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Section B: Herbal Chemistry

Research Article

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Cranberry a rich source of bioactive phenolic compounds

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Abstract: Cranberry (*Vaccinium*) contains large quantities of nutrients and bioactive phenolic compounds such as anthocyanins, flavonoids, proanthocyanidins, flavonols, phenolic acids. These fruits are commonly known as berries and for its bittersweet flavour are used as food source and has been used in treating a large number of disorders in traditional medicine. This review displays a comprehensive and updated information on the botanical, phytochemistry, and pharmacological effects of cranberry species to evaluate therapeutic potential of their phenolic compounds. Information on cranberry was gathered by searching of scientific databases such as Science Direct, Scopus, Google Scholar, Scopus, SciELO, Google Scholar, Web of Science, Scirus, Medline, Wiley, Scifinder and books on medicinal herbs. Approximately 56 compounds belonging to anthocyanins, flavonoids, proanthocyanidins, flavonols, phenolic acids have been characterized from cranberry. Experimental evidences supported that the *Vaccinium* species have a wide range of pharmacological effects that can be used in therapy of infections in the urinary tract, treatment of patients with type 2 diabetes, inflammatory diseases, periodontal disease, exert prebiotic actions, control of obesity and against influenza A (IAV) and B (IBV). In this manuscript, we reviewed several studies carried out in areas of phytochemistry and pharmacology of *Vaccinium* species, especially on extracts and its chemical content which have demonstrated an important therapeutic effect in infections in the urinary tract as well as other disorders related to oxidative stress which need further attention to investigate its clinically effective use.

Keywords: American cranberry, edible plant, *Vaccinium*, phenolic compounds, proanthocyanidins

1. INTRODUCTION

The term berry or fruits of the forest refers to small fruits without seeds that can eat whole. Berries are generally tasty, semi-oblong or round, juicy, bittersweet and brightly coloured. Several fruits, usually referred as berries, considering the scientific definition are not properly berries for example strawberry, mulberry, raspberry, blackberry, Eastern shadbush, and hawthorn. Cranberries are a group of evergreen plants of the genus *Vaccinium* and subgenus *Oxycoccus* which are added in cuisine and traditional medicine. For this reason, is transcendent to quantify and characterize bioactives contained in these plants. Cranberry is used as medicinally mainly by their bioactive compounds such as anthocyanins, flavonoids, and proanthocyanidins with a high potential antioxidant effect[1]. Cranberry is able to control urinary tract infections due to the content of proanthocyanidins[2]. In addition, phenolic compounds avoid oxidative stress, and chronic inflammation among other[3]. The aim of this review was organized information of phenolic on botanical, phytochemistry and biological properties of cranberry. This review could promote future research on this fruit as well as assist chemists and pharmacologists to develop new drugs.

2. RESEARCH METHODOLOGY

Relevant information of cranberry on botany, phytochemistry content, and pharmacological effects was compiled via electronic based scientific literature using databases such as Scopus, PubMed, Google Scholar, Scirus, Science Direct, Scielo, Web of Science, Medline, Springerlink, BioMed Central (BMC), and SciFinder. The literature was taken from the databases employing the keywords 'cranberry" "*V. macrocarpon"* and *V. oxycocco".* Furthermore, relevant scientific publications were consulted to get data applied in different categories

3. TAXONOMY

The cranberry, also called American cranberry is the fruit of the species *Vaccinium macrocarpon* Aiton belonging to the genus *Vaccinium L*. of the family Ericaceae. This genus is complex, is divided into subgenres such as *Oxycoccos* in which species such as *V. macrocarpon* and *V. oxycoccos L.* are grouped, called the latter as the "true blueberry" and also referred to in the literature as *Oxycoccus macrocarpus* (Ait.) Pers. In North America, cranberry may refer to *V. erythrocarpon* or *V. microcarpon*, or *V. macrocarpon* whereas in United Kingdom, cranberry nevertheless usually refers to the native *V. oxycoccos.*Cranberry is a dwarf shrub or woody vine, of the perennial type, slow growing and with a height of 10 to 20 cm. This plant is native to the eastern United States, although wild plants have been introduced on the Pacific Coast[4].

The stems of the plant are crawling, thin and have a length of up to one meter. These cover the surface where it is grown forming a thick mat. From the axillary buds of these creeping stems, vertical straight branches arise that have a height of 5 to 7 cm. The roots are very thin and fibrous, and lack root hairs, so they are usually associated with mycorrhizal fungi. This root system is very superficial and allows the plant to live and develop in humid and swampy soils. The leaves are perennial, with a length of between 1 and 2 cm, with an oval-elongated shape and leathery appearance. The blade of the leaf has entire margins and are slightly revolute, have a light green color on the abaxial side and darker green on the adaxial side. During the growth the leaves are intense green, while in the dormant season where cooler temperatures predominate, the leaves turn a reddish-brown color. The flowers are bell shaped and are pink with recurved petals that expose the stamens. On each vertical stem 2 to 7 flowers may appear. The fruits are initially white subspherical berries that turn reddish pink or bright crimson when ripe. They have a diameter of 9 to 14 mm and smooth appearance. The epidermis of the berry is firm and solid, and due to these properties, the fruit can stand several months after harvesting without deteriorating. The fruits are edible and have a bitter taste. Inside the berry appear locules that house the seeds, his number varies from 0 to 50.

