19α-dihydroxyurs-12-en-24, 28-dioic ester, 2α,3β,19α-trihydroxyurs-12-en-24, 28-dioic ester and 2α, 3β,19α-trihydroxyurs-12-en-24, 28-dioic ester.

Scientists herein report the isolation and structural elucidation of the 24- methyl esters of three new triterpenoid glycosyl esters, 3fl, 19e-dihydroxyurs- 12-en-24,28-dioic acid-28-*O*- (6'-*O*-methyl-fl-D-glucopyranosyl) ester (20), 2, 3fl, 19ct-trihydroxyurs- 12-en-24,28-dioic acid-28-*O*-(6'-*O*-methyl- fl-D-glucopyranosyl) ester (21) and 2ct, 3fl,19c (trihydroxyurs-I 2-en-24, 28-dioic acid-28-*O*-(3'-Omethyl- fl-D-glucopyranosyl) ester (22) (Fig. 4) [23].



		R1	R2
Figure 4:	20)	H	6'-*O*-Methyl-β-D-glucopyranosyl
	21)	OH	6'-*O*-Methyl-β-D-glucopyranosyl
	22)	OH	3'-*O*-Methyl-β-D-glucopyranosyl

Rubitic Acid, A New Triterpene Acid from Rubus fruticosus

A new triterpene acid, rubitic acid was isolated from *Rubus fruticosus.* On the basis of physical methods coupled with chemical investigations, the structure of rubitic acid was shown to be 7α-hydroxy ursolic acid [25].

A Dimeric Triterpene-Glycoside from Rubus coreanus

A dimer of glucosyl esters of A-ring oxygenated 19 α-hydroxyursolic acids was isolated from leaves of *Rubus* coreanus together with the monomers of the related glucosyl esters. The structure of this compound, named coreanoside F1, was elucidated by spectroscopic methods. The significance of coreanoside F1 in the identification of the source plants of an oriental traditional medicine 'Bog-bun-ja' is discussed [30].

A New Triterpene Glucosyl Ester from the Fruit of the Blackberry (Rubus allegheniensis)

A new triterpene glucosyl ester, rubusside A, has been isolated from the fruit of the blackberry (*Rubus* allegheniensis PORT.) along with a known triterpene glucosyl ester, niga-ichigoside F1 [42].

Sesquiterpenoids

The Constituents of Rubus rosifolius

Chemical investigation of the steam-volatile oil of *Rubus rosifolius* yielded pregeijerene, β-caryophyllene, humulene, dihydroagarofuran, an unidentified sesquiterpene ether, hedycaryol and the novel epieudesmol rosifoliol [28].

Two Rhamnogalacturonide Tetrasaccharides lsolated from Semi-Retted Flax Fibers are Signaling Molecules in Rubus fruticosus L. Cells

Water extraction of semi-retted flax (*Linum usitafissimum* 1.) fiber bundles yielded a mixture of pectic oligosaccharides and two acidic rhamnogalacturonide tetrasaccharides. The two tetrasaccharides have a common primary structure, i.e. cw-D-AGalpA(1--22)-(-1- Rhap(l+4)-c~-~GalpA-(l-+2)-~-cw, p-Rwhaitph, a rhamnopyranose as terminal reducing end, and a 4-deoxy-p-i-fhreo-hex-4-enopyranosiduronic acid at the nonreducing end. However, the two tetrasaccharides differ by an acetyl group located at the 03 position of the interna1 galacturonic acid residue. These two tetrasaccharides induce the activation of D-glycohydrolases of *Rubus fructicosus* [43].

The Anti-Gastropathic and Anti-Rheumatic Effect of Niga-Ichigoside F1 and 23-Hydroxytormentic Acid Isolated from the Unripe Fruits of Rubus coreanus in a Rat Model

To produce the clinical merits of two natural antinociceptive anti-inflammatory triterpenoids this study was undertaken, which synthetic anti-inflammatory drugs do not have. The triterpenoid glycoside niga-ichigoside F1 and its aglycone 23-hydroxytormentic acid, which were isolated from the unripe fruits of *Rubus coreanus,* reduced rheumatoid arthritis factor and C-reactive protein factor in Freund's complete adjuvant reagent-induced rats, suggesting that these two triterpenoids had an anti-rheumatic effect. It was also shown that treatment with niga-ichigoside F1 or 23-hydroxytormentic acid reduced gastric lesion extent, acidity and total gastric acid output induced by EtOH plus sodium salicylate in a gastric secretion test. Moreover, 23-hydroxytormentic acid had a greater effect than the glycoside, niga-ichigoside F1. To clarify the anti-gastropathic mechanism of these two compounds, their free radical scavenging activities in the gastric mucosa were examined in a rat EtOH-sodium salicylate-induced gastropathy model. The two compounds significantly increased superoxide dismutase and glutathione peroxidase activities, indicating that the healing effects of niga-ichigoside F1 and 23-hydroxytormentic acid against gastropathy are associated with free radical scavenging enzyme activities. These results support the notion that the long-term administration of niga-ichigoside F1 or 23-hydroxytormentic acid should overcome the adverse effects of synthetic anti-inflammatory drugs [44].

Anthrones

Three Anthrones from Rubus ulmifolius

From the aerial parts of *Rubus* ulmifolius Schott three new anthrones, rubanthrone A, B and C, have been isolated. Rubanthrone A showed antimicrobial activity against *Staphylococcus aureus* at 4.5mg/ml [21].

Biological Activity

Biological Activity Due to Pure Compounds

Triterpenoids

Much of the work done on the *Rubus* genus to date has been focused on either the anthocyanin content of the fruits or the phytochemistry of the aerial parts. Of the compounds isolated from this genus, triterpenoids of the ursane and oleanane types are among those reported. The methanolic extract of the aerial parts of *R. rosifolius* was shown to possess strong analgesic properties, the active principle being identified as 28-methoxytormentic acid. Several sesquiterpenoids including bcaryophyllene, humulene, bicyclygermacrene and rosifoliol, the latter of which was first isolated from *R. rosifolius,* were isolated from the essential oil. Herein scientists report the isolation of eight 19a-hydroxyursolic acid analogues and their COX-1 and COX-2 enzyme, lipid peroxidation and tumour cell proliferation inhibitory activities.

Novel Compounds from Rubus sieboldii, Triterpenoids, are Inhibitors of Mammalian DNA Polymerases

Two anti-inflammatory triterpenoids, tormentic acid and euscaphic acid, were found from the plant *Rubus sieboldii.* These triterpenoids showed an inhibitory effect against enzymes involved in replication, such as calf DNA polymerase alpha and rat DNA polymerase beta. The IC_{50} values of tormentic acid and euscaphic acid were 37 and 61 microM for pol alpha and 46 and 108 microM for pol beta, respectively. However, tormentic acid and euscaphic acid did not influence the activities of plant DNA polymerases, DNA primase, human immunodeficiency virus type-1 reverse transcriptase, terminal deoxynucleotidyl transferase, any of the prokaryotic DNA polymerases or DNA and RNA metabolic enzymes tested. Tormentic acid and euscaphic acid could prevent the growth of BALL-1 cancer cells, and the LD50 values were 11 and 48 microM, respectively. The cells were halted at G1 phase in the cell cycle. The mode of action of the triterpenoids against anti-inflammatory activity and their relationships to the DNA polymerase inhibitory activity and cell growth inhibition were discussed [45].

Antinociceptive Activity of Niga-Ichigoside F1 from Rubus imperialis

This work describes the antinociceptive effect of a triterpene glycoside, niga-ichigoside F1 (23), obtained from an EtOAc extract of the aerial parts of *Rubus imperialis*. When evaluated against an HOAc-induced writhing model, it exhibited an ID50 value of 3.1mg/kg (ip). Moreover, in a formalin-induced pain model, both phases of pain were inhibited by compound 23, with ID_{50} values of 2.6 (first phase) and 2.7 (second phase)mg/kg, (ip), respectively (Fig. 5) [46].

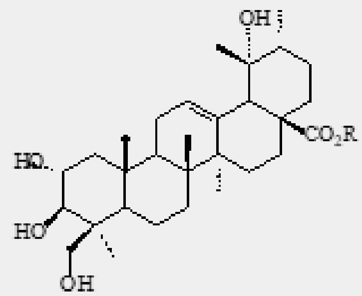
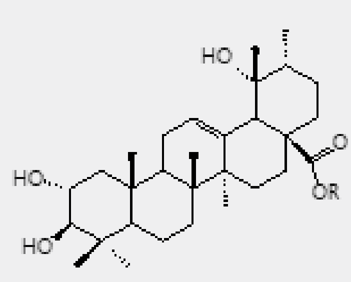


Figure 5: 23-Niga-ichigoside-F1 (R= Glc)
24- 23-Hydroxytormentic acid (R=H)

Phytochemical and Analgesic Activity of Extracts Fractions and a 19-Hydroxyursane-Type Triterpenoid Obtained from Rubus rosaefolius (Rosaceae)

The *Rubus* species has been used in folk medicine to treat several ailments, including infectious and dolorous diseases. The scientists evaluate the phytochemical and analgesic activity of hydroalcoholic extract, some fractions, as well as a pure compound denoted as 28-methoxytormentic acid (25) obtained from aerial parts of *R. rosaefolius*. The antinociceptive action was evaluated by two well known models of pain in mice: writhing and formalin induced-pain. The results showed that the hydroalcoholic extract, fractions and 28-methoxytormentic acid, exhibits potent and dose-related analgesic activity when evaluated in both models of pain. 28-Methoxytormentic acid), which seems to be the main active principle, showed promising analgesic effects, being several times more potent than aspirin and paracetamol, two well-known analgesic and antiinflammatory drugs used as reference. In the writhing test, it showed an ID$_{50}$ of 5.10 (3.64-7.14) mgkg_1 and maximum inhibition (MI) of 64.22%. When analyzed by formalin induced-pain test, this compound showed ID$_{50}$ values of 9.98 (8.08- 12.31) and 6.31 (5.07-7.98) mgkg 1^{-} and MI of 59.37 and 90.37% for the first and second phases, respectively. The results justify, at least partially the popular use of this plant for the treatment of dolorous processes, suggesting that 28-methoxytormentic acid is one of the active principles of this plant. Plant fractions giving a mixture of two pentacyclic triterpenes 28-methoxytormentic acid (25), tormentic acid (26) and its glycosides (27) [47].



25 R = CH_3 27 R = B- D-Glucopyranoside
26 R = H

Gallic Acid

Anticancer Effects of Gallic Acid from Indonesian Herbal Medicine, Phaleria Macrocarpa Boerl, on Human Cancer Cell Lines

The natural antioxidant gallic acid was isolated from fruits of a medicinal Indonesian plant, *Phaleria macrocarpa* (Scheff.) Boerl. Gallic acid demonstrated a significant inhibition of cell proliferation in a series of cancer cell lines and induced apoptosis in esophageal cancer cells (TE-2) but not in non-cancerous cells (CHEK-1). Observation of the molecular mechanism of apoptosis showed that gallic acid up-regulated the pro-apoptosis protein, Bax, and induced caspase-cascade activity in cancer cells. On the other hand, gallic acid down-regulated anti-apoptosis proteins such as Bcl-2 and Xiap. In addition, gallic acid also induced down-regulation of the survival Akt/mTOR pathway. In non-cancerous cells, Scientists observed delayed expression of pro-apoptosis related proteins. The results suggest that gallic acid might be a potential anticancer compound [48].

Gallic Acid is Partially Responsible for the Antiangiogenic Activities of Rubus Leaf Extract

An aqueous extract of leaves from *Rubus suavissimus S.* Lee or sweet leaf tea was tested for antiangiogenic activity in a human tissue-based fibrin-thrombin clot angiogenesis assay. Further fractionation of this crude extract was performed and the antiangiogenic effect of individual fractions was assessed. The extract was also tested for its oral bioavailability by using the serum of normal rats gavaged with the extract in the assay. At a 0.1% w/v concentration, the extract inhibited initiation of the angiogenic response and subsequent neovessel growth from samples that had already initiated an angiogenic response. Two subfractions of the extract showed significant inhibition of angiogenesis at 0.1% w/w. Gallic acid was elucidated as one of the active angiogenesis inhibitors in one fraction. A 1mM concentration of gallic acid totally inhibited angiogenesis. In the form of leaf extract, a one-tenth concentration produced the same total inhibition as pure gallic acid. The 10-fold difference in potency suggests the presence of other active compounds contributing to the overall antiangiogenic effect of the extract. The oral absorption of this extract was tested by using serum from rats given the extract orally in the angiogenesis assay system. The serum of rats orally administered the sweet leaf tea extract at doses of 0.1% w/w and 0.3% w/w did not significantly inhibit angiogenesis. However, the serum of rats injected intraperitoneally at a dose of 0.1% w/w caused a 41% inhibition of angiogenesis compared with saline injected controls. These preliminary results warrant further bioassay directed identification of other responsible compounds [49].

Anthrones

Three anthrones from *Rubus ulmifolius* uido from the aerial parts of *Rubus ulmifolius* Schott three new anthrones, rubanthrone A (29), B (30) and C (31), have been isolated. Rubanthrone A showed antimicrobial activity against *Staphylococcus aureus* at 4.5mg/ml (Fig. 7) [21].

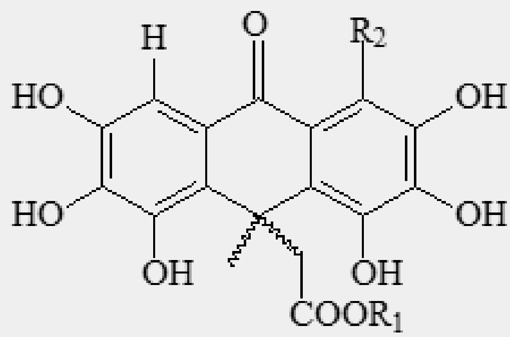


Figure. 7: Rubenthone A (**29**) R1= CH3, R2 = OH
Rubenthone B (**30**) R1= CH3, R2 = H
Rubenthone C (**31**) R1= H, R2 = OH

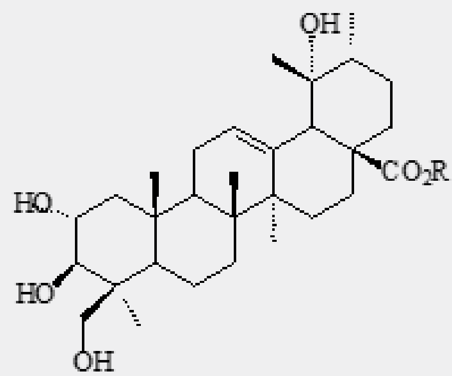
Anthocyanin

A Novel Zwitterionic Anthocyanin from Blackberry

A novel zwitterionic anthocyanin cyanidin 3-dioxalylglucoside was isolated from evergreen blackberry (*Rubus laciniatus* Willd.). Until now, oxalic acid as an acyl moiety of anthocyanins has been reported only in orchid flowers, but never in fruits or in the Rosaceae. This is the first report of an anthocyanin diacylated with oxalic acid, establishing a more widespread occurrence of anthocyanins substituted with aliphatic acids than hitherto believed [50].

Antioxidants in Raspberry: On-Line Analysis Links Antioxidant Activity to a Diversity of Individual Metabolites

The antioxidant compounds in raspberry *(Rubus idaeus)* fruits by high performance liquid chromatography coupled to an on-line postcolumn antioxidant detection system were studied. Both developmental and genetic factors were assessed by comparing fruits from a single cultivar of different ripening stages and by comparing ripe fruits of 14 raspberry cultivars, respectively. The HPLC-separated antioxidant compounds were identified using HPLC-photodiode array coupled to mass spectrometry (quadrupole time-of-flight tandem mass spectrometry), using a reference lock mass for determining accurate masses. The dominant antioxidants could be classified as anthocyanins, ellagitannins, and proanthocyanidin-like tannins. During fruit ripening, some anthocyanins were newly produced, while others, like cyanidin-3-glucoside, were already present early in fruit development. The level of tannins, both ellagitannins and proanthocyanidin-like tannins, was reduced strongly during fruit ripening. Among the 14 cultivars, major differences (>20-fold) were observed in the levels of pelagonidin type anthocyanins and some proanthocyanidin type tannins. The content of ellagitannins varied approximately 3-fold. The findings presented here suggest that the content of individual health promoting compounds varies significantly in raspberry, due to both developmental and genetic factors. This information will assist in the future development and identification of raspberry lines with enhanced health-promoting properties [51].



23- Niga-ichigoside-F1 (R= Glc)
24- 23-Hydroxytormentic acid (R=H)

Antinociceptive and Antiinflammatory Effects of Niga-Ichigoside F1 (23) and 23-Hydroxytormentic Acid (24) from Rubus coreanus

As an attempt to search for bioactive natural constituents exerting antinociceptive and antiinflammatory activities, scientists examined the potency of the extract of *Rubus coreanus* fruits by the activity-guided fractionation. The EtOAc- and BuOH fraction and those alkaline hydrolysates showed significant antinociceptive effects as assessed by writhing, hot plate and tail flicks tests in mice and rats as well as antiinflammatory effect in rats with carrageenan- induced edema. BuOH extract was subjected to column chromatography to obtain a large amount of niga-ichigoside F1 (1,23-hydroxytormentic acid 28-*O*-glc), which was again hydrolyzed in NaOH solution to yield an aglycone 23-hydroxytormentic acid (1a). The aglycone, 23-hydroxytormentic acid, was much more potent in both antinociceptive and antiinflammatory tests than the glycoside, niga-ichigoside F1. The antiinflammatory effects of these compounds were further supported by the reduction of carrageenan-induced lipid peroxidation and hydroxyl radical in serum. These results suggested that 23-hydroxytormentic acid (24) might be an active moiety of niga-ichigoside F1 present in *R. coreanus* [52].