Fig.1: Cranberry morphology

4. NUTRITIONAL PARAMETERS

The nutritional composition of cranberry can be affected by the variety, the region where it is grown and cultural practices. Cranberries also present a broad spectrum of bioactive substances such as vitamin C, vitamin A, β-carotene and phenolic compounds. Among the phenolic compounds, the metabolites that predominate are the flavonoids, and particularly the anthocyanins[4]. Among the most important nutrients are the following: Protein 0.39, total lipids 0.13 carbohydrates 12.20, total dietary fibre 4.6, sugars 4.4, (values given in g/ 100g). Cranberry contain minerals such as calcium 8, iron 0.25, magnesium 6, phosphorus, 13, potassium 85, sodium 2, and zinc 0.10 (values given in mg/ 100g). Among vitamins find thiamine 0.12, riboflavin 0.20, vitamin C 13.3, niacin 0.1, pantothenic acid 0,.29, vitamin B6 0.057, total folate 1, betaine 0.2, vitamin A 0.3, carotene beta 36, lutein + zeaxanthin 91, vitamin E 1.20, gamma tocopherol 0.04 and vitamin K 0.05 (values given in mg/ 100g). In addition, contain saturated fatty acids 0.011, monounsaturated fatty acids 0.018 and polyunsaturated fatty acids

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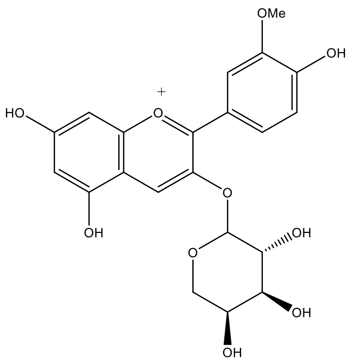
0.055 (values given in g/ 100g). Actually, in the market there is a wide variety products from cranberry fruit such as extracts, sauces, cereal bars, juices, and desserts etc [5]. Cranberry products are very popular in the United States since currently more of 10 million barrels with a value of 400 million, were generated in the United States[6] in 2014.

5. PHYTOCHEMICAL COMPOSITION

Cranberry fruits are a rich source of anthocyanins, flavonoids, proanthocyanidins, flavonols, phenolic acids[7]. In a HPLC analysis of *Vaccinium macrocarpon* Aiton were identified five anthocyanins such as peonidin-3-O-arabinoside (**1**; 1.1 mg/L), peonidin-3-O-galactoside (**2**; 2.8 mg/L), cyanidin-3-O-arabinoside (**3**; 1.4 mg/L), cyanidin-3-O-glucoside (4; 0.1 mg/L), and cyanidin-3-O-galactoside (**5**; 1.4 mg/L) [8].



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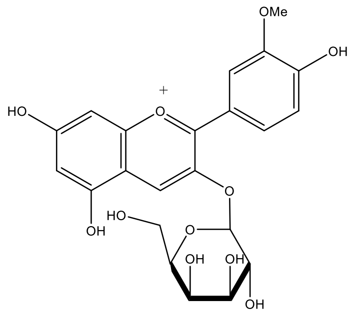

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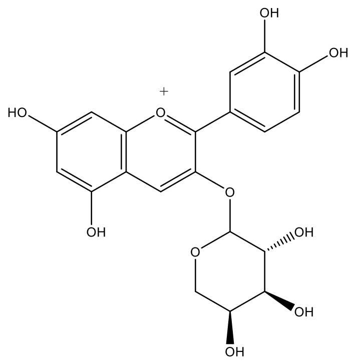

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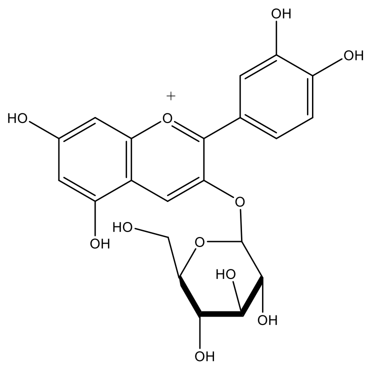

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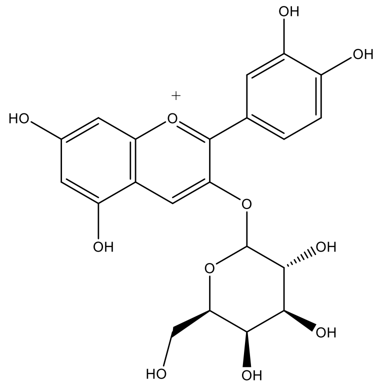

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The main cranberry anthocyanins, are peonidin, petunidin, pelargonidin, malvidin, delphinidin, and cyanidin which are bound to different sugar moieties among them are peonidin-3-O-glucoside (**6**; 0.3 mg/L), peonidin 3,5-digalactoside (**7**), malvidin-3-O-arabinoside (**8**), malvidin-3-O-galactoside (9), pelargonidin-3-O-arabinoside (**10**), pelargonidin-3-O-galactoside (**11**), delphinidin-3-O-arabinoside (**12**) and petunidin-3-*O*-galactoside (**13**) [9,10].

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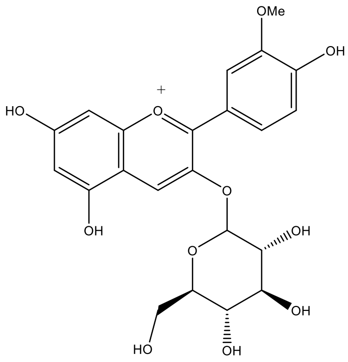

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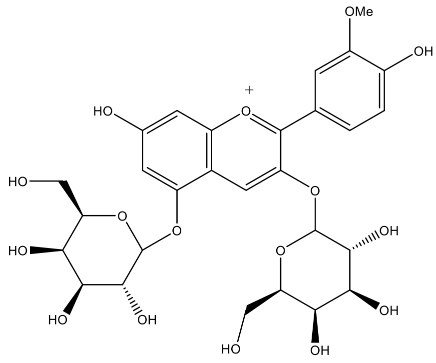

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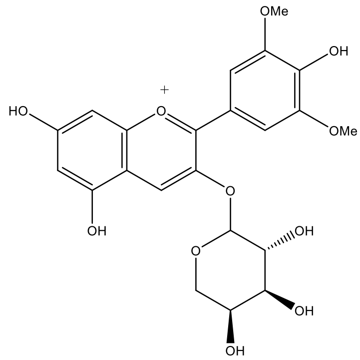

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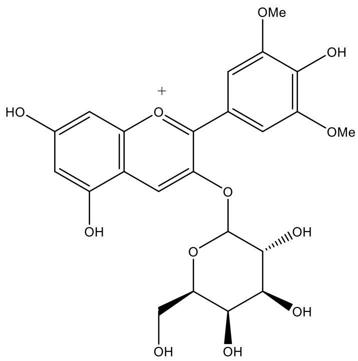

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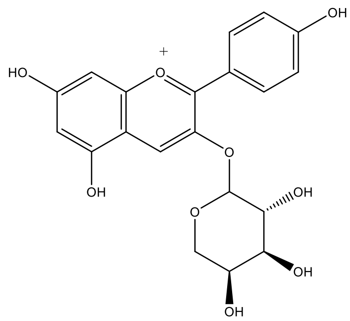

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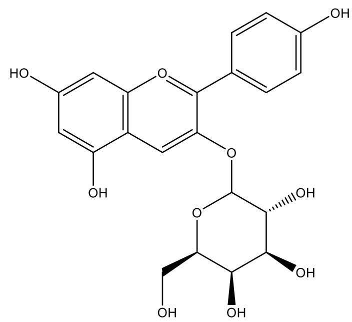

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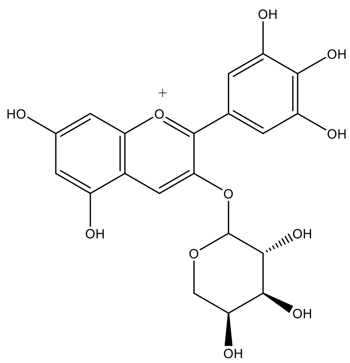

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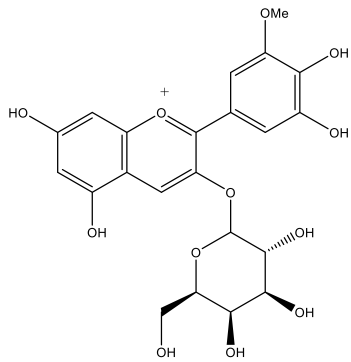

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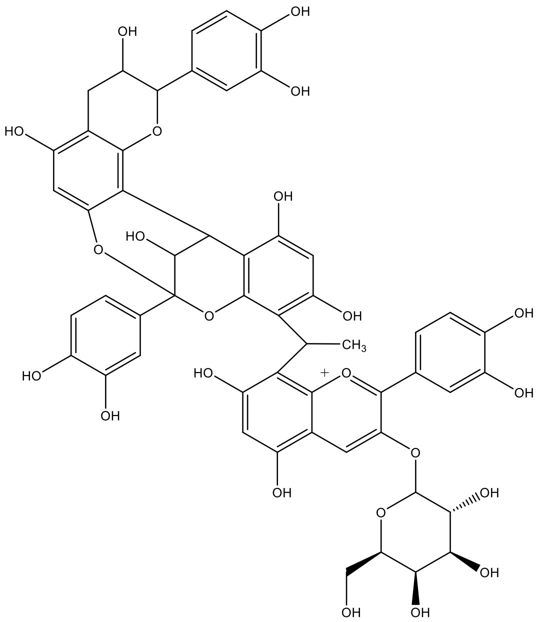
Two procyanidin dimers A2 (**14**) and B2 (**15**) were isolated from cranberry fruits which are constituted by three units catechin, epigallocatechin and epicatechin with three kinds of linkages one A-kind ether linkage (C2→O→C7) and two B-kind linkages (C4→C6 and C4→C8). In cranberry is common to presence of terminal A-type bonds which is very rare in other foods only plums and peanuts contain it's in small quantities[11].



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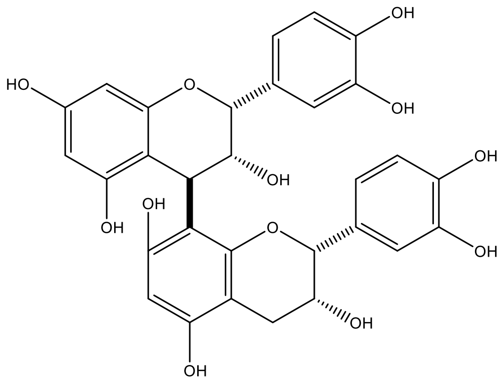

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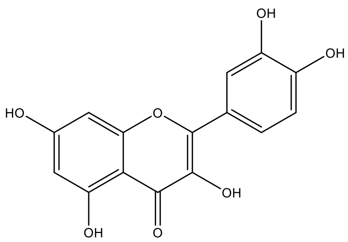
Flavonols are the most exceptional phytochemicals in cranberry such as quercetin (**16;** 104 mg/kg), myricetin (17) and kaempferol (**18**), myricetin β-xylopyranoside (**19**) and myricetin 3-α-arabinoside (**20**), kaempferol-3-glucoside (**21**; 5.6 μg/g), myricetin-3-β-xylopyranoside (**22**; 3.3 μmol/L), myricetin 3-α-arabinofuranoside (**23**) which are found mainly in the cortex[10,11].