Effect of Processing and Storage on the Antioxidant Ellagic Acid Derivatives and Flavonoids of Red Raspberry Jams

From red raspberries *(Rubus idaeus),* ellagic acid, its 4-arabinoside, its 4¢ (4¢¢-acetyl) arabinoside, and its 4¢ (4¢¢- acetyl)xyloside, as well as quercetin and kaempferol 3-glucosides, were identified. In addition, two unidentified ellagic acid derivatives were detected. The free radical scavenging activity of the ellagic acid derivatives was evaluated by using the DPPH method and compared to that of Trolox. All of the isolated compounds showed antioxidant activity. The effect of processing to obtain jams on raspberry phenolics was evaluated. The flavonol content decreased slightly with processing and more markedly during storage of the jams. The ellagic acid derivatives, with the exception of ellagic acid itself, remained quite stable with processing and during 6 months of jam storage. The content of free ellagic acid increased 3-fold during the storage period. The initial content (10mg/kg of fresh weight of raspberries) increased 2-fold with processing, and it continued increasing up to 35mg/kg after 1 month of storage of the jam. Then a slight decrease was observed until 6 months of storage had elapsed. The increase observed in ellagic acid could be explained by a release of ellagic acid from ellagitannins with the thermal treatment [53].

Ellagic Acid and Natural Sources of Ellagitannins as Possible Chemopreventive Agents against Intestinal Tumorigenesis in the Min Mouse

Ellagic acid has been shown to have chemopreventive effects in various experimental cancer models. To examine whether pure ellagic acid and natural ellagitannins from cloudberry *(Rubus chamaemorus)* seed and pulp have any effect on adenoma formation in Apc-mutated Min mice. From the age of 5 week, the mice were fed either a control diet, a diet containing pure ellagic acid at 1,564mg/kg, or diets containing 4.7% (wt/wt) cloudberry seeds or 5.3% cloudberry pulp. The concentrations of ellagitannins and free ellagic acid in the seed diet were 807 and 42mg/kg and in the pulp diet 820 and 34mg/kg, respectively. After the 10 week feeding period, ellagic acid had no effect on the number or size of adenomas in the distal or total small intestine, but it increased adenoma size in the duodenum when compared with the control diet (1.50+/-0.29 vs. 1.16+/-0.31 mm; P = 0.029). Neither cloudberry seed nor pulp diets had any effect on the adenoma formation. Chemopreventive effects and mechanisms of whole cloudberry and other similar sources of phenolic compounds should, however, be studied, further taking into account food matrix and interactions with other dietary constituents that may be involved in the bioavailability and metabolism of ellagitannins [54].

The Preotective Rffects of Total Glycosides of Rubus parviflolius on Cerebral Ischemic in Rat

To observe the protective effects of total glycosides *Rubus parviflolius* on local cerebral ischemic, the local cerebral ischemia in rat was made by middle cerebral artery occlusion. The infraction weight was determined by TTC stain. SOD, MDA, GSH and apoptotis were determined with different method respectively. Total glycosides *Rubus parviflolius* 20, 10 mg x kg^{-1} is markedly improved the abnormal nervous symptoms, increased the SOD, GSH activity and reduced contentes of MDA in brain of middle cerebral artery occlusion rat, total glycosides *Rubus parviflolius* 20 mg x kg (-1) is significantly decreased the numbers of apoptotic cells in ischemic cortex. Total glycosides *Rubus parviflolius* has protective effects against cerebral infraction, and its mechanism may be related to anti-apoptotis and free radical [55].

Biological Activity Due to Rubus Species Crude Extract

The dried unripe fruit of *Rubus coreanus,* which is well-known in Korea and referred to as 'Bok-bun-ja', has been employed as a traditional medicine for centuries. This crude drug is utilized in Korea for the management of impotence, spermatorrhea, enuresis, asthma and allergic diseases. The principal objective of the present study was to conduct a comparison of the antiinflammatory effects of ethanol extracts of the unripe, half-ripened and ripe fruits of *Rubus coreanus.* Half-ripened and unripe were found to reduce the production of nitric oxide and prostaglandin E2 as well as pro-inflammatory cytokines, in lipopolysaccharide -stimulated RAW264.7 murine macrophages. However, ripe fruits exerted no inhibitory effects against the production of nitric oxide and IL-6. The results of the study show that the degree of fruit ripening of *Rubus coreanus* affects the production of inflammatory mediators such as nitric oxide, prostaglandin E2 and inflammatory cytokines [56].

The unripe fruits of *Rubus coreanus* have been used to remit diabetes mellitus and sexual disinclination. This crude drug contains triterpenoid glycosides such as coreanoside F1, suavissimoside, niga-ichigoside F1 and -F2. In addition to triterpenoids, the constituents of tannins, diterpenes, catechins have been also isolated from certain parts of other *Rubus sp* [47].

Activity of Rubus Crataegifolius Roots Extract as a Potent Apoptosis Inducer and DNA Topoisomerase I Inhibitor

The effects of methanol extract of *Rubus crategifolius* roots and its solvent fractions were investigated on the proliferation of MCF-7 human breast carcinoma cells. The methanol extract inhibited the proliferation of MCF-7 cells in a concentration dependent manner. Moreover, their methanol soluble (W-M) fraction had the greatest inhibitory effect on the growth of MCF- 7 cells. To evaluate whether the W-M fraction affects on the cell cycle of MCF-7 cells, cells treated with this fraction were analyzed with flow cytometry. The W-M fraction increased G0/G1 phase after 24 h-treatment and induced apoptosis after 48 h-treatment. The hallmark of apoptosis, DNA fragmentation, also appeared by W-M fraction after 48 hr treatment. Furthermore, the methanol extract and its WoM fraction inhibited the activity of the topoisomerase I enzyme in the relaxation assay. From these results, their W-M fraction as well as methanol extract of *R. crategifolius* roots are necessary for further studies as a potent inhibitor of the growth of cancer cells [57].

Antiinflammatory Activities of Rubus coreanus Depend on the Degree of Fruit Ripening

The dried unripe fruit of *Rubus coreanus,* which is referred to as 'Bok-bun-ja', has been employed as a traditional medicine for centuries. This crude drug is utilized in Korea for the management of impotence, spermatorrhea, enuresis, asthma and allergic diseases. The principal objective of the present study was to conduct a comparison of the antiinflammatory effects of ethanol extracts of the unripe, half-ripened and ripe fruits of *Rubus coreanus.* Unripe and half-ripened were found to reduce the production of nitric oxide and prostaglandin E2 as well as pro-inflammatory cytokines, in lipopolysaccharide-stimulated RAW264.7 murine macrophages. However, ripe fruits exerted no inhibitory effects against the production of nitric oxide and IL-6. The results of the study show that the degree of fruit ripening of *Rubus coreanus* affects the production of inflammatory mediators such as nitric oxide, prostaglandin E2 and inflammatory cytokines [58].

Anxiolytic Effect of Rubus brasilensis in Rats and Mice

The aim of the present work was to investigate if infuse and ethanolic extracts (aqueous, butanolic and wax fractions) of *Rubus brasiliensis* Martius (Rosaceae) induce anxiolytic effect. The extracts were administered to male Wistar rats and Swiss mice per oral route, at 50, 100 and 150 mg:kg, 30 min before the behavioral evaluation in the elevated plus maze. Both infuse and wax ethanolic fraction at the dosage 150mg/kg, increased the number and the percentage of open arm entries of rats and mice. The aqueous and butanolic fractions, obtained from ethanolic extract, failed to induce anxiolytic effect. The treatment of mice with flumazenil (Ro 15-1788), 1.5, 2.0 and 2.5 mg:kg, i.p., 15-min before the administration of infuse or wax fraction, 150 mg:kg, vo, blocked the infuse or wax fraction-induced anxiolytic effect. The LD_{50} for the wax fraction was 1000 mg:kg. The infuse and wax ethanolic fraction of *R. brasiliensis* present anxiolytic effect in rats and mice. The anxiolytic effect may be attributed at least to one liposoluble principle with low acute toxicity which may be acting as an agonist on GABAA-benzodiazepine receptor complex [59].

Rubus coreanus Miq. Extract Promotes Osteoblast Differentiation and Inhibits Bone-Resorbing Mediators in MC3T3-E1 Cells

To prevent bone loss that occurs with increasing age, certain nutritional and pharmacological factors are needed, the ethanol extract from the fruit of *Rubus coreanus* Miq. *Rubus coreanus* Miq was investigated for its effect on the function of osteoblastic MC3T3-E1 cells. *Rubus coreanus* Miq (10~50μg/ml) caused a significant elevation in cell viability, alkaline phosphatase activity, collagen content, and osteocalcin secretion in the cells. The effect of *Rubus coreanus* Miq (50μg/ml) in increasing cell viability, ALP activity, and collagen content was prevented by the presence of 10^{-6} M cycloheximide and 10–6 M tamoxifen, suggesting that RCE's effect results from a newly synthesized protein component and might be partly involved in estrogen action. It was examined the effect of *Rubus coreanus* Miq on the H_2O_2-induced apoptosis and production of local factors in osteoblasts. Treatment with *Rubus* coreanus Miq (10~50 μg/ml) decreased the 0.2 mM H2O2-induced apoptosis and production of tumor necrosis factor -α, interleukin (IL)-6 and nitric oxide in osteoblasts. Data indicate that the enhancement of osteoblast function by *Rubus coreanus* Miq. may result in the prevention of osteoporosis and inflammatory bone diseases [60].

Antibacterial Effect of a Magnetic Field on Serratia marcescens and Related Virulence to Hordeum vulgare and Rubus fruticosus callus Cells

The exposure to a static magnetic field of 80"20 Gauss (8"2 mT) resulted in the inhibition of *Serratia marcescens* growth. Callus cell suspensions from *Hordeum vulgare* and *Rubus fruticosus* were also examined and only the former was found to be affected by the magnetic field, which induced a decreased viability. *S. marcescens* was shown to be virulent only toward *H. vulgare* and this virulence was reduced by the presence of the magnetic field. The modification of glutathione peroxidase activity under the different experimental conditions allowed us to speculate on the possibility of an oxidative-stress response of *H. vulgare* both to *S. marcescens* infection and magnetic field exposure. Since the control of microbial growth by physical agents is of interest for agriculture, medicine and food sciences, the investigation presented herein could serve as a starting point for future studies on the efficacy of static magnetic field as low-costy easy-handling preservative agent [61].

Antigiardial Activity of Rubus coriifolius Focke in Suckling Mice CD-1

The antigiardial activity of crude methanolic extracts from *Helianthemum glomeratum* and *Rubus coriifolius,* plants used in Mexican traditional medicine for the treatment of diarrhea and dysentery, were demonstrated using experimental infections of *Giardia lamblia* in suckling female CD-1 mice. *In vivo* antigiardial activity was studied to determine the dose required to kill 50% of the trophozoites (ED50). Five single-doses between 1.25 and 20 mg extract/kg body weight were tested. Drugs metronidazole and emetine were used as reference. The ED50 (mg/kg) obtained for the extracts and drugs used as reference was 0.125 for *Helianthemum glomeratum,* 0.506 for *Rubus coriifolius,* 0.194 for metronidazole and 0.167 for emetine. Both methanolic extracts showed antigiardial activity, the extract of *Helianthemum glomeratum* was more active than *Rubus coriifolius,* and its activity is comparable to metronidazole and emetine. These results hold the perspective for the utilization of the extracts of these plants as an option to develop of novel antigiardial phytodrugs [62].

Induction of Heme Oxygenase-1 Mediates the Anti-Inflammatory Effects of Rubus coreanus Extract in Murine Macrophages

Foods of plant origin, especially fruits and vegetables, draw increased attention because of their potential benefits to human health. The aim of the present study was to determine *in vitro* anti-inflammatory activity of four different extracts obtained from the fruits of *Rubus coreanus* (aqueous and ethanol extracts of unripe and ripe fruits). Among the four extracts, the ethanol extract of unripe fruits of *R. coreanus* suppressed nitric oxide and prostaglandin E2 (PGE2) production in lipopolysaccharide (LPS)-stimulated RAW264.7 murine macrophages. Unripe fruits of *R. coreanus* by itself is a potent inducer of heme oxygenase-1 (HO-1). Inhibition of HO-1 activity by tin protoporphyrin, a specific HO-1 inhibitor, suppressed the unripe fruits of *R. coreanus* -induced reductions in the production of nitric oxide and PGE2 as well as the expression of inducible nitric oxide synthase and cyclooxygenase 2. The data suggest that URCE exerts anti-inflammatory effects in macrophages via activation of the HO-1 pathway and helps to elucidate the mechanism underlying the potential therapeutic value of *R. coreanus* extracts [63].

Antimicrobial Activity of Rubus chamaemorus Leaves

The antibacterial activity of *Rubus chamaemorus* leaf butanolic fraction of the methanol extract and ellagic acid was evaluated against some Gram-positive and Gram-negative bacteria. Antimycotic activity was assayed against *Candida albicans.* MICs and MBCs were determined by broth dilution test and by disc diffusion method [64].

Radical Scavenging Activity and Composition of Raspberry (Rubus idaeus) Leaves from Different Locations in Lithuania

Raspberry *(Rubus idaeus)* leaves, collected in different locations of Lithuania were extracted with ethanol and the extracts were tested for their antioxidant activity by using ABTSU+ decolourisation and DPPHU scavenging methods. All extracts were active, with radical scavenging capacity at the used concentrations from 20.5 to 82.5% in DPPHU reaction system and from 8.0 to 42.7% in ABTSU+ reaction. The total amount of phenolic compounds in the leaves varied from 4.8 to 12.0mg of gallic acid equivalents in 1g of plant extract. Quercetin glucuronide, quercetin-3-*O*-glucoside and rutin were identified in the extracts [65].

Antioxidant Status in Humans after Consumption of Blackberry (Rubus fruticosus L.) Juices with and Without Defatted Milk

The present study was designed to evaluate the possible effect of the consumption of blackberry juices prepared with water and defatted milk on the plasma antioxidant capacity and the enzymatic and nonenzymatic antioxidants. A significant ($p < 0.05$) increase in the ascorbic acid content in the plasma was observed after intake of both blackberry juices. However, no changes were observed in the plasma urate and R-tocopherol levels. An increase on the plasma antioxidant capacity, by ORAC assay, was observed only after consumption of BJW but not statistically significant. Plasma antioxidant capacity had a good positive correlation with ascorbic acid (*r*) 0.93) and a negative correlation with urate level (*r*) -0.79). No correlation was observed between antioxidant capacity and total cyanidin or total ellagic acid contents. Further, it was observed that plasma catalase increased following intake of BJ's. No change was observed on the plasma and erythrocyte CAT and glutathione peroxidase activities. A significant decrease ($p < 0.05$) in the urinary antioxidant capacity between 1 and 4h after intake of both blackberry juices was observed. A good correlation was observed between total antioxidant capacity and urate and total cyanidin levels. These results suggested association between anthocyanin levels and CAT and a good correlation between antioxidant capacity and ascorbic acid in the human plasma after intake of blackberry juices. Follow-up studies investigating the antioxidant properties and health benefits are necessary to demonstrate the health benefits of polyphenols [66].

Characterization of Increased Phenolic Compounds from Fermented Bokbunja (Rubus coreanus Miq.) and Related Antioxidant Activity

This study examined the changes in the phenolic acid-content and antioxidant activity of Rubi Fructus, the fruit of *Rubus coreanus* Miq., after fermentation with yeast (Saccharomyces cerevisiae). The phenolic acids were fractionated into three forms, free (Fr. A), ester (Fr. B), and insoluble-bound phenolic acids (Fr. C) and quantified by high performance liquid chromatography with a diode array detector (HPLC-DAD). This method was validated and allowed the successful identification of 11 phenolic acids in the Rubi Fructus extracts. HPLC-DAD analysis of the samples showed substantial increases in the levels of protocatechuic, vanillic and p-coumaric acid as the result of yeast fermentation. The total phenolic content was also increased by fermentation. The total phenolics in Fr. A and Fr. B increased from 117 to 173mg GAE/100g and from 488 to 578mg GAE/100g, respectively. The total phenolics in Fr. C decreased from 264 to 175mg GAE/100g. The antioxidant activity of the fermented Rubi Fructus was measured as the 1,1-diphenoly-2-picrylhydrazyl radical scavenging capacity, which is expressed as the IC50. The IC50 for Fr. A and Fr. B decreased from 5.9 to 4.0mg/ml (mg of dried Rubi Fructus equiv./ml) and from 1.2 to 0.8mg/ml, respectively. In Fr. C, the IC50 value increased from 2.1 to 2.8mg/ml. In summary, the fermented Rubi Fructus had a higher total phenolic content and better 1,1-diphenoly-2-picrylhydrazyl radical-scavenging activity than the unfermented material [67].

Antiviral Activities of Rubus coreanus against Hepatitis B Virus

The antiviral effects of aqueous extracts of *Terminalis chebula* Retz., *Sanguisorba officinalis* L., *Rubus coreanus* Miq. and *Rheum palmatum* L. were examined by a cell culture system using a hepatitis B virus producing cell line, Hep G2 2.2.15. The extracts were assayed for the inhibition of HBV multiplication by measurement of HBV DNA and surface antigen (HBsAg) levels in the extracellular medium of HepG2 2.2.15 cells after an 8-day treatment. All extracts decreased the levels of extracellular hepatitis B virus virion DNA at concentrations ranging from 64 to 128g/ml and inhibited the secretion of HBsAg dose dependently [68].

Involvement of GABAA-Benzodiazepine Receptor in the Anxiolytic Effect Induced by Hexanic Fraction of Rubus brasiliensis

To investigate the ability of hexanic ethanolic fraction of *Rubus brasiliensis* Martius, to induce anxiolytic effect and also the possible involvement of the GABAA-benzodiazepine receptor complex, male Wistar rats and Swiss mice behaviour were tested in the elevated plus maze. All the doses of the extract, 50, 100 and 150mg/kg, administered per gavage, 30 min before the behavioural evaluation, induced an anxiolytic effect expressed by: increased number of entries in and time spent in the open arms and percentage of open arm entries; and decreased number of entries and time spent in the closed arms. The treatment of mice with flumazenil (Ro 15-1788), 0.5, 1.0 and 1.5 mg:kg, i.p., 15-min before the administration of hexanic fraction, 100 mg:kg, blocked the hexanic fraction-induced anxiolytic effect. The LD50 for the hexanic fraction was 1512 mg:kg. It was shown that the hexanic fraction of *R. brasiliensis* induced an anxiolytic effect in rats and mice. This effect can be attributed to a liposoluble principle with low toxicity which may be acting as an agonist on GABAA-benzodiazepine receptor complex [69].

4-Coumarate: Co Aligase Gene Family in Rubus idaeus: cDNA Structures, Evolution, and Expression

The enzyme 4-coumarate: CoAligase (4CL) activates cinnamic acid and its hydroxylated derivatives by forming the corresponding CoA thioesters. These serve as substrates for biosynthesis of phenylpropanoid-derived end-products that are important determinants of fruit quality in raspberry (*Rubus idaeus* L.). In higher plants, 4CL is typically encoded by a gene family. To investigate the participation of distinct *4CL* genes in the process of fruit ripening, scientists have characterized this gene family in raspberry. By complementing a PCR-based homology search with lowstringency cDNA library screening, Scientists have isolated three classes of raspberry *4CL* cDNAs (*Ri4CL1*, *Ri4CL2*, and *Ri4CL3*). Phylogenetic analysis places the three raspberry *4CL* gene family members into two distinct groups, a pattern consistent with an ancient divergence from an ancestral progenitor. Quantitative RT-PCR assay reveals a differential pattern of transcription of each of the three genes in various organs, as well as distinct temporal patterns of expression during flower and fruit development. The regulatory elements thus appear to have evolved independently of the genes themselves. Based on phylogenetic classification, expression patterns and recombinant protein activities the different *Ri4CL* genes are likely to participate in different biosynthetic pathways leading to the various phenylpropanoid-derived metabolites that help create flavor and color in raspberry fruit (Fig. 8) [70].

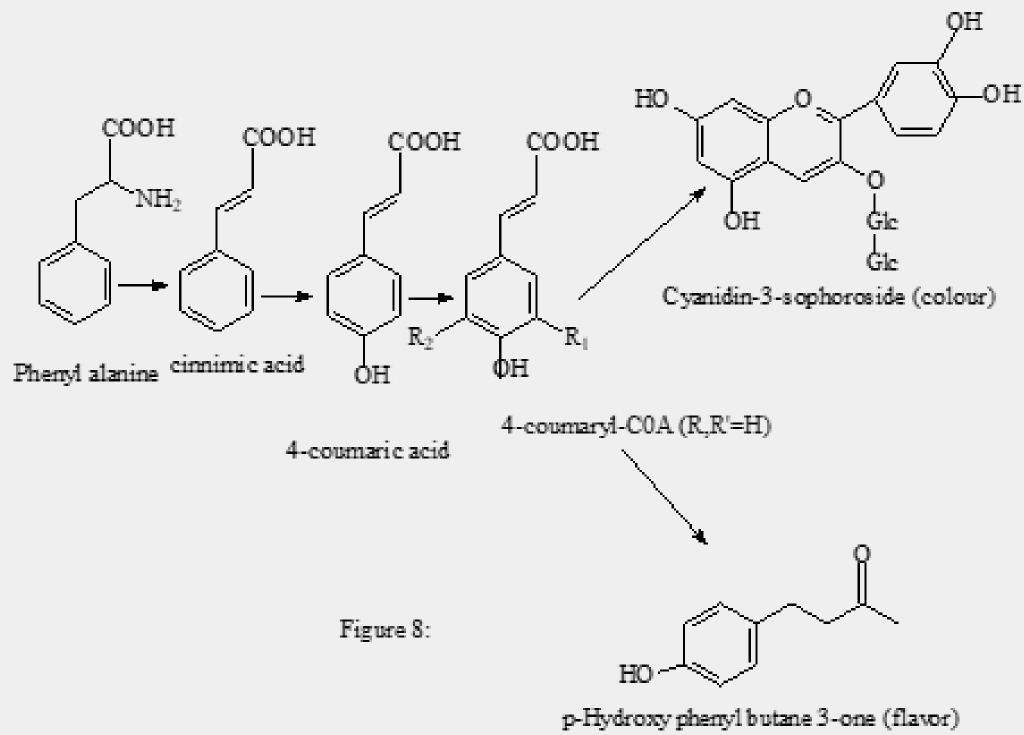


Figure 8:

Some plant extracts containing gallic acid as one of the constituent of *Rubus* specie have been tested for various biological and microbial activities by different scientists.

Blackberry (Rubus spp.). a pH-dependent Oral Contrast Medium for Gastrointestinal Tract Images by Magnetic Resonance Imaging

Seven fruits have been tested on their magnetic properties, paramagnetic metal content and contrast enhancement in magnetic resonance imaging of phantom and *in vivo.* Magnetic susceptibility was determined for the fruit pulps, as well as the contents of paramagnetic metals; iron, manganese and copper. The total content of these metals was 4.3, 8.6, 11.1, 10.9, 12.3, 8.3 and 29.3mg/kg of fruit for plum, blueberry, apple, pineapple, beet, grape, blackberry, respectively, and with magnetic susceptibility of 2.29F0.07, 2.43F0.07, 2.13F0.07, 1.84F0.02, 1.75F0.01, 1.78F0.06, 2.18F0.07 SI, respectively. T1- and T2-weighted MR images were performed for the seven fruits and water (v = 9.98 10 3 SI) and in one subject. While there was no correlation between the magnetic susceptibility and contrast enhancement, there is a correlation with the total paramagnetic metal content determined with contrast enhancement in magnetic resonance imaging. Thus, blackberry contrast enhancement was the highest among the fruits in T1-weighted images. Furthermore, this fruit's contrast enhancement shows to be pH-dependent. These characteristics and the wide availability of the *Rubus* spp. suggest that it should be implemented as an oral contrast agent in images by MR to assess the function of the gastric section of the GI tract. Furthermore, it has the advantage of being a natural meal, so that it can be well tolerated by the patients and use as much as it is needed without side effects [71].

Hypoglycaemic Effect of Rubus fructicosis L. in Normal and Streptozotocin-Induced Diabetic Rats

The effect of oral administration of the aqueous extract of *Rubus fructicosis* L. and *Globularia alypum* L. leaves on blood glucose levels in normal and streptozotocin diabetic rats investigated. In normal rats, single and repeated oral administration of *Rubus fructicosis* lowered significantly the blood glucose levels, while, Globularia alypum treatment did not change blood glucose levels. In streptozotocin rats, single and repeated oral administration of both *Rubus fructicosis* and Globularia alypum produced significant decrease of blood glucose levels. *Rubus fructicosis* and Globularia alypum treatments did not affect insulin secretion both in normal and streptozotocin rats, indicating that mechanism by which these plants decrease blood glucose levels is extra-pancreatic at least, for the doses used. In addition, the acute toxicity study revealed that the aqueous extracts may be considered relatively safe since that the LD_{50} value was over 8.1 and 14.5g/kg for *Rubus fructicosis* and Globularia alypum respectively. These findings indicate that *Rubus fructicosis* and *Globularia alypum* represent an effective blood glucose lowering and a potential source for discovery of new orally active component for future therapy [72].

Influence of Cultivar, Maturity, and Sampling on Blackberry (Rubus L. Hybrids) Anthocyanins, Polyphenolics, and Antioxidant Properties

Total anthocyanin pigments increased from 74.7 to 317mg/100g fresh weight from underripe to overripe for Marion blackberries and from 69.9 to 164 mg/100 g fresh weight for evergreen blackberries. Total phenolics did not show a marked change with maturity with values slightly decreasing from underripe to ripe. Antioxidant activities, while increasing with ripening, also did not show the marked change that total anthocyanins exhibited. The impact of variation due to plots, subsampling, sample preparation, and measurement on Marion composition was examined in detail. Plot-to-plot and sample differences were the major contributors to variation, with sample preparation being an important contributor for some parameters. Measurement variation was a relatively small component of the total variation. Total anthocyanins for 11 blackberry cultivars ranged from 131 to 256mg/100 g FW (mean) 198), total phenolics ranged from 682 to 1056mg GAE/100g FW (mean) 900), oxygen radical absorbance capacity ranged from 37.6 to 75.5 ímol TE/g FW (mean) 50.2), and ferric reducing antioxidant power ranged from 63.5 to 91.5 ímol TE/g FW (mean) 77.5) [73].

Protective Effects of Cyanidin-3-O-Glucoside from Blackberry Extract against Peroxynitrite-Induced Endothelial Dysfunction and Vascular Failure

Anthocyanins are a group of naturally occurring phenolic compounds as colorants in several plants, flowers and fruits. These pigments have a great importance as quality indicators, as chemotaxonomic markers and antioxidants. The content of blackberry (*Rubus* species) juice was investigated by HPLC/ESI/MS using narrow bore HPLC columns. Using this method we demonstrated that cyanidin-3-*O*-glucoside represents about 80% of the total anthocyanin contents in blackberry extract. Here we investigated antioxidant activity of the blackberry juice and cyanidin-3-*O*-glucoside on the endothelial dysfunction in cells and in vascular rings exposed to peroxynitrite. In human umbilical vein endothelial cells *in vitro,* peroxynitrite caused a significant suppression of mitochondrial respiration (38 F 2.1% of control cells), as measured by the mitochondrial-dependent conversion of the dye MTT to formazan. Peroxynitrite caused DNA strand breakage (63 F 1.9% single strand vs 3 F 0.9% single strand in control cells), as measured by the alkaline unwinding assay, and caused an activation of PARS, as measured by the incorporation of radiolabeled NAD+ to nuclear proteins. Blackberry juice (different dilutions that contained 80ppm; 40ppm;14.5ppm of cyanidin-3-*O*-glucoside) and cyanidin-3-*O*-glucoside (as chloride) (0.085 AM; 0.028 AM; 0.0085 AM) reduced the peroxynitrite-induced suppression of mitochondrial respiration, DNA damage and PARS activation in human umbilical vein endothelial cells. Vascular rings exposed to peroxynitrite exhibited reduced endothelium-dependent relaxant responses in response to acetylcholine as well as a vascular contractility dysfunction in response to norepinephrine. The development of this peroxynitrite-induced vascular dysfunction was ameliorated by the blackberry juice (different dilutions that contained 80ppm; 40ppm; 14.5ppm of cyanidin-3-*O*-glucoside) and cyanidin-3-*O*-glucoside (as chloride) (0.085 AM; 0.028 AM; 0.0085 AM). Blackberry juice containing cyanidin-3-*O*-glucoside is a scavenger of peroxynitrite and that exert a protective effect against endothelial dysfunction and vascular failure induced by peroxynitrite [74].

Therapeutic Constituents and Actions of Rubus Species

In the search for biologically active compounds, one of the most frequently documented species of the genus is the raspberry plant *R. idaeus,* the leaves of which have been used traditionally as a uterine relaxant and stimulant during confinement, for the treatment of diarrhoea and similar enteric disorders and as an astringent. Investigations of other *Rubus* species have been conducted in the last twenty-five years, and have shown possible application for a wide range of indications, including bacterial infections, anxiety, pain and inflammation [10].

Hyaluronidase Inhibitory Activity from the Polyphenols in the Fruit of Blackberry (Rubus fruticosus B.)

The hyaluronidase inhibitory activity of different fractions obtained from aqueous extract of blackberry fruits was evaluated. Scientists found that only two fractions inhibit the tested enzyme. Blackberry (*Rubus fruticosus* B.), from rosaseae family, is a small tree with red-blackish fruit containig polyphenols w1x. There is a large number of biological activities due to polyphenols in various plants w2–7x. In particular, anti-inflammatory activity was described for blackberry fruit [75].

Analysis of Phenolic Compounds in Two Blackberry Species (Rubus glaucus and Rubus adenotrichus) by High-Performance Liquid Chromatography

High-performance liquid chromatography with diode array and electrospray ionization mass spectrometric detection was used to analyze phenolic compounds of two blackberry species (*Rubus glaucus* Benth. and *Rubus adenotrichus* Schlech.) growing in South America. UV visible spectrophotometry was a valuable tool for identifying the class of phenolic compound. Ellagitannins were the major compounds, with sanguiin H-6 and lambertianin C being the predominant ones. The anthocyanin composition as well as the presence or absence of kaempferol glycosides can be used to distinguish the Rubus species studied. Flavonol hexoside-malonates were identified in both berries. Hydroxycinnamic acids were minor compounds and found as ferulic, caffeic, and p-coumaric acid esters. Similar contents were obtained by analysis of soluble ellagitannins and ellagic acid glycosides as ellagic acid equivalents and by analysis of ellagic acid equivalents released after acid hydrolysis [76].

Changes in Wall-Bound Polysaccharidase Activities During the Culture Cycle of a Rubus fruticosus Cell Suspension

Several hydrolytic enzyme activities were detected in the wall of developing cells of *Rubus fruticosus* in suspension culture. The corresponding substrates of the enzymes are mostly polysaccharide wall constituents, except for chitinase activity. The activities measured when the enzymes were in the free state or wall-bound showed the positive influence of the cell wall micro-environment. Changes in the activities during a cell culture cycle demonstrated that those enzymes acting on xyloglucans behaved differently from the others, and suggest that xyloglucans undergo modifications *in vivo* over a longer period of time during the exponential growth phase. The same activities were identified in the culture medium. Endo- 1, 4-fl- D-glucanase activities which depolymerized carboxymethylcellulose and xyloglucans were assayed viscosimetrically. It was found that xyloglucans oligosaccharides exhibited an inhibitory effect on the depolymerization of xyloglucans but not on that of carboxymethylcellulose. This suggests that true xyloglucanases are present in the culture of *Rubus* cells [77].

In-vitro Mutagenic Potential and Effect on Permeability of Co-administered Drugs across Caco-2 Cell Monolayers of Rubus idaeus

This study investigated the mutagenic, anti-mutagenic and cytotoxic effects of acetone extract of raspberry, *Rubus idaeus* L. Rosaceae, and the isolated and characterized ellagitannin and anthocyanin fractions thereof, suitable for food applications. The studied raspberry extract and fractions did not show any mutagenic effects determined in the miniaturized Ames test and were not cytotoxic to Caco-2 cells at the used concentrations. However, the anti-mutagenic properties were changed (i.e. decreased mutagenicity of 2-nitrofluorene in strain TA98, and slightly increased mutagenicity of 2-aminoanthracene in strain TA100) with metabolic activation. Further, their influence on the permeability of co-administered common drugs (ketoprofen, paracetamol, metoprolol and verapamil) across Caco-2 monolayers was evaluated. The apical-to-basolateral permeability of highly permeable verapamil was mostly affected (decreased) during co-administration of the raspberry extract or the ellagitannin fraction. Ketoprofen permeability was decreased by the ellagitannin fraction. Consumption of food rich in phytochemicals, as demonstrated here with chemically characterized raspberry extract and fractions, with well-absorbing drugs would seem to affect the permeability of some of these drugs depending on the components [78].

Cell Wall Disassembly Events in Boysenberry (Rubus idaeus L. Rubus ursinus Cham. & Schldl.) Fruit Development

Boysenberry fruit was harvested at five developmental stages, from green to purple, and changes in pectin and hemicellulose solubilisation and depolymerisation, polymer neutral sugar contents, and the activities of cell wall degrading enzymes were analysed. The high xylose to glucose ratio in the 4% KOH-soluble hemicellulose fraction suggests that xylans are abundant in the boysenberry cell wall.

Although the cell wall changes associated with fruit development do not proceed in discrete stages and the cell wall disassembly is a consequence of highly regulated changes occurring in a continuum, the results suggest that the temporal changes in cell wall degradation in boysenberry account for at least three stages: an early stage (green to 75% red colour), associated with metabolism of cellulose and cross-linking glycans; an intermediate period (75 to 100% red colour), characterised by substantial pectin solubilisation without depolymerisation in which α-arabinofuranosidase increases markedly and 50% of the wall arabinose is lost; and a final stage (100% red colour to purple), characterised mainly by a reduction of pectic galactose content and a dramatic increase in pectin depolymerisation associated with higher polygalacturonase, pectin methylesterase, acetyl esterase and β-galactosidase activities. From a biotechnological perspective enzymes involved in pectin matrix disassembly seem to be the better candidates to affect boysenberry fruit late-softening by genetic intervention [79].

Environmental and Seasonal Influences on Red Raspberry Anthocyanin Antioxidant Contents and Identification of Quantitative Traits Loci

Consumption of raspberries promotes human health through intake of pharmaceutically active antioxidants, including cyanidin and pelargonidin anthocyanins; products of flavonoid metabolism and also pigments conferring colour to fruit. Raspberry anthocyanin contents could be enhanced for nutritional health and quality benefits utilising DNA polymorphisms in modern marker assisted breeding. The objective was to elucidate factors determing anthocyanin production in these fruits. HPLC quantified eight anthocyanin cyanidin and pelargonidin glycosides: -3-sophoroside, -3-glucoside, -3-rutinoside and -3-glucosylrutinoside across two seasons and two environments in progeny from a cross between two *Rubus* subspecies, *Rubus idaeus* (cv. Glen Moy)x *Rubus strigosus* (cv. Latham). Significant seasonal variation was detected across pigments less for different growing environments within seasons. Eight antioxidants mapped to the same chromosome region on linkage group 1, across both years and from fruits grown in field and under protected cultivation. Seven antioxidants also mapped to a region on LG 4 across years and for both growing sites. A chalcone synthase (PKS 1) gene sequence mapped to linkage group 7 but did not underlie the anthocyanin quantitative traits loci identified. Other candidate genes including basic-helix-loop-helix, NAM/CUC2-like protein and bZIP transcription factor underlying the mapped anthocyanins were identified [80].