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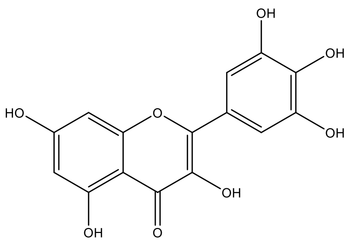

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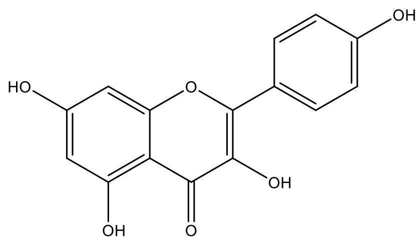

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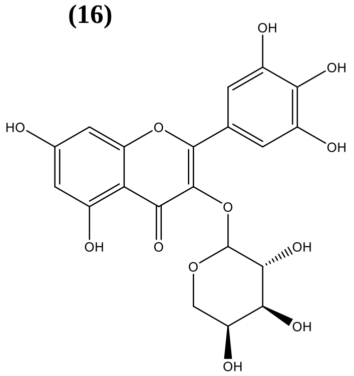

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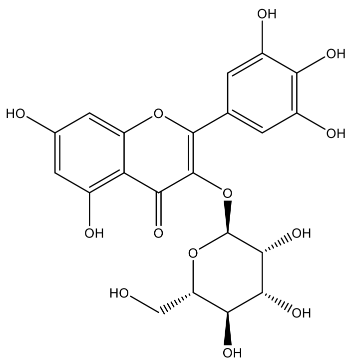

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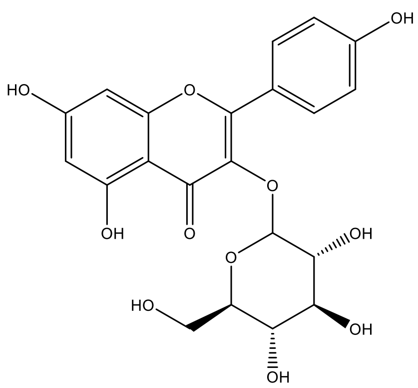

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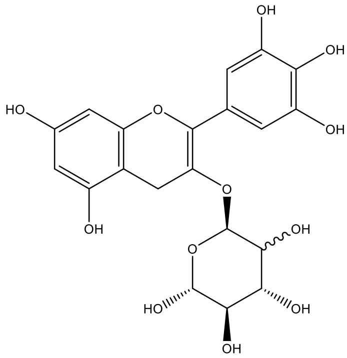

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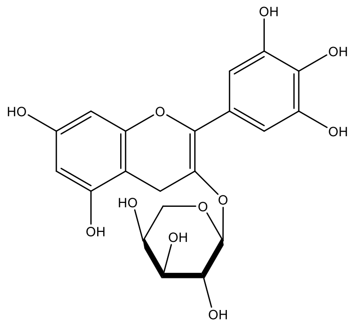

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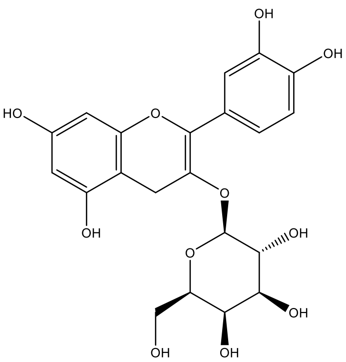
Nine quercetin derivatives have been quantified from cranberry such as quercetin-3-O-galactoside (**24**; 35.6 mg/kg^{-1}), quercetin-3-O-glucoside (**25**; 9.9 mg/kg^{-1}), quercetin-3-O-xyloside (**26**; 7.3 mg/kg^{-1}), quercetin-3-O-arabinopyranoside (**27**; 7.5 mg/kg^{-1}), quercetin-3-O-arabinofuranoside (**28**; 32.7 mg/kg^{-1}), quercetin-3-O-rhamnoside (**29**; 72.3 mg/kg^{-1}), and quercetin-3-O-acetyl rhamnoside (**30**; 48.0 mg/kg^{-1}), quercetin-3-*O*-(6-*p*-coumaroyl)-*β*-galactoside (**31**); quercetin-3-*O*-(6-benzoyl)-*β*-galactoside (**32**) [12,13]. The sugar moiety plays an important role in the bioavailability of flavonols and the conjugation of sugar to the polyphenolic moiety afford additional knowledge on their nutritional properties. However, glycosides of kaempferol, isorhamnetin and myricetin were identified in small quantities in cranberry and only have been detected in bilberry and highbush blueberry belonging to the Ericaceae family[14].



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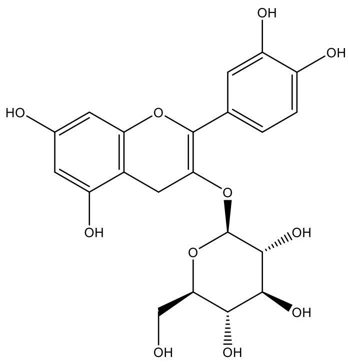

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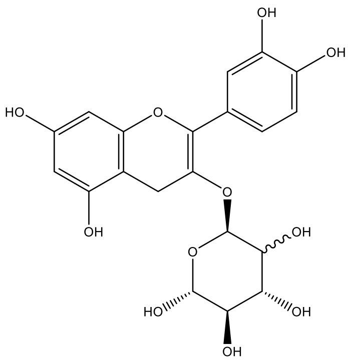

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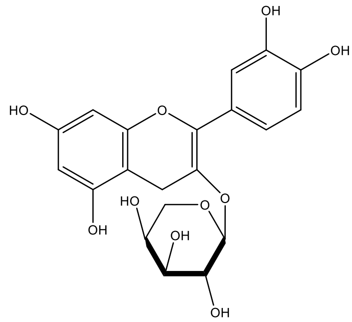

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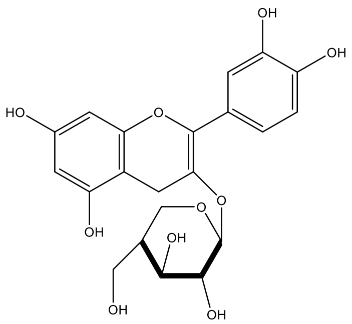