Plant Extracts as Natural Amoebicidal Agents

Strains of Acanthamoeba sp. constitute a factor contributing to the occurrence of chronic granulomatous amoebic encephalitis, keratitis, pneumonia, as well as inflammations of other organs. Treatment of these diseases is very difficult and not always effective. The aim of our study was to examine the amoebicidal or amoebistatic activity of plant extracts from *Rubus chamaemorus,* Pueraria lobata, Solidago virgaurea and Solidago graminifolia. For the purpose of isolation of pharmacologically active substances, Scientidts used the aboveground parts of plants, together with flowers, roots and leaves. It was established that extracts from *S. virgauera, P. lobata* and *R. chamaemorus* displayed chemotherapeutic properties *in vitro* in concentrations of approximately 0.01-0.05 mg extract/mL, i.e. in concentrations of 0.350 mug/mL expressed in ellagic acid for R. chamaemorus and 0.053 mug/mL expressed in puerarin for P. lobata. Therapeutic index values is 3.5-20. As a result of *in vivo* experiments, it was found out that, following therapy using the extracts, animals infected with Acanthamoeba sp. survived for an extended period (2.5-3 times longer). It was determined that plant extracts may be used both externally and internally in the case of a combined therapy for acanthamoebiasis. The tested extracts are not toxic for animals [81].

Anti-allergic Effects of Rubus suavissimus Extract

To investigate the effects of *Rubus suavissimus S.* Lee extract on mice, and its influence on release of histamine from rat peritoneal mast cells induced by compound 48/80 *in vitro*. To establish murine delayed-type-hypersensitive model induced by 2, 4-dinitrofluotobenzene and sheep red blood cell; murine type I allergic reaction induced by PCA, and then to observe the anti-allergic effect of RSE. HPLC-ECD methods were performed to detect the contents of histamine released from rat peritoneal mast cells induced by compound 48/80 *in vitro.* Compared with the model group, RSE could ameliorate the ear swelling and capillary permeability in mice induced by 2,4-dinitrofluotobenzene and PCA. *Rubus suavissimus S.* Lee also reduced the thickness of the mice hind paw induced by sheep red blood cell in significant dose-dependent manner. Meanwhile, *Rubus suavissimus S.* Lee obviously inhibited the release of histamine in rat peritoneal mast *in vitro*, a dose-dependent manner. *Rubus suavissimus S.* Lee extract exerts potential anti-allergy effects and the mechanisms may be partly related to its inhibitory effect on the release of histamine from mast cells [82].

Quantitative Determination of *Rubus* Species Contents

Identification and Quantification of Phenolic Compounds in Berries of Fragaria and *Rubus* Species

High-performance liquid chromatography combined with diode array and electrospray ionization mass spectrometric detection was used to study soluble and insoluble forms of phenolic compounds in strawberries, raspberries (red and yellow cultivated and red wild), arctic bramble, and cloudberries. Hydroxycinnamic acids were present as free forms in cloudberries and mainly as sugar esters in the other berries. Quercetin 3-glucuronide was the typical flavonol glycoside in all of the berries studied. The composition of the predominant anthocyanins can be used to distinguish the studied red *Rubus* species from each other since cyanidin was glycosylated typically with 3-sophorose (56%) in cultivated red raspberry, with 3-sophorose (30%) and 3-glucose (27%) in wild red raspberry, and with 3-rutinose (80%) in arctic bramble. Ellagic acid was present as free and glycosylated forms and as ellagitannins of varying degrees of polymerization. Comparable levels of ellagitannins were obtained by the analysis of soluble ellagitannins as gallic acid equivalents and by the analysis of ellagic acid equivalents released by acid hydrolysis of the extracts [29].

Study on Quality Control of *Rubus suavissimus*

To control the quality of *Rubus suavissimus.* scientists inspected the character observation, microscopic, physical and chemical identification, TLC, the examination of water and extraction of *Rubus suavissimus,* then used HPLC to assay the contents of the principal sweet taste component. The quality control indexes of *Rubus suavissimus* were founded. The method is feasible and can control the quality of *Rubus suavissimus* [83].

Quantitative and Fingerprint Analyses of Chinese Sweet Tea Plant (*Rubus suavissimus S.* Lee)

An HPLC fingerprinting method for the quality evaluation of *Rubus suavissimus* leaves possessing multiple bioactivities was developed. Five constituents, gallic acid, rutin, ellagic acid, rubusoside, and steviol monoside, were quantified and used in developing qualitative chromatographic fingerprints. The limits of detection and quantification ranged from 0.29 to 37.86 mug/mL. The relative standard deviations of intra- and interday precisions were no more than 3.14 and 3.01%, respectively. The average recoveries were between 93.1 and 97.5%. The developed method was validated in the analysis 14 leaf samples with satisfactory results. The contents of the five marker compounds accounted for an average of about 6% w/w with a variability of 16% among the 14 samples collected from a single site and year. Gallic acid was the least, whereas steviol monoside the most, variable compound among the 14 leaf samples. The characteristic compound rubusoside that is responsible for the sweet taste accounted for 5% of leaf weight. The validated method can now be used to quantitatively and qualitatively assess the quality of *R. suavissimus* leaves as traditional beverage or potential medicines [84].

Identification, Characterization, and Detection of Black Raspberry Necrosis Virus

A serious disease was observed in black raspberry *(Rubus occidentalis)* in Oregon in the last decade. Plants showing mosaic symptoms declined rapidly and, in many cases, died after several years. Double-stranded RNA extraction from symptomatic black raspberry revealed the presence of two high molecular weight bands which were cloned and sequenced. Sequence analysis disclosed the presence of a novel virus that was tentatively named Black raspberry decline-associated virus (BRDaV). The complete sequences of the two genomic RNAs, excluding the 3' poly-adenosine tails, were 7, 581 and 6,364 nucleotides, respectively. The genome organization was identical to that of Strawberry mottle virus, a member of the genus Sadwavirus. The C terminus of the RNA 1 poly-protein is unique within the genus Sadwavirus, with homology to AlkB-like domains, suggesting a role in repair of alkylation damage. A reverse-transcriptase polymerase chain reaction test was designed for the detection of BRDaV from *Rubus* tissue, and tests revealed that BRDaV was associated consistently with the observed decline symptoms. While this publication was under review, it came to our attention that scientists at the Scottish Crop Research Institute had molecular data on Black raspberry necrosis virus (BRNV), a virus that shared many biological properties with BRDaV. After exchange of data, we concluded that BRDaV is a strain of BRNV, a previously described yet unsequenced virus. The North American strain was vectored nonpersistently by the large raspberry aphid and the green peach aphid. Phylogenetic analysis indicates that BRNV belongs to the genus Sadwavirus [85].

Mapping QTLs for Developmental Traits in Raspberry from Bud Break to Ripe Fruit

Protected cropping systems have been adopted by the UK industry to improve fruit quality and extend the current season. Further manipulation of season, alongside consideration of climate change scenarios, requires an understanding of the processes controlling fruit ripening. Ripening stages were scored from May to July across different years and environments from a raspberry mapping population. Here the interest was in identifying QTLs for the overall ripening process as well as for the time to reach each stage, and principal coordinate analysis was used to summarise the ripening process. Linear interpolation was also used to estimate the time (in days) taken for each plot to reach each of the stages assessed. QTLs were identified across four chromosomes for ripening and the time to reach each stage. A MADS-box gene, Gene H and several raspberry ESTs were associated with the QTLs and markers associated with plant height have also been identified, paving the way for marker assisted selection in *Rubus idaeus* [86].

Migration and Bioavailability of (137) Cs in Forest Soil of Southern Germany

To give a quantitative description of the radiocaesium soil-plant transfer for fern (Dryopteris carthusiana) and blackberry *(Rubus fruticosus),* physical and chemical properties of soils in spruce and mixed forest stands were investigated. Of special interest was the selective sorption of radiocaesium, which was determined by measuring the Radiocaesium Interception Potential. Forest soil and plants were taken at 10 locations of the Altdorfer Wald (5 sites in spruce forest and 5 sites in mixed forest). It was found that the bioavailability of radiocaesium in spruce forest was on average seven times higher than in mixed forest. It was shown that important factors determining the bioavailability of radiocaesium in forest soil were its exchangeability and the radiocaesium interception potential of the soil. Low potassium concentration in soil solution of forest soils favors radiocaesium soil-plant transfer. Ammonium in forest soils plays an even more important role than potassium as a mobilizer of radiocaesium. The availability factor - a function of Radiocaesium Interception Potential, exchangeability and cationic composition of soil solution characterized reliably the soil-plant transfer in both spruce and mixed forest. For highly organic soils in coniferous forest, radiocaesium sorption at regular exchange sites should be taken into account when its bioavailability is considered [87].

Benzothiadiazole Affects the Leaf Proteome in Arctic Bramble (*Rubus* arcticus)

Benzothiadiazole induces resistance to the downy mildew pathogen, Peronospora sparsa, in arctic bramble, but the basis for the Benzothiadiazole -induced resistance is unknown. Arctic bramble cv. Mespi was treated with Benzothiadiazole to study the changes in leaf proteome and to identify proteins with a putative role in disease resistance. First, Benzothiadiazole induced strong expression of one PR-1 protein isoform, which was also induced by salicylic acid (SA). The PR-1 was responsive to Benzothiadiazole and exogenous salicylic acid despite a high endogenous SA content (20-25 microg/g fresh weight), which increased to an even higher level after treatment with Benzothiadiazole. Secondly, a total of 792 protein spots were detected in two-dimensional gel electrophoresis, eight proteins being detected solely in the Benzothiadiazole -treated plants. Benzothiadiazole caused up- or down-regulation of 72 and 31 proteins, respectively, of which 18 were tentatively identified by mass spectrometry. The up-regulation of flavanone-3-hydroxylase, alanine aminotransferase, 1-aminocyclopropane-1-carboxylate oxidase, PR-1 and PR-10 proteins may partly explain the Benzothiadiazole -induced resistance against P. sparsa. Other proteins with changes in intensity appear to be involved in, for example, energy metabolism and protein processing. The decline in ATP synthase, triosephosphate isomerase, fructose bisphosphate aldolase and glutamine synthetase suggests that Benzothiadiazole causes significant changes in primary metabolism, which provides one possible explanation for the decreased vegetative growth of foliage and rhizome observed in Benzothiadiazole -treated plants [88].

Arsenic, Lead and Nickel Accumulation in *Rubus ulmifolius* Growing in Contaminated Soil in Portugal

This work investigates the potential of *Rubus ulmifolius,* indigenous to a metal contaminated site - Esteiro de Estarreja - for phytoremediation purposes. The site has a long history of metal contamination.

The accumulation of lead, arsenic and nickel in different sections - roots, stems and leaves - of the plant was assessed and compared to the levels of those metals in the soil and in the available fraction. The distribution of metals throughout the area was quite heterogeneous, presenting levels of As, Pb and Ni of up to 3078, 1400 and 135mgkg^{-1}, respectively, and the metal content in the sections of *R. ulmifolius* collected in the banks of the stream varied among sites of collection. Levels of metals were higher in the plant roots: As levels (mg kg^{-1}) ranged from 277 to 1721 in the roots, 30 to 110 in the stems, and 60 to 265 in the leaves; Pb concentrations (mgkg^{-1}) ranged from 248 to 1178 in the roots, 35 to 133 in the stems, and 25 to 149 in the leaves; and Ni (mgkg^{-1}) ranged from 48 to 151 in the roots. Significant correlations were found between the total levels of Pb and As in the soil and the levels in the roots of the plant; further correlations between total and available levels in the soil and metals in other plant tissues were generally found as non-significant According to the metal accumulation patterns of *R. ulmifolius,* this species seems to be valuable for application in phytostabilisation strategies [89].

Storage Stability of Microencapsulated Cloudberry *(Rubus chamaemorus)* Phenolics

Cloudberries *(Rubus chamaemorus)* contain phenolics (mainly ellagitannins), which have recently been related to many valuable bioactivity properties. In general, phenolics are known to react readily with various components, which may create an obstacle in producing stable functional components for food and pharmaceutical purposes. In this study, the aim was to improve the storage stability of cloudberry phenolic extract by microencapsulation. The phenolic-rich cloudberry extract was encapsulated in maltodextrins DE5-8 and DE18.5 by freeze-drying. Water sorption properties and glass transition temperatures of microcapsules and maltodextrins were determined. Microcapsules together with unencapsulated cloudberry extract were stored at different relative vapor pressures (0, 33, and 66% RVP) at 25 degrees C for 64 days, and storage stability was evaluated by analyzing phenolic content and antioxidant activity. Compared to maltodextrin DE18.5, maltodextrin DE5-8 had not only higher encapsulation yield and efficiency but also offered better protection for phenolics during storage. Without encapsulation the storage stability of cloudberry phenolics was weaker with higher storage RVP. Microencapsulation improved the storage stability of cloudberry phenolics. The physical state of microcapsules did not have a significant role in the stability of cloudberry phenolics because phenolic losses were observed also in amorphous glassy materials. The antioxidant activity of the microencapsulated cloudberry extract remained the same or even improved slightly during storage, which may be related to the changes in phenolic profiles [64].

Populations of *Xylella fastidiosa* in Plants Required for Transmission by an Efficient Vector

Xylella fastidiosa, a xylem-limited bacterium that causes Pierce's disease of grapevine and other diseases, is transmitted efficiently by xylem-feeding leafhoppers. Acquisition of a Pierce's disease strain of X. fastidiosa by the blue-green sharpshooter from five plant host species-grapevine (Vitis vinifera), Himalayan blackberry (*Rubus* discolor), California mugwort (Artemisia douglasiana), watergrass (Echinochloa crus-galli), and Bermuda grass (Cynodon dactylon)-was tested at various time intervals after vector inoculation. The minimum incubation periods in plant hosts before BGSS acquired X. fastidiosa were 4, 22, 29, and 25 days for grapevine, blackberry, mugwort, and watergrass, respectively. There were no transmissions by vectors or recoveries of X. fastidiosa by culturing from Bermuda grass in 133 attempts, including 80 attempts with the green sharpshooter, Draeculacephala minerva. The first acquisitions and subsequent transmissions by

BGSS occurred after X. fastidiosa multiplied to a population of about 10(4) CFU/g of stem tissue. Higher populations of bacteria in plants resulted in higher rates of transmission. In grapevine, the rate of transmission increased over time (4.5% in the first 10 days to 55% after day 25) as the maximum number of viable CFU of X. fas-tidiosa recovered by culturing also increased (from 5 x 10(5) CFU/g during the first 10 days to 5 x 10 (8) after day 25) [90].

Rubus Chlorotic Mottle Virus, A New Sobemovirus Infecting Raspberry and Bramble

The complete nucleotide sequence of a new member of the unassigned genus Sobemovirus, isolated from raspberry and bramble plants in north east Scotland and given the name *Rubus chlorotic mottle* virus, was obtained. The virus has a single, positive-strand RNA genome of 3,983 nucleotides and, in common with other sobemoviruses, contains four open reading frames (ORFs) encoding, from 5' to 3', the P1 protein that is likely to be a suppressor of RNA silencing, ORF2a that has homology to serine-proteases, ORF2b that is the probable RNA dependent RNA polymerase, and ORF3 that is the coat protein. ORF2b protein is potentially expressed as a fusion with ORF2a protein by a -1 frameshift at the heptanucleotide sequence UUUAAAC. Phylogenetic analyses showed that RuCMV is a distinct virus not closely related to any of the other sequenced sobemoviruses. Based on the obtained sequence a full-length cDNA copy of *Rubus chlorotic mottle* virus was cloned and *in vitro* transcripts derived from this clone were shown to be fully infectious [91].

Trait-Mediated Effects on Flowers: Artificial Spiders Deceive Pollinators and Decrease Plant Fitness

Although predators can affect foraging behaviors of floral visitors, rarely is it known if these top-down effects of predators may cascade to plant fitness through trait-mediated interactions. In this study scientists manipulated artificial crab spiders on flowers of *Rubus rosifolius* to test the effects of predation risk on flower-visiting insects and strength of trait-mediated indirect effects to plant fitness. In addition, they tested which predator traits (e.g., forelimbs, abdomen) are recognized and avoided by pollinators. Total visitation rate was higher for control flowers than for flowers with an artificial crab spider. In addition, flowers with a sphere (simulating a spider abdomen) were more frequently visited than those with forelimbs or the entire spider model. Furthermore, the presence of artificial spiders decreased individual seed set by 42% and fruit biomass by 50%. Our findings indicate that pollinators, mostly bees, recognize and avoid flowers with predation risk; forelimbs seem to be the predator trait recognized and avoided by hymenopterans. Additionally, predator avoidance by pollinators resulted in pollen limitation, thereby affecting some components of plant fitness (fruit biomass and seed number). Because most pollinator species that recognized predation risk visited many other plant species, trait-mediated indirect effects of spiders cascading down to plant fitness may be a common phenomenon in the Atlantic rainforest ecosystem) [92].