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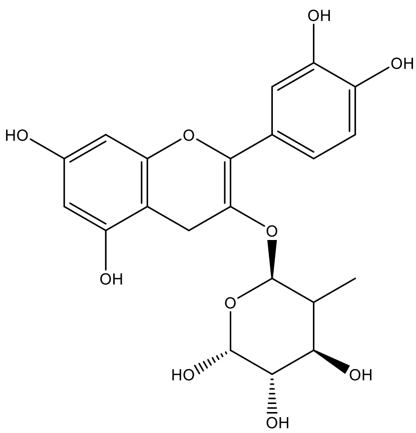

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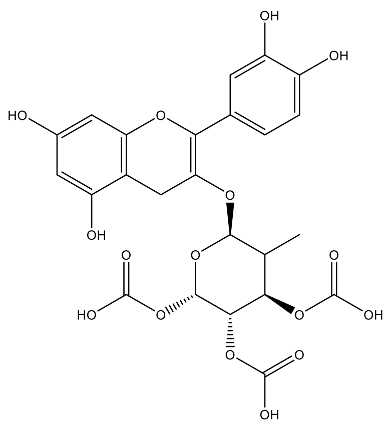

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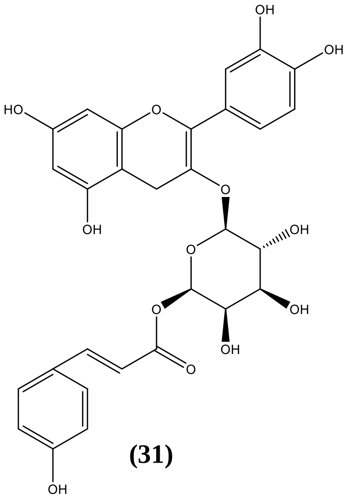

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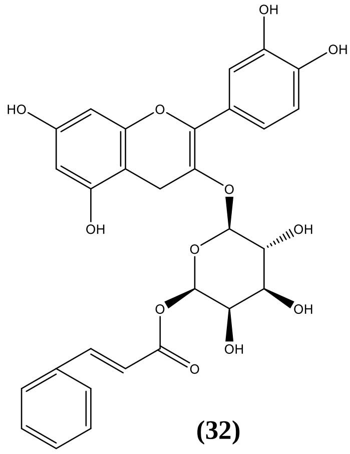

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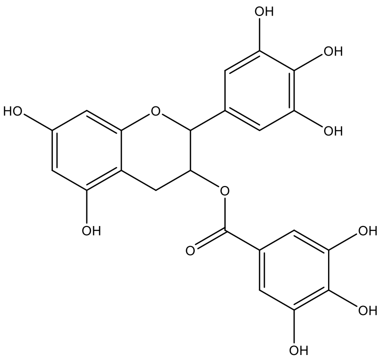
Flavan-3-ols occur as aglycons of epigallocatechin gallate (**33**), epigallocatechin (**34**), epicatechin (**35**) and catechin (**36**) [9,10].



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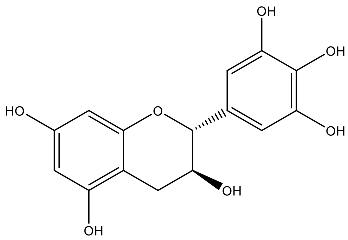

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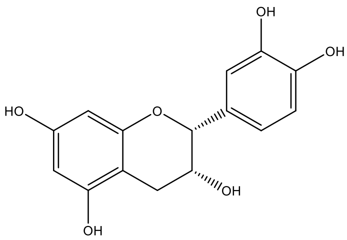

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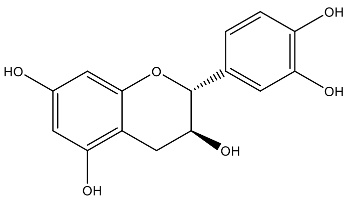

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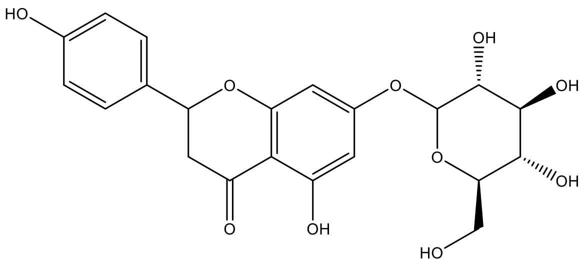
The major flavanone of cranberries, was identified as naringenin 7-glucoside or Prunin (**37**) [15,16].



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Phenolic acids as ellagic acid (**38**; detected in small amount; 120 µg/g dry weight), hydroxycinnamic acid (**39**), caffeoylquinic acid (**40**), feruloylquinic acid (**41**), salicylic acid (**42**), vanillic acid (**43**) and

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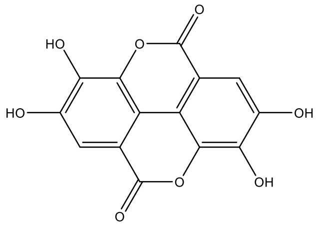
2,4-dihydroxy benzoic acid (**44**) were found in cranberry fruits[12].