Blackberry *(Rubus spp.)* a pH-dependent oral contrast medium for gastrointestinal tract images by magnetic resonance imaging. In this study, seven fruits have been tested on their magnetic properties, paramagnetic metal content and contrast enhancement in magnetic resonance imaging of phantom and *in vivo*. Magnetic susceptibility was determined for the fruit pulps, as well as the contents of paramagnetic metals; iron, manganese and copper. The total content of these metals was 4.3, 8.6, 11.1, 10.9, 12.3, 8.3 and 29.3mg/kg of fruit for plum, blueberry, apple (red), pineapple, beet, grape, blackberry, respectively, and with magnetic susceptibility of -2.29+/-0.07, -2.43+/-0.07, -2.13+/-0.07, -1.84+/-0.02, -1.75+/-0.01, -1.78+/-0.06, -2.18+/-0.07 SI, respectively. T(1)- and T(2)-weighted MR images were performed for the seven fruits and water (chi = -9.98 x 10 (-3) SI) and in one subject. While there was no correlation between the magnetic susceptibility and contrast enhancement, there is a correlation with the total paramagnetic metal content determined with contrast enhancement in magnetic resonance imaging. Thus, blackberry contrast enhancement was the highest among the fruits in T (1) weighted images. Furthermore, this fruit's contrast enhancement shows to be pH-dependent. These characteristics and the wide availability of the *Rubus* spp. suggest that it should be implemented as an oral contrast agent in images by MR to assess the function of the gastric section of the GI tract. Furthermore, it has the advantage of being a natural meal, so that it can be well tolerated by the patients and use as much as it is needed without side effects [71].

Evaluation of the Relaxant Action of Some Brazilian Medicinal Plants in Isolated Guinea-Pig ileum and Rat Duodenum

To evaluate the possible antispasmodic activity *in vitro* of methanolic extracts of six Brazilian medicinal plants, the extracts were evaluated on isolated guinea-pig ileum and rat duodenum preparations. R*ubus imperialis, Maytenus robusta, Ipomoea pes caprae* and *Epidendrum mosenii* did not inhibit the contractile response elicited by acetylcholine on guinea-pig ileum. On the other hand, methanolic extracts from *Calophyllum brasiliense* and *Cynara scolymus* exhibited significant inhibitory activity for the contractile response elicited by acetylcholine on guinea-pig ileum and on rat duodenum in a noncompetitive and concentration-dependent manner. This study suggests that, of the six medicinal plants evaluated, only the methanolic extract of *Calophyllum brasiliense* and *Cynara scolymus* show probable antispasmodic activity, confirming and justifying their use in folk medicine for the treatment of intestinal disorders [93].

Prolonged Herbicide-Induced Vegetation Changes in a Regenerating Boreal Aspen Clearcut

A soil-active herbicide (hexazinone) was applied (0, 2, and 4 kg/ha of active ingredient) in a 3-year-old regenerating boreal Populus tremuloides Michx. (aspen) clearcut to determine its effect on the compositional and structural development of the vegetation. Woody stem densities and plant foliar cover were evaluated prior to and 2, 6, and 17 years after treatment. Herbicide treatment at the 2 and 4kg/ha rates reduced tree and total woody stem densities relative to the 0kg/ha level. The 4kg/ha level reduced stem densities by 27% 17 years after treatment. The primary reductions occurred in Amelanchier alnifolia (Nutt.) Nutt. ex M. Roemer (saskatoon) and *Rosa acicularis* Lindl. (wild rose); whereas *Corylus cornuta* Marsh. (beaked hazelnut) and *Viburnum edule* (Michx.) Raf. (low-bush cranberry) stem densities increased. Notable herbicide-caused foliar cover reductions at the 4kg/ha level occurred in *Eurybia conspicua* (Lindl.) Nesom. (showy aster), *Mertensia paniculata* (Ait.) G. Don. (tall mertensia), *Rubus pubescens* Raf. (dewberry), and *Spiraea betulifolia* Pallas (spiraea), but *Aralia nudicaulis* L. (sarsaparilla), Cornus canadensis L. (bunchberry), and *Symphyotrichum ciliolatum* (Lindl.) A.& D. Lve (Lindley's aster) increased. Less distinctive but similar changes occurred in the 2kg/ha treatment. Total plant cover, species richness, and species dominance concentration were similar among treatments. Eight distinctive forest understory-types were recognized among treatments in Year 17. Between the 0 and 4kg/ha treatments, five understory-types differed in their frequency of occurrence. Hexazinone did not improve the survival of silviculturally planted *Picea glauca* (Moench), Voss (white spruce) seedlings relative to untreated sites, but the 4kg/ha treatment level did increase Pinus contorta Dougl. ex

Loud. (lodgepole pine) survival from 12 to 34%. Surviving seedlings had significantly greater height and basal diameter growth than those at the 0kg/ha sites, particularly the 4kg/ha treatment [94].

Sanguiin H-6 Blocks Endothelial Cell Growth Through Inhibition of VEGF Binding to VEGF Receptor

The vascular endothelial growth factor plays a key role in angiogenesis, which is a process where new blood vessels develop from the endothelium of a pre-existing vasculature. Vascular endothelial growth factor exerts its activity by binding to its receptor tyrosine kinase, KDR/Flk-1, which is expressed on the surface of endothelial cells. A methanol extract and organic solvent fractions from *Rubus coreanus* were examined for their inhibitory effects on vascular endothelial growth factor binding to the vascular endothelial growth factor receptor. The methanol extract from the crude drug were found to significantly inhibit vascular endothelial growth factor binding to the vascular endothelial growth factor receptor (IC_{50} approximately = 27microg/ml). Among the fractions examined, the aqueous fraction from the medicinal plant showed potent inhibitory effects against the binding of KDR/Flk-1-Fc to immobilized vascular endothelial growth factor 165 in a dose-dependent manner (IC_{50} approximately = 11microg/ml). Sanguiin H-6 was isolated as an active principle from the aqueous fraction, and inhibited the binding of KDR/Flk-1-Fc to immobilized vascular endothelial growth factor 165 in a dose-dependent manner (IC_{50} approximately = 0.3microg/ml). In addition, sanguiin H-6 efficiently blocked the vascular endothelial growth factor-induced HUVEC proliferation in a dose-dependent manner (IC_{50} approximately = 7.4microg/ml) but had no effect on the growth of HT1080 human fibrosarcoma cells. This suggests that sanguiin H-6 might be a potential anti-angiogenic agent [95].

Urinary Excretion of Black Raspberry *(Rubus occidentalis)* Anthocyanins and Their Metabolites

To examine human absorption and metabolism of black raspberry anthocyanins when administered at high doses (2.69 +/- 0.085 g/day) this study was developed. Ten healthy men consumed 45g of freeze-dried black raspberries daily for 1 week. Urine samples were collected over a 12h period in 4h intervals at day 1 and day 7. Urinary anthocyanins were analyzed by HPLC coupled to a photodiode array detector and a tandem mass spectrometer using precursor ion and product ion analyses. Anthocyanins were excreted in intact forms and metabolized into methylated derivatives in human urine. The urinary excretion of anthocyanins reached a maximum concentration (1091.8 +/- 1081.3 pmol/L, n = 10) during the 4-8h period after black raspberry ingestion. As compared to the anthocyanin distribution in black raspberries, urinary cyanidin 3-xylosylrutinoside was detected at a higher concentration than that of cyanidin-3-rutinoside [96].

Identification Study of Mongolian Herbal Medicine *Rubus* Sachalinesis Leveille and its Forgeries by UV/Fluorescence/IR Spectroscopy

Identification study of four species of Mongolian herbal medicine by UV/fluorescence/IR spectroscopy was carried out. Ultrasonic extracts of Mongolian herbal medicine *Rubus Sachalinesis* Leveille and its substitute materials *Sambucus williamsii* Hance and *Uncaria rhynchophylla* (Miq.) Jacks, and its false medicine Cinnamomum cassia Presl by methyl alcohol, petroleum ether and chloroform were obtained respectively, UV/fluorescence spectral scans for the above herbal medicines were taken and the spectra obtained were compared. Besides, the IR spectra obtained from the herbal medicines were compared. It was shown that the absorption peaks of UV spectra of the four species of Mongolian herbal medicine differ from each other when the methyl alcohol, petroleum ether and chloroform were used as extracting solvent, while there is a selectivity for the solvent when fluorescence spectrum was used to differentiate those medicines. Only when the methyl alcohol was used as extracting solvent, there are clear differences among the IR spectra of the four species of medicine. Therefore, three kinds of spectra are available in identifying the four species of herbal medicine. Among them, IR spectroscopy is noted for its more information about the fingerprints of herbal medicines, and being direct and simple, which is one of the methods worth recommending for identifying Mongolian herbal medicine [97].

Antioxidants in Raspberry: On-line Analysis Links Antioxidant Activity to a Diversity of Individual Metabolites

The antioxidant compounds in raspberry *(Rubus idaeus)* fruits were determined by high-performance liquid chromatography coupled to an on-line postcolumn antioxidant detection system. Both developmental and genetic factors were assessed by comparing fruits from a single cultivar of different ripening stages and by comparing ripe fruits of 14 raspberry cultivars, respectively. The HPLC-separated antioxidant compounds were identified using HPLC-photodiode array coupled to mass spectrometry (quadrupole time-of-flight tandem mass spectrometry), using a reference lock mass for determining accurate masses. The dominant antioxidants could be classified as anthocyanins, ellagitannins, and proanthocyanidin-like tannins. During fruit ripening, some anthocyanins were newly produced, while others, like cyanidin-3-glucoside, were already present early in fruit development. The level of tannins, both ellagitannins and proanthocyanidin-like tannins, was reduced strongly during fruit ripening. Among the 14 cultivars, major differences (>20-fold) were observed in the levels of pelagonidin type anthocyanins and some proanthocyanidin type tannins. The content of ellagitannins varied approximately 3-fold. The findings presented here suggest that the content of individual health-promoting compounds varies significantly in raspberry, due to both developmental and genetic factors. This information will assist in the future development and identification of raspberry lines with enhanced health-promoting properties [51].

Determination of Flavonoids, Tannins and Ellagic Acid in Leaves from *Rubus L.* Species

The quantitative determination of flavonoids, tannins and ellagic acid in the leaves from wild and cultivated variations of *Rubus L.* species (Rosaceae), raspberry (2 wild and 13 cultivars) and blackberry (3 wild and 3 cultivars) was carried out. The content of flavonoids was analyzed using spectrophotometric (the Christ-Mullers method) and HPLC analysis after acid hydrolysis. The content of tannins was determined by the weight method, with hide powder, described by German Pharmacopoeia 10 (DAB 10). Ellagic acid content was examined using the HPLC method after acid hydrolysis. Flavonoid content, determined using the Christ-Muller's method was higher for the blackberry leaves than for the raspberry leaves and varied between 0.46% and 1.05%. Quercetin and kaempferol were predominant in all samples analyzed using the HPLC method. The highest flavonoid content was found in the leaves of *R. nessensis* (1.06%); with results in all of the examined samples varying between 0.27% and 1.06%. The concentration of ellagic acid in all species was determined after acid hydrolysis and ranged from 2.06% to 6.89%. The leaves of raspberries are characterized by greater amounts of tannins (varying between 2.62% and 6.87%) than the leaves of other species. The results from this study indicate that the analyzed species are a rich source of flavonoids, ellagic acid and tannins, which may be used for the quality assessment of *Rubus L.* species leaves [98].

Rubus species is a rich source of gallic acid, ellagic acid. Gallic acid is cyclooxygenase-Inhibitor, Antiinflammatory, Antioxidant IC_{44} = 33 ppm, Antiperoxidant IC_{50} = 69M, Cyclooxygenase-Inhibitor. The natural antioxidant gallic acid was isolated from fruits of a medicinal Indonesian plant, *Phaleria macrocarpa* (Scheff.) Boerl. Gallic acid demonstrated a significant inhibition of cell proliferation in a series of cancer cell lines and induced apoptosis in esophageal cancer cells but not in non-cancerous cells (CHEK-1). Observation of the molecular mechanism of apoptosis showed that gallic acid up-regulated the pro-apoptosis protein, Bax, and induced caspase-cascade activity in cancer cells. On the other hand, gallic acid down-regulated anti-apoptosis proteins such as Bcl-2 and Xiap. In addition, gallic acid also induced down-regulation of the survival Akt/mTOR pathway. In non-cancerous cells, scientists observed delayed expression of pro-apoptosis related proteins. These results suggest that gallic acid might be a potential anticancer compound. However, in depth *in vivo* studies are needed to elucidate the exact mechanism.

Triterpenoids and Steroids of Root of *Rubus biflorus*

To investigate the chemical constituents of root of *Rubus biflorus.* Isolation and purification were carried out by silica gel column chromatography. Five compounds were isolated and identified as lupeol acetate, corosolic acid, oleanic acid, 2α-hydroxyoleanolic acid, sitosterol [99].

Characteristics of the Composition of Caucasian Blackberry (*Rubus caucasicus* L.) Leaves as a Raw Material for Tea Production

The composition of Caucasian blackberry six-leaf shoot was studied. The weight of the stem reached 50% of the total weight of the shoot. The content of moisture, extractive substances, and phenolic compounds was minimal at the beginning and end of the vegetation season. Phenolic compounds were represented by catechins, leukoanthocyanidins, and flavonols. The most abundant phenolic compounds in all parts of the blackberry shoot were leukoanthocyanidins, which accounted for approximately 50% of all compounds of this class. Phenolic compounds accumulated most actively in July and August. The average content of free amino acids in the blackberry leaf during the vegetation season was 26.68mg/g. Among the total free amino acids, eleven have been identified, five of which proved to be essential (His, Arg, Met, Leu, Val) and accounted for 40% of the total amount of amino acids. The oxidability of acetone extract of the blackberry leaf was compared to the oxidability of total phenolic compounds and tea tannin. The tea product obtained from the blackberry leaf had good organoleptic parameters and a saturated extractive complex [100].

The new natural caffeoyl esters, 3, 6-di-*O*-caffeoyl-(alpha/beta)-glucose and 1-*O*-caffeoyl-beta-xylose, together with the hitherto unknown natural tannin, 2, 3-*O*-hexahydroxydiphenoyl-4,6-*O*-sanguisorboyl-(alpha/beta)-glucose, have been isolated from the aqueous alcohol aerial part extract of *Rubus sanctus* [20].

Urinary Excretion of Black Raspberry *(Rubus occidentalis)* Anthocyanins and Their Metabolites

Anthocyanins are the most abundant phenolic compounds, widely distributed in fruits and vegetables, and exhibit potent antioxidant capacity. Humans ingest a significant amount of anthocyanins in the daily diet. To examine human absorption and metabolism of lack raspberry anthocyanins, when administered at high doses (2.69 (0.085g/day) the current study was carriedout. Ten healthy men consumed 45g of freeze-dried black raspberries daily for 1 week. Urine samples were collected over a 12h period in 4h intervals at day 1 and day 7. Urinary anthocyanins were analyzed by HPLC coupled to a photodiode array detector and a tandem mass pectrometer using precursor ion and product ion analyses. Anthocyanins were excreted in intact orms and metabolized into methylated derivatives in human urine. The urinary excretion of anthocyanins reached a maximum concentration (1091.8 (1081.3 pmol/L 10) during the 4-8 period after black raspberry ingestion. As compared to the anthocyanin distribution in black raspberries, urinary cyanidin 3-xylosylrutinoside was detected at a higher concentration than that of cyanidin-3-rutinoside [96].

Transgenic Peas *(Pisum sativum)* Expressing Polygalacturonase Inhibiting Protein from Raspberry *(Rubus idaeus)* and Stilbene Synthase from Grape *(Vitis vinifera)*

The pea (*Pisum sativum* L.) varieties Baroness and Baccara were transformed via *Agrobacterium tumefaciens*-mediated gene transfer with pGPTVbinary vectors containing the *bar* gene in combination with two different antifungal genes coding or polygalacturonase-inhibiting protein from raspberry (*Rubus idaeus* L.) driven by a double 35S promoter, or the stilbene synthase (*Vst*1) from grape (*Vitis vinifera* L.) driven by its own elicitor-inducible promoter. Transgenic lines were established and transgenes combined via conventional crossing. Resveratrol, produced by *Vst*1 transgenic plants, was detected using HPLC and the polygalacturonase-inhibiting protein expression was determined in functional inhibition assays against fungal polygalacturonases. Stable inheritance of the antifungal genes in the transgenic plants was demonstrated [101].

***Rubus* Chlorotic Mottle Virus, A New Sobemovirus Infecting Raspberry and Bramble**

The complete nucleotide sequence of a new member of the unassigned genus *Sobemovirus,* isolated from raspberry and bramble plants in north east Scotland and given the name *Rubus* chlorotic mottle virus, was obtained. The virus has a single, positive-strand RNA genome of 3983 nucleotides and in common with other sobemoviruses, contains four open reading frames encoding, from 5 to 3, the P1 protein that is likely to be a suppressor of RNA silencing, ORF2a that has homology to serine-proteases, ORF_2b that is the probable RNA dependent RNA polymerase, and ORF_3 that is the coat protein. ORF_2b protein is potentially expressed as a fusion with ORF2a protein by a −1 frameshift at the heptanucleotide sequence UUUAAAC. Phylogenetic analyses showed that *Rubus* chlorotic mottle virus is a distinct virus not closely related to any of the other sequenced sobemoviruses. Based on the obtained sequence a full-length cDNA copy of *Rubus* chlorotic mottle virus was cloned and *in vitro* transcripts derived from this clone were shown to be fully infectious [91].