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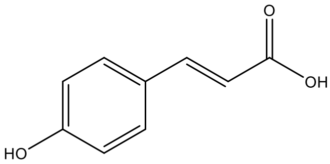

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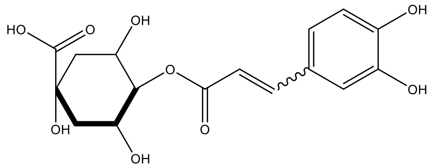

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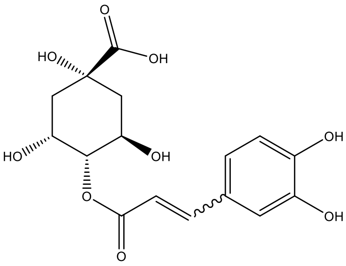

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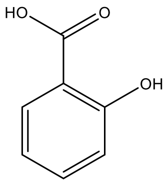

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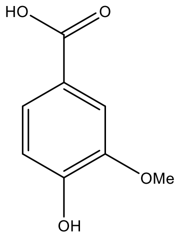

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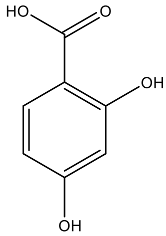

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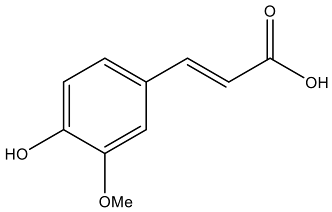
Hydroxycinnamic acids in cranberry such as ferulic acid (**45**), caffeic acid (**46**), p-coumaric acid (**47**), *trans*-Cinnamic acid (**48**), and sinapic acid (**49**) are in a range of 8.9 to 24 mg/100 g FW[17].



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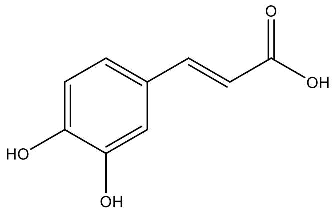

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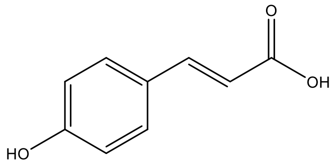

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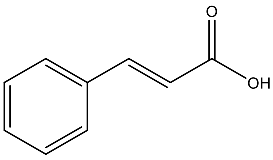

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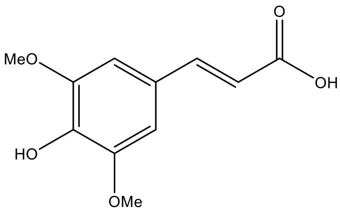

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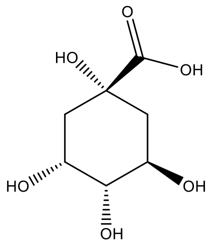

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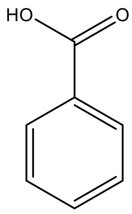

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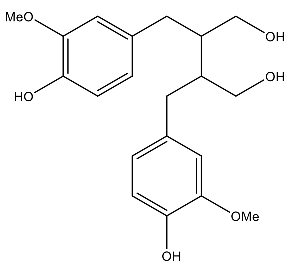
The low content of quinic acid (50) not produce an important conservative effect in cranberries. However, benzoic acid (51) content in most species of cranberries with values of 0.030% to 0.099% is responsible to keep the cranberries in perfect condition in storage as well as the products manufactured[18].

Phenols identified in cranberry include secoisolariciresinol (**52**), trans-resveratrol (**53**; 0.2 mg/L), 2-O-(3,4-dihydroxybenzoyl)-2,4,6-trihydroxyphenylmethylacetate (54), phloridzin (**55**) [19].



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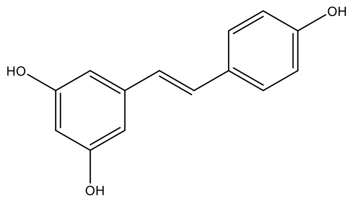

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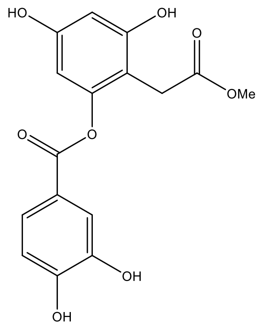

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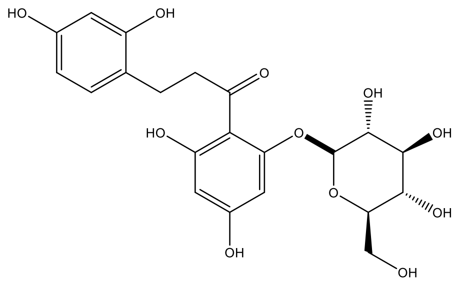

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5. THERAPEUTIC EFFECT OF CRANBERRY

1. Anti-Cancer Effect: The second leading cause of cancer deaths is colon cancer which have been associated with physical inactivity, obesity/overweight, smoking, certain types of diets, and alcohol abuse[20]. Chronic inflammation increases production pro-inflammatory cytokines activating pro-carcinogenic signalling related with initiation of colitis which promoted colon tumorigenesis[21]. Oral treatment of cranberry significantly reduced colonic inflammation at both protein and gene levels, has a significantly inhibitory activity on the activation of PI3K/Akt/ COX-2 signalling pathway, significantly reduced the protein levels of NQO1 and HO-1 in the colonic mucosa of AOM/DSS, reduced VEGF, MMP-2 and MMP-9 expression in treated mice[22].

Proanthocyanidins with A-linkage induces apoptosis in cancer cells, by inhibition of matrix metalloproteinase (MMP) expression and angiogenesis and inflammatory processes[23]. In addition, extracts of cranberry, induce the xenobiotic detoxification enzyme quinone reductase (QR) and reduce ornithine decarboxylase (ODC) expression and in vitro[24]. Cranberry prevent MDA-MB-435 and MCF-7 cells from proliferation without killing the cells. Components of cranberry can accrue in cells in both G1 and G2/M, indicated that may exert at different stages of the cell cycle different effects. The percentage of cells in S-phase was significantly reduced by cranberry indicated that detention in both G1 and G2 phases is an explanation for the reduction in S-phase[25]

Cranberry extract was tested on the early neovascular reaction to syngeneic tumour cells transplantation. Supplementation of cranberry extract to recipient mice markedly reduced the new blood vessels formed in the site of intradermal tumour cells injection. The polyphenol content in the extract reduced proliferation of prostate cancer cell lines, oral (KB, CAL27) and colon (SW620, SW480, HCT-116, and HT-29). These effects are associated with their antiangiogenic effect inhibiting metastasis and tumour progression[26]. Assay in human keratinocytes exhibits a reduction in the expression of TNF-α and VEGF induced by H_2O_2. In tumor endothelialcell line (EOMA) of a hemangioma in children also was observed antiangiogenic effect. In addition, showed inhibition of the factor produced by macrophages transcription of MCP-1 stimulate angiogenesis[27].