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Production and Elicitation of Benzalacetone and the Raspberry Ketone in Cell Suspension Cultures of *Rubus* idaeus

Production levels of *p*-coumaric acid, *p*-hydroxyphenylbut-3-ene-2-one and *p*-hydroxyphenyl-2-butanone were measured in raspberry cell suspension cultures to investigate metabolite dynamics in a short pathway. Intracellular concentrations of benzalacetone and the raspberry ketone fluctuated during the time course of a normal batch culture cycle but showed higher levels during periods of rapid growth. Cells elicited with the signal coupler methyl jasmonate yielded a 2- to 3-fold increase in metabolite concentrations after 24h. The results suggest that raspberry ketone production is rapidly inducible during periods of high carbohydrate utilization. It is not an end product, however, and undergoes conversion to subsequent metabolites [102].

Anthocyanins, Phenolics, and Antioxidant Capacity in Diverse Small Fruits: Vaccinium, *Rubus* and Ribes

Fruits from 107 genotypes of *Vaccinium* L., *Rubus* L., and *Ribes* L., were analyzed for total anthocyanins, total phenolics and antioxidant capacities as determined by oxygen radical absorbing capacity and ferric reducing antioxidant power. Fruit size was highly correlated with analyzed for total anthocyanins within *Vaccinium* corymbosum L., but was not correlated to analyzed for total anthocyanins cross eight other *Vaccinium* species, or within 27 blackberry hybrids. Certain Vaccinium and Ribes fruits with pigmented flesh were lower in analyzed for total anthocyanins, total phenolics, oxygen radical bsorbing capacity and ferric reducing antioxidant power compared to those values in berries with nonpigmented flesh. Oxygen radical absorbing capacity values ranged from 19 to 131 ímol Trolox equivalents/g in *Vaccinium,* from 13 to 146 in *Rubus,* and from 17 to 116 in Ribes. Though analyzed for total anthocyanins may indicate total phenolics, the range observed in analyzed for total anthocyanins/ total phenolics ratios precludes prediction of analyzed for total anthocyanins from total phenolics and vice versa for a single genotype. In general, total phenolics was more highly correlated to antioxidant capacity than analyzed for total anthocyanins. This study demonstrates the wide diversity of phytochemical levels and antioxidant capacities within and across three genera of small fruit [103].

The Isolation of RNA from Raspberry *(Rubus idaeus)* Fruit Chris

A quick and simple method of extracting total RNA from raspberry fruit was developed. Using this method, high yields of good quality, undegraded RNA were obtained from fruit at all stages of ripening. The RNA is of sufficient quality for northern analysis and cDNA library construction [104].

Determination of Flavonoids, Tannins and Ellagic Acid in Leaves from *Rubus* L. Species

The quantitative determination of flavonoids, tannins and ellagic acid in the leaves from wild and cultivated variations of *Rubus* L. species, raspberry and blackberry was determined. The content of flavonoids was analyzed using spectrophotometric and HPLC analysis. The content of tannins was determined by the weight method, with hide powder, described by German Pharmacopoeia 10 (DAB 10). Ellagic acid content was examined using the HPLC method after acid hydrolysis. Flavonoid content, determined using the Christ-Muller's method was higher for the blackberry leaves than for the raspberry leaves and varied between 0.46% and 1.05%. Quercetin and kaempferol were predominant in all samples analyzed using the HPLC method. The highest flavonoid content was found in the leaves of *R. nessensis* (1.06%); with results in all of the examined samples varying between 0.27 and 1.06%. The concentration of ellagic acid in all species was determined after acid hydrolysis and ranged from 2.06 to 6.89%. The leaves of raspberries are characterized by greater amounts of tannins (varying between 2.62 and 6.87%) than the leaves of other species. The analyzed species are a rich source of flavonoids, ellagic acid and tannins, which may be used for the quality assessment of *Rubus* L. species leaves [98].

Concentration and Mean Degree of Polymerization of *Rubus Ellagitannins* Evaluated by Optimized Acid Methanolysis

Ellagitannins are a major class of phenolics largely responsible for the astringent and antioxidant properties of raspberries and blackberries. The *Rubus ellagitannins* constitute a complex mixture of monomeric and oligomeric tannins. *Rubus* oligomeric ellagitannins contain, beside the well known ellagic acid and gallic acid moieties, the sanguisorboyl linking ester group. When exposed to acids or bases, ester bonds are hydrolyzed and the hexahydroxydiphenic acid spontaneously cyclizes into ellagic acid. This study describes a new, rapid procedure for the acid hydrolysis of *Rubus ellagitannins* in methanol, which results in maximal yield and enables the quantification of all the major reaction products. Additionally, the method provides the rationale for estimating the mean degree of polymerization of *Rubus ellagitannins* [105].

Impact of Growing Environment on Chickasaw Blackberry *(Rubus L.)* Aroma

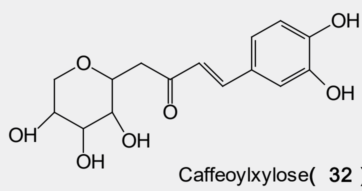
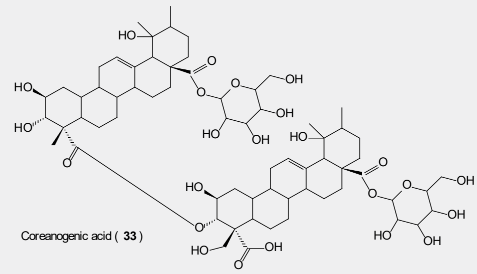
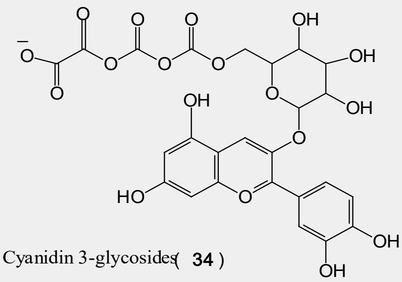
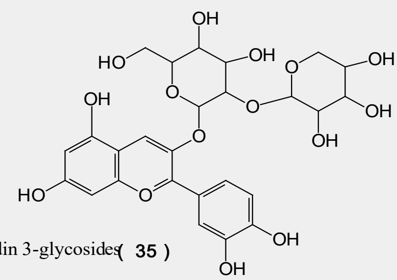
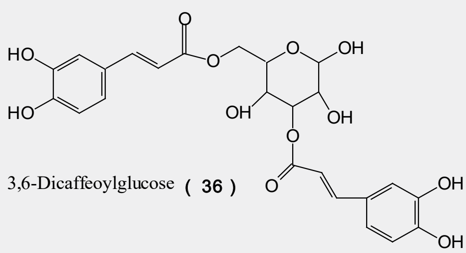
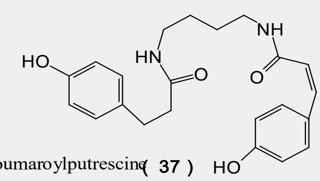
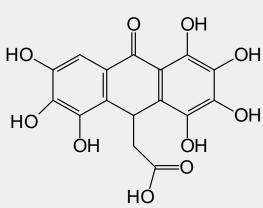
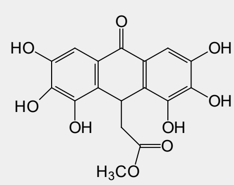
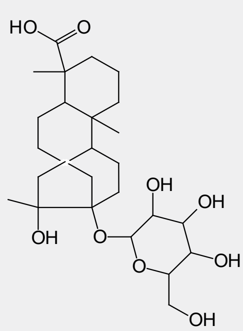
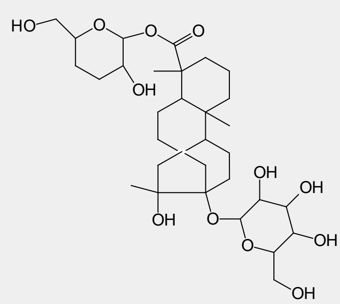
The aroma extract of Chickasaw blackberry *(Rubus L.)* was separated with silica gel normal phase chromatography into six fractions. Gas chromatography-olfactometry was performed on each fraction to identify aroma active compounds. Aroma extraction dilution analysis was employed to characterize the aroma profile of Chickasaw blackberries from two growing regions of the United States: Oregon and Arkansas. Comparative Aroma extraction dilution analysis showed that the berries grown in the two regions had similar aroma compositions; however, those odorants had various aroma impacts in each region. The compounds with high flavor dilution factors in Oregon's Chickasaw were ethyl butanoate, linalool, methional, trans,cis-2,6-nonadienal, cis-1,5-octadien-3-one, and 2,5-dimethyl-4- hydroxy-3 (2H)-furanone, whereas in the Chickasaw grown in Arkansas, they were ethyl butanoate, linalool, methional, ethyl 2-methylbutanoate, *â*-damascenone and geraniol [35].

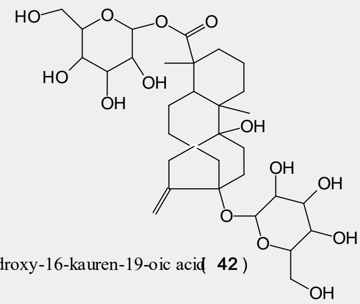
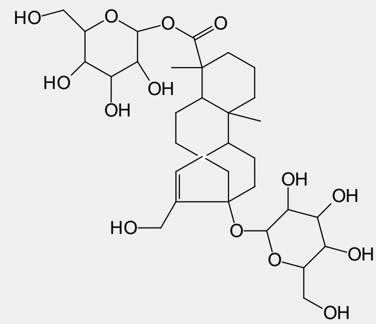
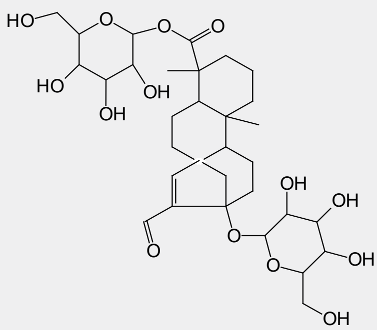
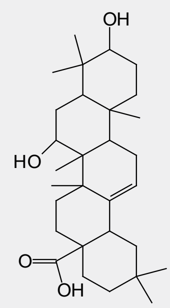
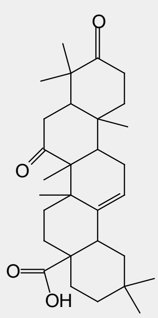
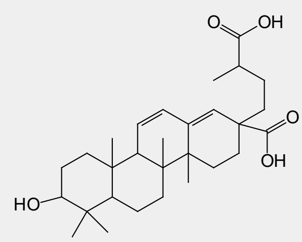
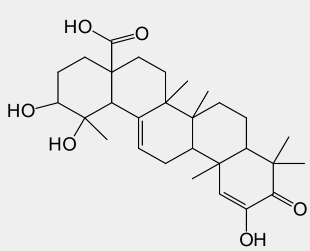
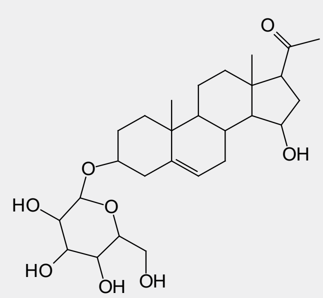
Aroma Extract Dilution Analysis of cv. Meeker (*Rubus idaeus* L.) Red Raspberries

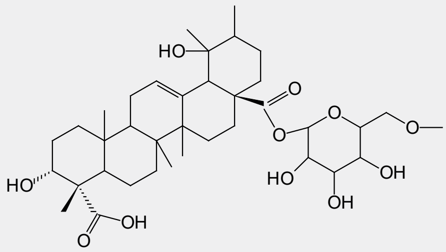
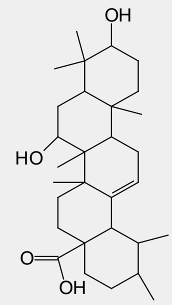
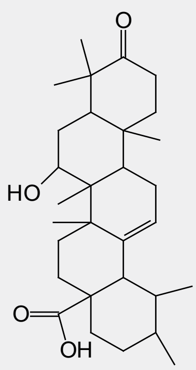
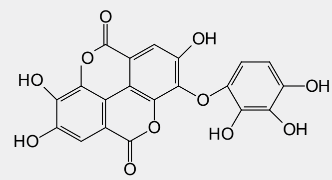
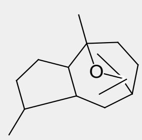
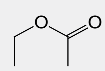
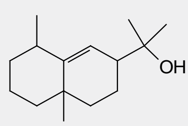
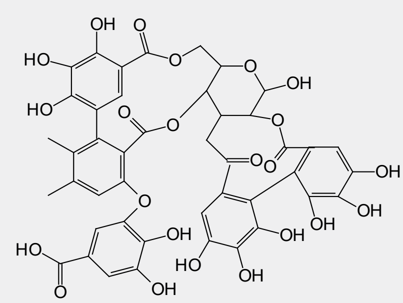
The aromas of cultivar Meeker red raspberry from Oregon and Washington were analyzed by aroma extract dilution analysis. Seventy-five aromas were identified by mass spectrometry and gas chromatography-retention index; 53 were common to both, and 22 have not been previously reported in red raspberry. Twenty-one compounds had an equivalent odor impact in both: 2,5-dimethyl-4-hydroxy-3-(2H)-furanone, hexanal, 4-(2,6,6-trimethyl-1-cyclohexen-1-yl)-3- buten-2-one, (E)-*â*-3,7-dimethyl-1,3,6-octatriene, 6,6-dimethyl-2 methylenebicyclo[3.1.1]heptane, 1-(2,6,6-trimethyl-1,3-cyclohexadien-1-yl)-2-buten-1-one, ethanoic acid, (Z)-3-hexenal, 3-methylmercaptopropionaldehyde, (Z)-3-hexenol, 2,6-dimethyl-2,7-octadien-6-ol, butanoic acid, ethyl 2- methylpropanoate, (E)-2-hexenal, hexyl formate, 2,3-butanedione, heptanal, thiacyclopentadiene, cyclohexane carbaldehyde, (E)-3,7-dimethyl-2,6-octadien-1-ol, and 4-(p-hydroxyphenyl)-2-butanone. Oregon Meeker had 14 odorants with higher flavor dilution (FD) factors than Washington Meeker: 4-(2,6,6-trimethyl-2-cyclohexen-1-yl)-3-buten-2-one, 1-octanol, 5-isopropyl-2-methylcyclohexa-1,3- dieneT, 7-methyl-3-methylene-1,6-octadiene, ethyl hexanoate, 3-methylbutyl acetateT, ethyl propanoate, 4-(4-hydroxy-3-methoxyphenyl)-2-butanone, 2-methylbutanoic acid, 1-octen-3-ol, ethyl cyclohexane carboxylate, 2-methylthiacyclopentadiene, (Z)-3-hexenyl acetate, and 4-(2,6,6-trimethyl-2-cyclohexen-1-yl)-3-buten-2-ol. Washington Meeker had 16 odorants with higher FD factors than Oregon Meeker: 5-ethyl-3-hydroxy-4-methyl-2-(5H)-furanone, dimethyl sulfide, 2-ethyl-4-hydroxy-5-methyl-3-(2H)-furanone, 1-hexanol, ethyl 2-methylbutanoate, 3,7-dimethyl-1,6-octadien- 3-yl acetate, methyl hexanoate, phenyl ethanoic acid, neo-allo-3,7-dimethyl-1,3,6-octatriene, 2-nonanone, 2-(4-methylcyclohex-3-enyl) propan-2-ol, phenylmethanol, 5-octanolide, 2-phenylethanol, 1-isopropyl-4-methylenebicyclo [3.1.0] hexane, and 2-undecanone [106].

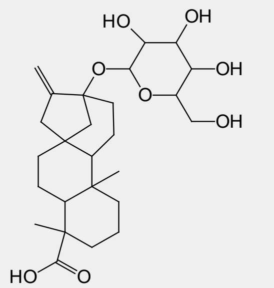
Table 1 showed the isolation of various natural products 32-139 from *Rubus* species. Including, 1-caffeoylxylose (32) [20], cyanidin 3-glycosides (34-35) [20,107-129], 9,10-dihydro-1, 2, 3, 4, 6, 7, 8-heptahydroxy-10-oxo-9-anthracene acetic acid (37, 40) [20, 21], Di-p-coumaroyl putrescine (37) [130,131,19], 13,16-dihydroxy-19-kauranoic acid (41) [19,24], 9,13-dihydroxy-16-kauren-19-oic acid (42) [24], 13,17-dihydroxy-15-kauren-19-oic acid (43, 44) [24], 3,7-dihydroxy-12-oleanen-28-oic acid (45-46) [132], 2,19-dihydroxy-3-oxo-1,12-ursadien-28-oic acid (48) [133], 3,15-dihydroxypregn-5-en-20-one, 9CI (49) [134,135], 3,19-dihydroxy-12-ursene-24, 28-dioic acid (50) [136-139,25], 3,7-dihydroxy-12-ursen-28-oic acid (51) [26,140], ellagic acid, INN (53) [141-174], 10,11-epoxyguaiane (54) [175-179], 5-eudesmen-11-ol (56) [180,181], 2, 3-dihydroxy-19-oxo-18,19-seco-11,13 (18)-ursadien-28-oic acid (47) [182], 2, 3: 4, 6-bis (hexa hydroxyl diphenoyl) glucose (57) [20,183-185,30], coreanogenic acid (33) [109], cyanidin 3, 5-diglycosides (35)[107,110-129,186-191], 3,6-dicaffeoylglucose (36) [192], 3, 19-dihydroxy-12-ursene-24, 28-dioic acid (73-77) [22,23]. 13-Hydroxy-16-kauren-19-oic acid (136-139) [21,19].

Table 1: *Reported acids, coumarines and triterpenoids from Rubus species*

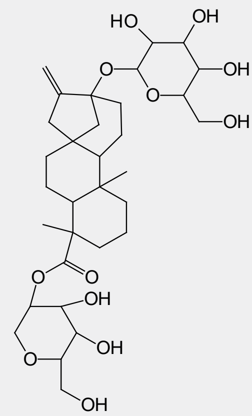
 Caffeoylxylose(32) 41	 Coreanogenic acid (33)
 Cyanidin 3-glycosides(34)	 Cyanidin 3-glycosides(35)
 3,6-Dicaffeoylglucose (36)	 Di-p-coumaroylputrescine(37)
 9,10-Dihydro-1,2,3,4,6,7,8-heptahydroxy-10-oxo-9-anthracene acetic acid(38)	 Rubanthrone C (39)
 9,10-Dihydro-1, 2, 3, 4, 6, 7, 8-heptahydroxy-10-oxo-9-anthracene acetic acid(40)	 13,16-Dihydroxy-19-kauranoic acid(41)

 Vic acid Dihydroxy-16-kauren-19-oic acid(42)	 13,17-Dihydroxy-15-kauren-19-oic acid(43)
 13,17-Dihydroxy-15-kauren-19-oic acid(44)	 3, 7-Dihydroxy-12-oleanen-28-oic acid(45)
 3, 7-Dihydroxy-12-oleanen-28-oic acid(46)	 2, 3-dihydroxy-19-oxo-18,19-seco-11,13 (18)-ursadien-28-oic acid(47)
 2,19-Dihydroxy-3-oxo-1,12-ursadien-28-oic acid(48)	 3,15-Dihydroxypregn-5-en-20-one, 9CI(49)

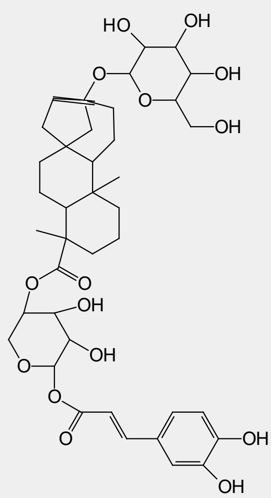
 3,19-Dihydroxy-12-ursene-24, 28-dioic acid (50)	 3, 7-Dihydroxy-12-ursen-28-oic acid (51)
 3 -Oxo, 7-hydroxy-12-ursen-28-oic acid (52)	 Ellagic acid, INN (53)
 10,11-Epoxyguaiane (54)	 ethyl acetate, 9CI (55)
 5-Eudesmen-11-ol (56)	 2, 3-Hexahydroxydiphenoyl-4, 6-sanguisorboyl glucose (57)



13-Hydroxy-16-kauren-19-oic acid (58)



13-Hydroxy-16-kauren-19-oic acid (59)



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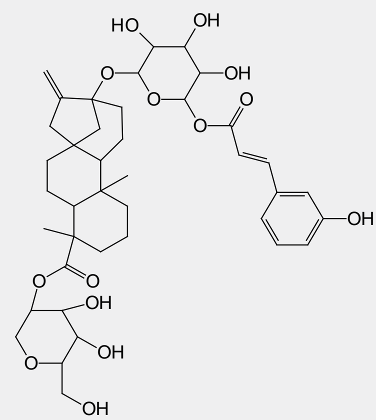

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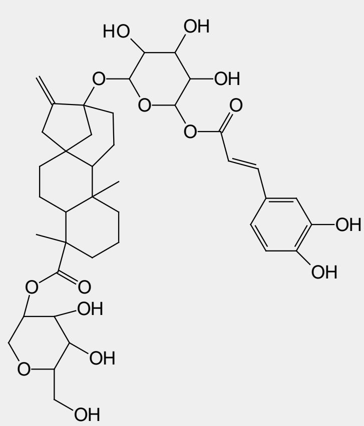
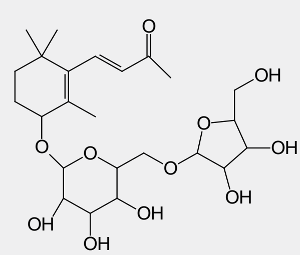
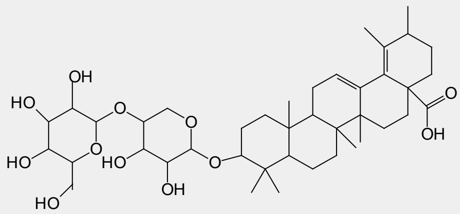
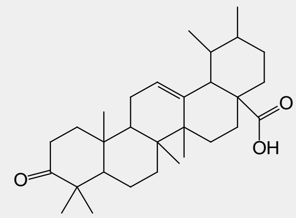
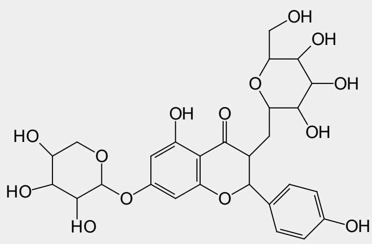
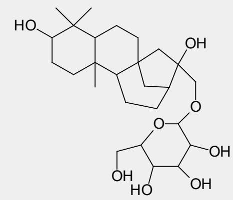
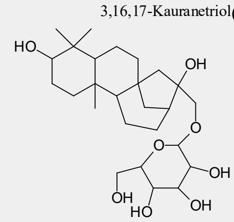
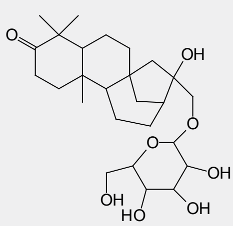
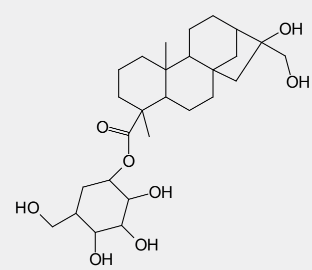
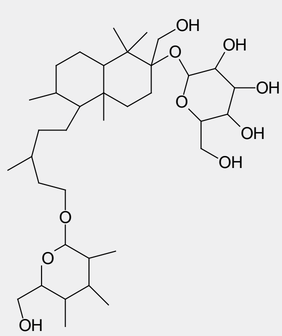
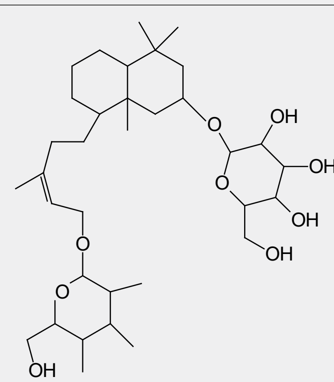
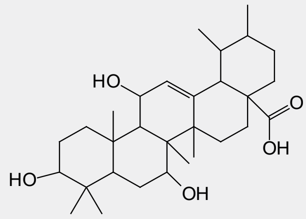
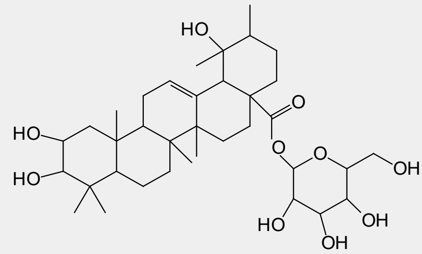
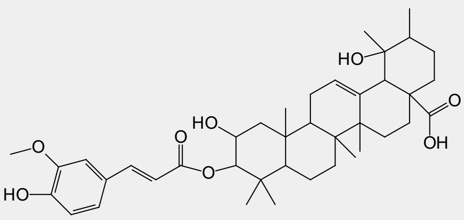
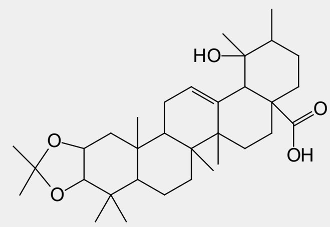
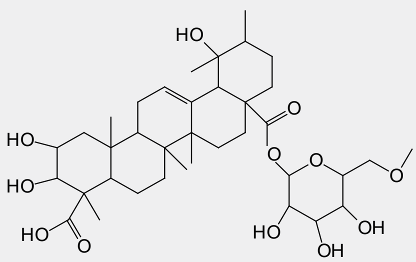
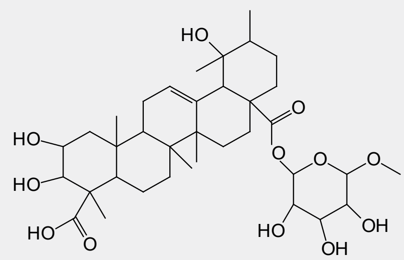
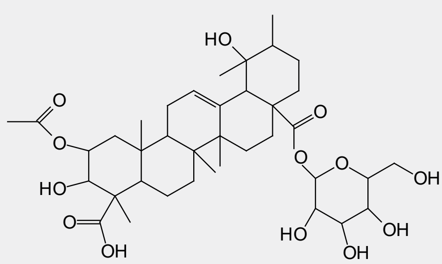
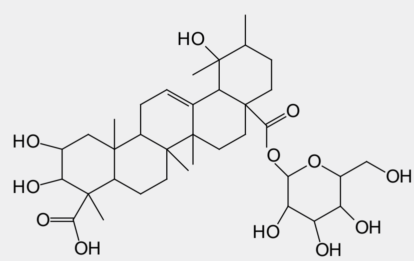
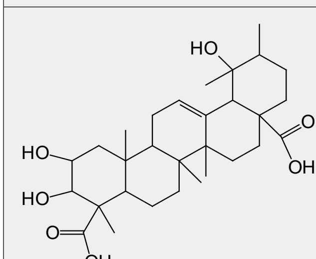
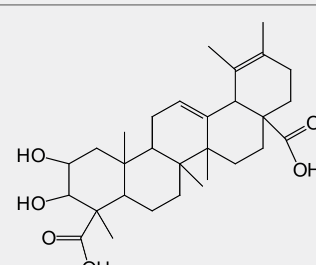


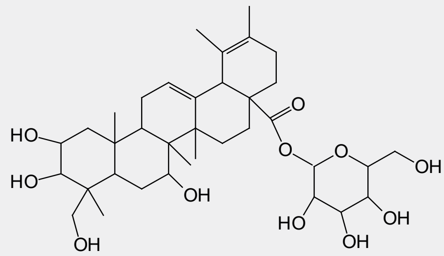
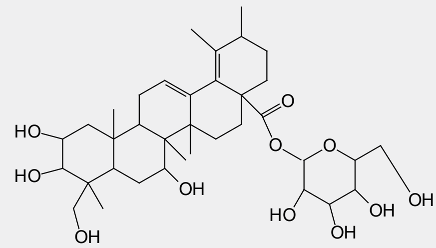
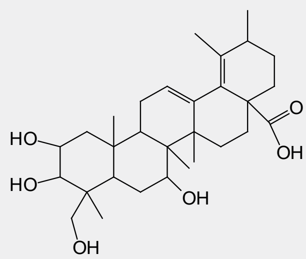
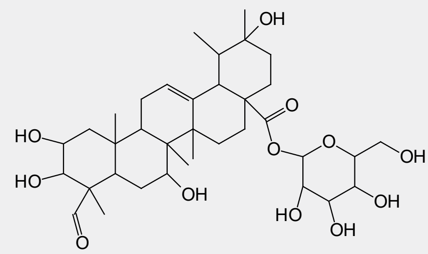
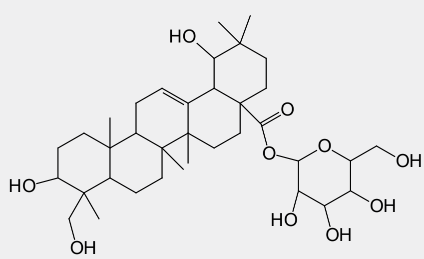
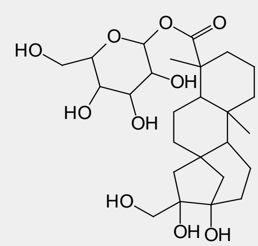
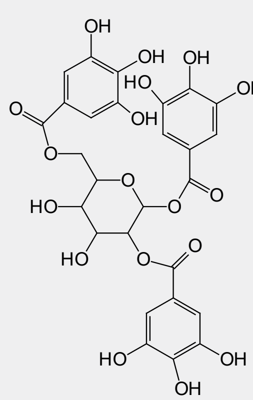
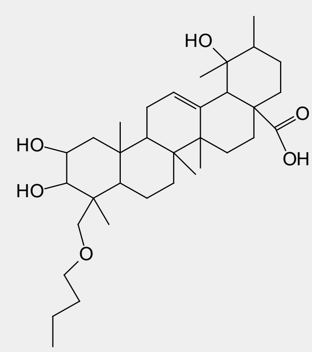
13-Hydroxy-16-kauren-19-oic acid (62)

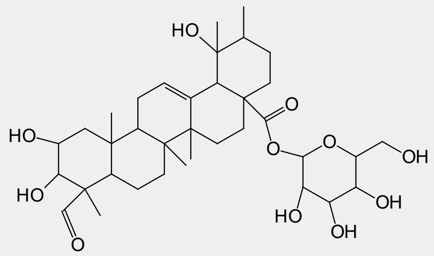


4-Hydroxy-5, 7-megastigmadien-9-one (63)

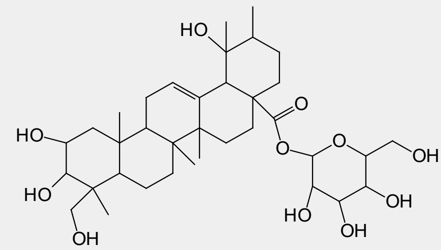
 3-Hydroxy-12,18-ursadien-28-oic acid(64)	 3-Hydroxy-12-ursen-28-oic acid (65)
 Kaempferol 3, 7-diglycosides (66)	 3,16,17-Kauranetriol(67)  3,16,17-Kauranetriol(67)
 3,16,17-Kauranetriol(68)	 16,17,19-kauranetriol(69)
 16,17,19-kauranetriol(70)	 8 (17) ,13-labdadiene-3,15-diol (71)

 3,7,11-Trihydroxyurs-12-en-28-oic acid(72)	 2, 3, 19-Trihydroxy-12-ursen-28-oic acid(73)
 2, 3, 19-Trihydroxy-12-ursen-28-oic acid (74)	 2, 3, 19-Trihydroxy-12-ursen-28-oic acid(75)
 2, 3,19-Trihydroxy-12-ursene-24, 28-dioic acid (76)	 2, 3,19-Trihydroxy-12-ursene-23, 28-dioic acid(77)
 2, 3,19-Trihydroxy-12-ursene-23, 28-dioic acid(78)	 2, 3,19-Trihydroxy-12-ursene-23, 28-dioic acid(79)
 2, 3,19-Trihydroxy-12-ursene-23, 28-dioic acid(80)	 2.3-Dihydroxy12,19-ursadiene-23,28-dioic acid (81)

 2, 3, 23-Trihydroxy-12,19-ursadien-28-oic acid (82)	 2, 3, 23-Trihydroxy-12,19-ursadien-28-oic acid (83)
 2, 3, 23-Trihydroxy-12,18-ursadien-28-oic acid (84)	 2, 3,19-trihydroxy-23-oxo-12-ursen-28-oic (85)
 3, 19, 23-Trihydroxy-12-oleanen-28-oic acid (86)	 13, 16, 17-Trihydroxy-19-kauranoic acid (87)
 1, 2, 6-Trigalloylglucose (88)	 2, 3,19, 24-Tetrahydroxy-12-ursen-28-oic acid (89)



2, 3,19-trihydroxy-24 oxo-12-ursen-28-oic acid (90)



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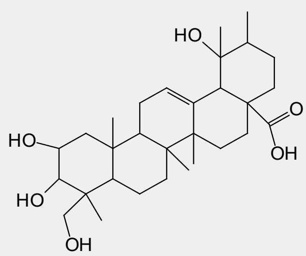

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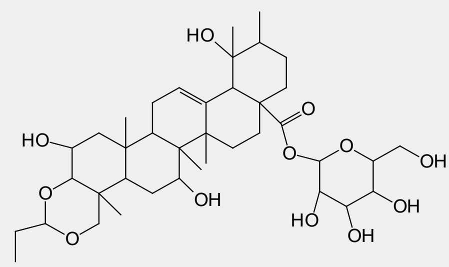

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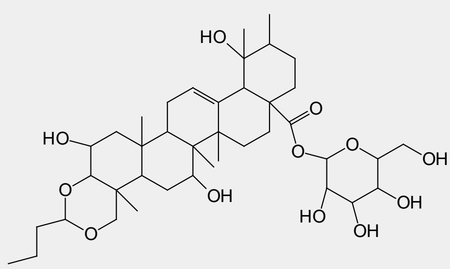

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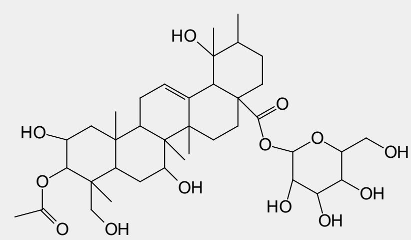

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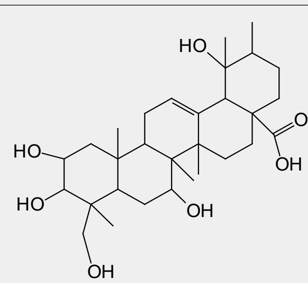

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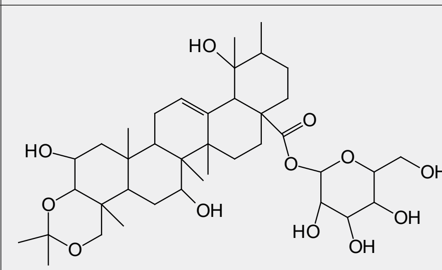
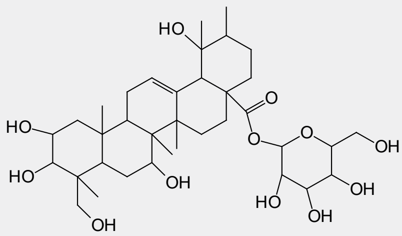