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2. Anti-inflammatory Effect: Capsules containing 365 mg of Vaccinum *macrocarpon* extract equivalent to 4325 mg of cranberry fruits, contenting 35 mg proanthocyanidins were supplemented at athletes for six weeks daily in the morning and in the evening (one each). *V. macrocarpon* increased total antioxidant capacity (TAC), in plasma in post-exercise and post-recovery compared with resting controls in athletes undergo to exhausting physical exercise. However, supplementation of cranberry did not show significant changes of TNF-alpha, IL-6, iron, myoglobin and hepcidin levels in serum [3.]

Oxycoccus quadripetalus reduced secretion of pro-inflammatory adipocytokines such as leptin, plasminogen activator inhibitor-1 (PAI-1), MCP-1, and IL-6 in adipose tissue reducing the inflammatory process induced-oxidative stress in adipose tissue[28]. In a study, 5% cranberry treatment in LPS-treated rats fed with atherogenic diet serum HDL-cholesterol level was significantly low compared with control animals. However, IL-1β, IL-6, CRP serum levels were lower, while NO and IL-10 levels showed higher values in the group cranberry suplementation[29]. Thirty-eight grams of cranberry juice consumed daily for 8 weeks demonstrated that P-selectin and mRNA expressions of angiotensin converting MCP-1, COX-2, and enzyme 1, were significantly diminished compared to control group[30]. These results indicated that cranberry juice has anti-atherothrombotic and anti-inflammatory activities in a long-term treatment.

A fraction from cranberry composed mainly of phenolic acids and anthocyanins was studied on Caco-2/15 monolayers which is widely used for the study of inflammation. Oxidative stress, lipid/lipoprotein homoeostasis, and gut absorption. Treatment of fraction from cranberry resulted a tight junction protein, increased occluding, and produce no cell damage indicated that ameliorated intestinal mucosal barrier and the mucosal intestinal. However, also stimulate endogenous antioxidant mechanisms protecting Caco-2/15 monolayers from Fe/Asc-induced oxidative stress. In addition, avoid generation in LPS-mediated pro-inflammatory cytokines such as PGE2 (by via COX-2 decrease), reduced inflammation process and NF-κB activation restoring mitochondrial function[31].

3. Clinical Trials: In a trial was evaluated cranberry in the treatment of lower urinary tract symptoms (LUTS) specifically in men with non-bacterial prostatitis, elevated prostate-specific antigen (PSA) levels and benign prostatic hyperplasia (BHP). Finding, indicated that cranberries ameliorate prostate health in men with elevated PSA enhancing voiding dysfunction. Cranberry used as medication has no adverse effects[32]

Clinical trial on supplementation of cranberry juice have indicated that reduce recurrence of infections in the urinary tract and ameliorated the endothelial function[33]. In other meta-analysis with 1616 participants have revealed that cranberry protected women with recurrent UTIs [34]. Finding, in vitro test 1 have indicated that daily intake of 75 mg of cranberry protected urinary tract against bacterial adhesion. Instead in another trial 2 in the same conditions as in test 1 did not indicates protective activity [12]. Results support that supplementation of cranberry in certain populations may protect against UTIs being to be more effective in women with recurrent UTIs[35].In a crossover study in 35 overweight men which supplementing for 4 weeks 500 mL/d of commercially cranberry juice did not show changes in the Oxidized LDL-C [36] However, consuming for 8 weeks 480 mL/d of commercially cranberry juice malondialdehyde level, oxidized LDL-C, and plasma antioxidant capacity were significantly ameloriate[37].

Human trial testing unsweetened dried cranberries and cranberry juice shown to improvement responses in patients with type 2 diabetes in acute postprandial glycaemic level[38]. Nevertheless, all the studies carried out in subjects with T2D generated discordant results. In a clinical trial in 58 male adults with type 2 diabetes consumed for 12 weeks daily cranberry juice[37]. Reduce in fasting blood glucose

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compared with the placebo group. However, in other trial of 30 diabetic adults[39] results show no effect on consumption of cranberry for 12 weeks /d on glycated haemoglobin, fasting blood glucose. These results were confirmed in other trial of 27 patients with T2D, results show no effect on fasting blood glucose after treatment with cranberry extract[40]. In contrast, in 12 healthy volunteers founded that cranberry juice was able to reduce postprandial plasma response to sucrose[41].

4. Gut Microbiota: Gut microbiota is an important factor in health and nutrition, intervening in the bioavailability, metabolism of food and body systems, such as immune functions and brain. The integrity of the gut mucosal barrier is fundamental for holding a physical and chemical barrier against environmental antigens, food, and microorganisms[42]. The rich content of polyphenols, exercise actions on the cardiometabolic functions and gut microbiota which within the gastrointestinal lumen, could vary the dynamic cross-talk between the gut microbiota and intestinal epithelial cells, act modulate inflammatory pathways, quench reactive oxygen species, exert prebiotic actions, and adhere to proteins and carbohydrates on bacterial surfaces[42].