1,2,3,19-tetrahydroxy-12-ursen-28-oic acid(97)



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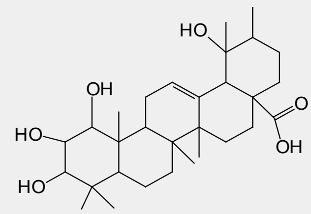

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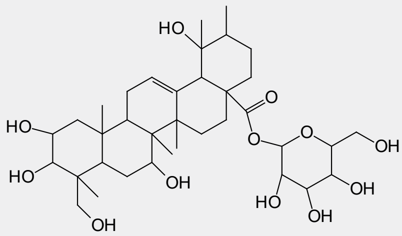

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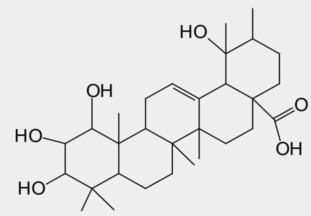

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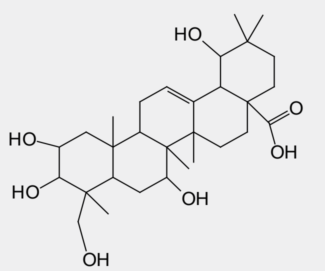
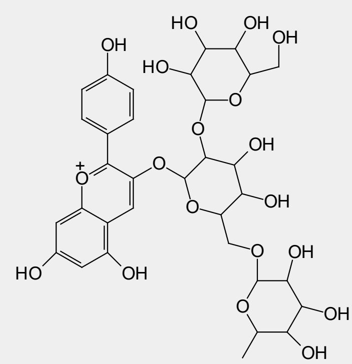
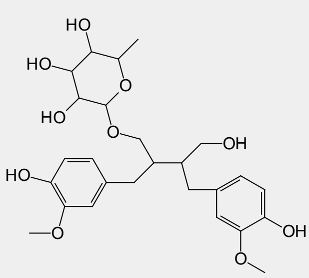


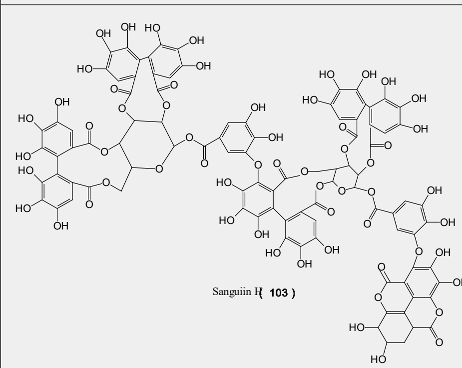
2,3,19,23-Tetrahydroxy-12-oleanen-28-oic acid(100)



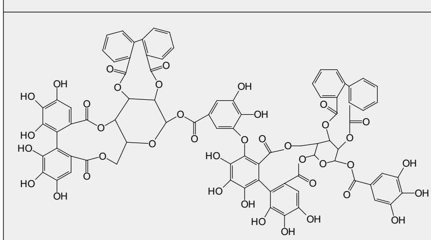
3, 4', 5, 7-Tetrahydroxyflavylium(1+), 8Cl(101)



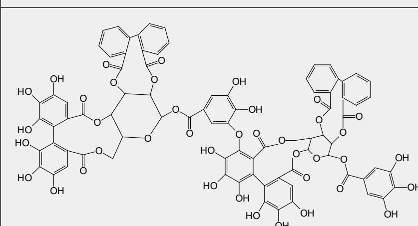
Secoisolariciresino(102)



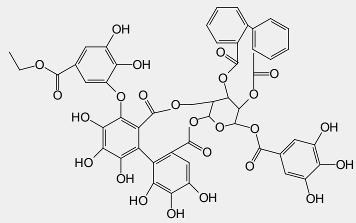
Sanguiin H(103)



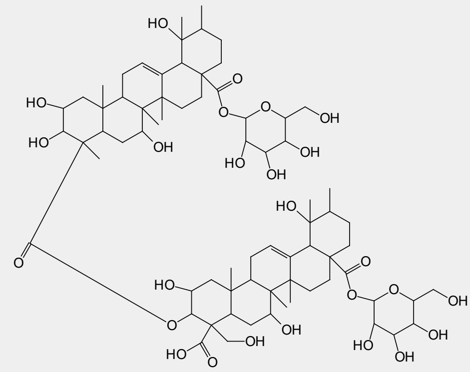
Sanguiin H6(104)



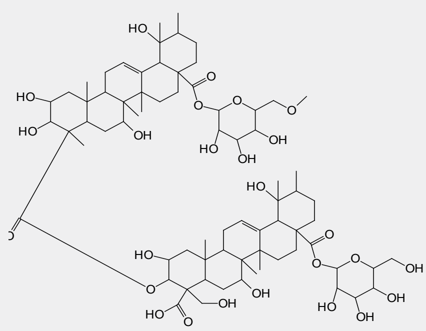
Sanguiin H6(105)



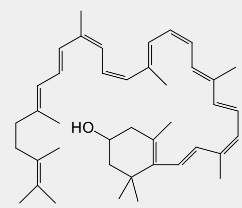
Sanguiin H2(106)



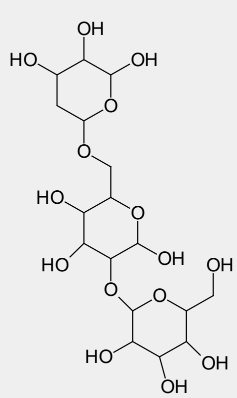
Rubupungenoside ARubupungenoside (107)



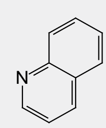
Rubupungenoside A (108)



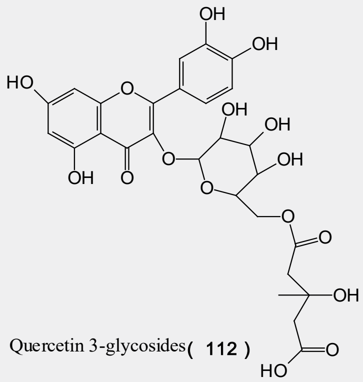
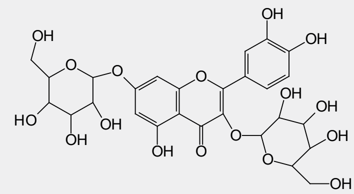
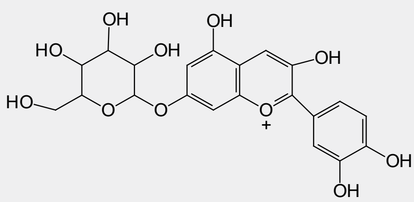
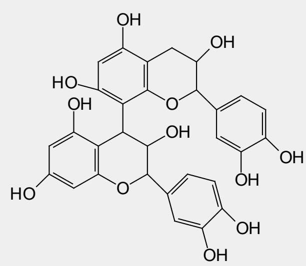
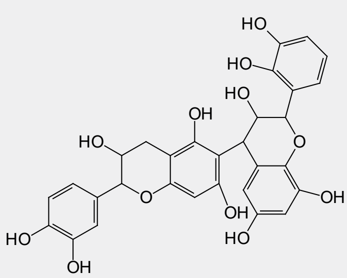
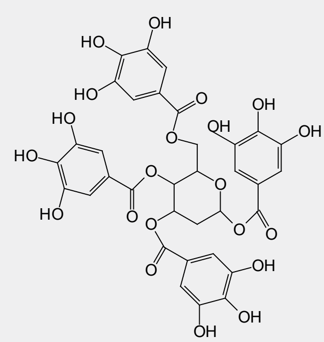
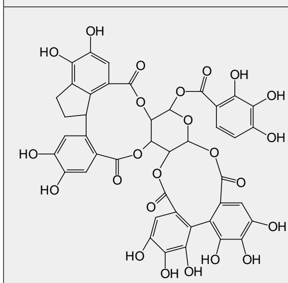
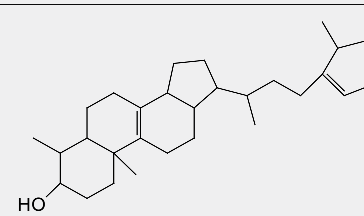
Rubixanthin(109)

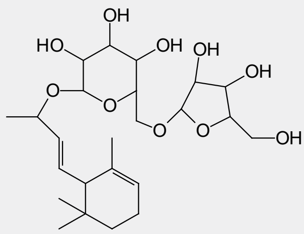
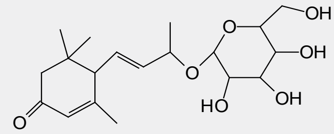
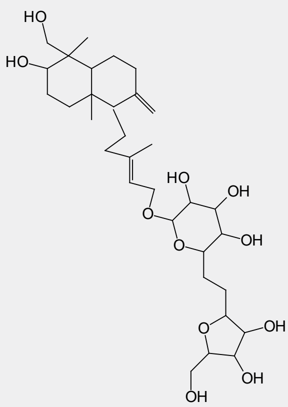
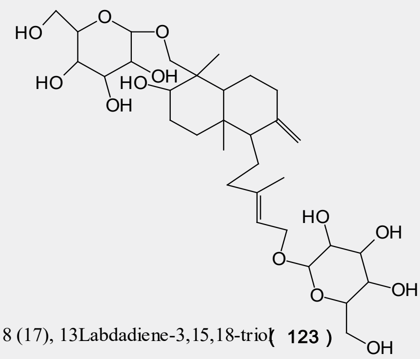
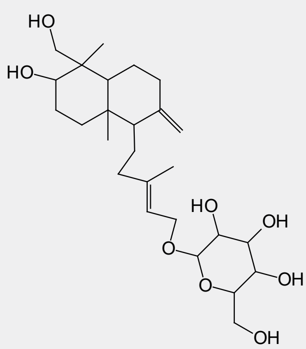
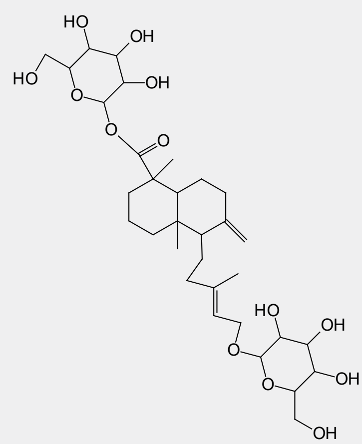


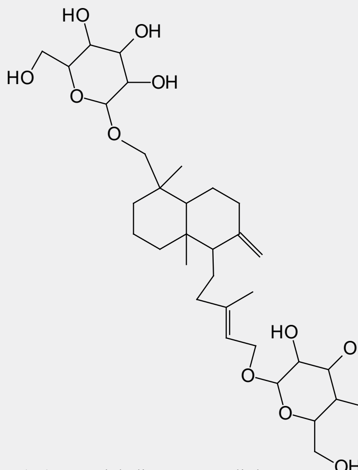
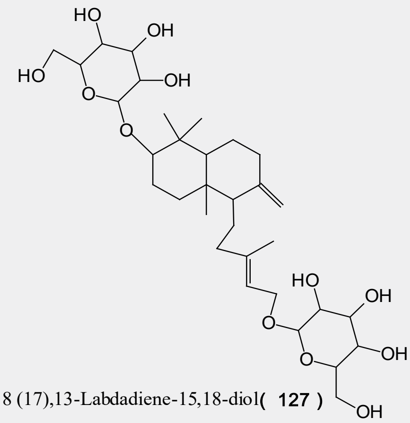
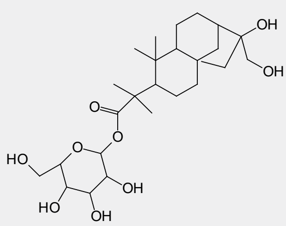
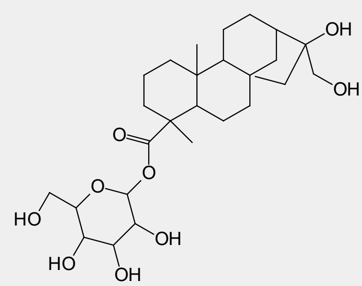
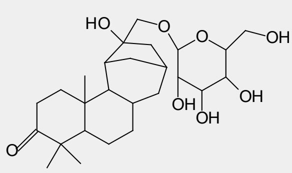
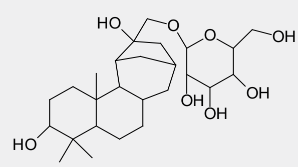
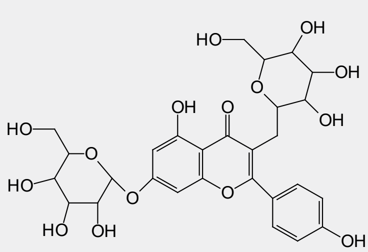
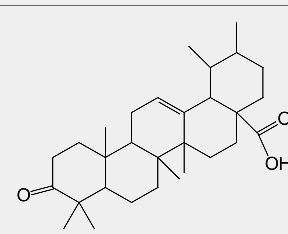
Rhamnopyranosyl-(16)-[-D-glucopyranosyl-(12)]-D-glucose(110)

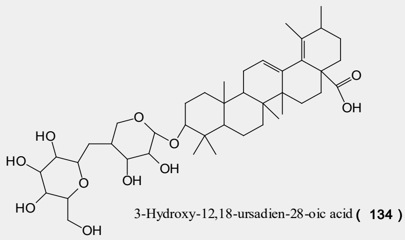


Quinoline(111)

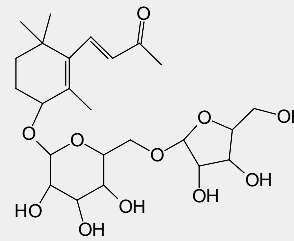
 Quercetin 3-glycosides(112)	 Quercetin 3, 7-diglycosides(113)
 3,3',4',5,7-Pentahydroxyflavylium (1+) (114)	 3,3',4',5,7-Pentahydroxyflavan(115)
 3,3',4',5,7-pentahydroxyflavan(116)	 1,2,3,4,6-Pentagalloyl glucose (117)
 Pedunculagin(118)	 4-Methyl stigmasta-8, 24 (28)-dien-3-ol (119)

 4, 7-Mega stigma dien-9-ol (**120**)	 4, 7-Mega stigma diene-3,9-diol (**121**)
 8 (17),13-labdadiene-3,15,18-triol (**122**)	 8 (17), 13Labdadiene-3,15,18-triol (**123**)
 8 (17), 13Labdadiene-3,15,18-triol (**124**)	 8 (17),13-labdadiene-3,15,18-triol (**125**)

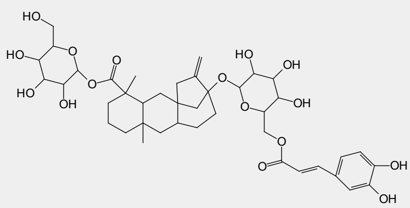
 8 (17),13-Labdadiene-15,18-diol(126)	 8 (17),13-Labdadiene-15,18-diol(127)
 16,17,19-Kauranetriol(128)	 16,17,19-Kauranetriol(129)
 3,16,17 kauranetriol(130)	 3,16,17 kauranetriol(131)
 kaempferol 3, 7-diglycosides(132)	 3-Hydroxy-12-ursen-28-oic acid (133)



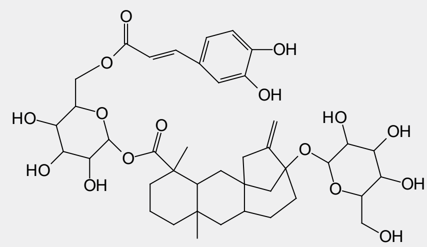
3-Hydroxy-12,18-ursadien-28-oic acid (134)



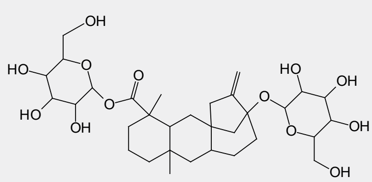
4-Hydroxy-5, 7-mega stigma dien-9-one (135)



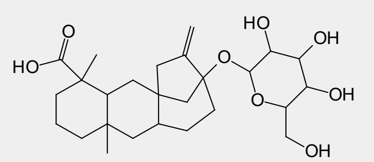
13-Hydroxy-16-kauren-19-oic acid(136)



13-Hydroxy-16-kauren-19-oic acid(137)



13-Hydroxy-16-kauren-19-oic acid (138)



13-Hydroxy-16-kauren-19-oic acid (139)

Conclusions

It is clear that raspberry fruit, represents a valuable contrasting source of potentially healthy compounds and can represent an important component of a balanced diet. The processing of caneberry fruit for juices and pure typically removes the seed as a byproduct. The development of a value-added use of seeds could expand the market for caneberry products and increase grower profit margins.

The literature survey reveals that gallic acid is an active ingredient from *Rubus* specie, a highly potent compound which shows variety of biological activities. Gallic acid can be an active ingredient in treating chemopreventive effects in various experimental cancer models so it attributes to anticancer activity. It is cyclooxygenase-Inhibitor, antiinflammatory, antioxidant, antiperoxidant, cyclooxygenase-Inhibitor. It also induced down-regulation of the survival Akt/mTOR pathway. It contributes to significant inhibition of colon, esophageal, liver, lung, tongue, and skin cancers. Also enhances the bioavailability of the active ingredient of the pharmaceutical compound.

In the end we can suggest that *Rubus specie,* which is a widely grown, could be used as a source of gallic acid. Further studies involving crude extracts of *Rubus specie* containing gallic acid would be highly economic and would account for useful consumption of the problem concern.

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