5. Neuroprotection: Cranberry treatment inhibited apoptosis in both reperfusion and ischemia model cultures as a consequence of the content of flavonols and anthocyanins who have the ability to inhibit stroke damage and enhance recovery as the mainly causing to neuroprotection. This ability of flavonoids to protect neurons against vascular dementia and oxidative stress may be due to inhibited calcium influx, augment glutathione, decreased thiobarbituric acid reactive species (TBARS), levels of ROS generation and thiobarbituric acid reactive species (TBARS). *V. macrocarpon* extract reduced necrosis in hydrogen-peroxide-induced necrosis compared to the control. However, increase SOD and CAT, showed anti-radical effects in ORAC and FRAP assays supported that the neuroprotective effect of these cranberry juices can be related to their participation in the cellular antioxidant response[43].

6. **Obesity:** In obese subject's excess of food consumption plays an important role in reactive oxygen species (ROS) generation to produce oxidative stress, leading to imbalance between antioxidant defences and cellular production of ROS. Chronic oxidative stress is related to different diseases, such as cancer, diabetes and obesity among others[44].

The obesity-inducing diet male Wistar rats (HFD) showed elevated total body fat mass, higher visceral fat mass (VFM) which was measured by higher weighing of mesenteric retroperitoneal, and epididymal adipose tissue. Also, triglycerides, total cholesterol, glucose, insulin, corticosterone, lipid peroxidation, protein oxidation and antioxidant enzymes were determined in plasma or liver. Supplementation of cranberry extract (200 mg/kg) for one month to obese rats did not changes were observed in visceral fat mass and body protein mass, but increased catalase level in liver and plasma, compared to the control groups. However, supplementation of cranberry extract (200 mg/kg) for two months avoid body fat accumulation, body mass gain, oxidative stress, insulin resistance and inflammation in mice[8].

Recently, was investigated the effect of cranberry on modulating fat accumulation in *Caenorhabditis elegans*. Cranberries dose-dependently decreased fat accumulation in *C. elegans* without change locomotive activities. Finding indicated that cranberry decrease fat accumulation in *C. elegans* depending mainly of nhr-49, cebp, and sbp-1 [45]. Differentiated murine 3T3-L1 adipocytes display biochemical properties and morphological characteristics like for adipose cells in vivo, secreting growth factors and hormones, enzymes and cytokines. Studies performed with cranberries (*Oxcoccus quadripetalus)* using 3T3-L1 adipocytes indicated in a dose-dependent manner decrease viability, proliferation of cells, decreasing their number and inhibiting adipogenesis down-regulated the expression of transcription factors of the adipogenesis pathway such as sterol regulatory element binding protein 1 (SREBP-1), peroxisome (PPAR-γ), and enhancer binding protein alpha (C/EBP-α) [19].

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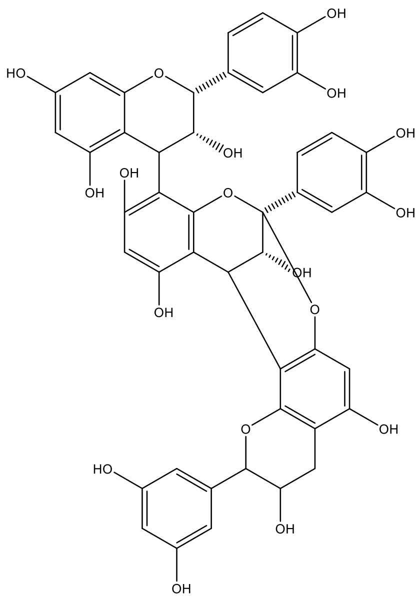
O. quadripetalus inhibit during preadipocyte differentiation the accumulation of lipids by down-regulation of the mRNA level of some genes related with lipid metabolism, such as perilipin 1 (PLIN1), hormone sensitive lipase (HSL), fatty acid synthase (FAS), lipoprotein lipase (LPL), protein (aP2) and leptin[28]. In addition, enhance secretion of adipocytokines and adiponectin gene expresión[28] which are considered important targets for the decrease of insulin resistance, prevention of obesity, dyslipidaemia and hypertension. Finding, indicated that *O. quadripetalus* modulate adipocyte function, adipose tissue mass production, inhibition of serum cholesterol, radical-scavenging and pro-inflammatory cytokines in adipose tissue[28].

7. **Pancreatic Inflammation and Lung Injury:** Treatment with hydroethanolic extract of fruits of *Vaccinium macrocarpon* reduced generation of cytokines such as IL-6, IL-1β, and TNF-α, interfere with the presence of neutrophil infiltration in the pancreas. The inhibition of oedema formation and neutrophil migration to the pancreas produced by *V. macrocarpon* is due to its inhibitory effect on proinflammatory cytokines. Pancreatic contents of IL-6, IL-1β, and TNF-α, were decreased by the supplementation with cranberry. These results were confirmed in other experiment where found that cranberry reduced prostaglandin E2, IL-8, and IL-6, IL-8, generation in gingival fibroblasts stimulated with lipopolysaccharide in vitro assay[46].In a model L-arginine-induced acute pancreatitis (AP) Vaccinium *macrocarpon* treatment reduce of AP-induced abdominal hyperalgesia as a consequence of the inhibition of pancreatic inflammatory cytokines, and block the stimulation of nociceptive pathways[47]. A secondary effect of pancreatitis is lung injury related to mortality in patients[48] In AP model lung MPO activity was significantly increased and cranberry treatment reduced MPO activity in lung as consequence of the reduction of pancreatic injury[49].

8. Periodontal Disease: Proanthocyanins with A-linkage (**8**, PACs) are capable of inhibiting osteoclast differentiation into bone-resorbing cells in the presence of osteoclast genesis mediators, indicating that proanthocyanins can act indirectly by interfering with those mediators implicated in the process of osteoclastogenesis as well as inhibiting bone resorption, MMP secretion and chemokine production in periodontal disease[50]. Effect of PACs is important for decreasing the resorption of the collagen-rich bone organic matrix.



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9. Urinary Tract Infections: Among the most common infections in adults older than 65 years of age are urinary tract protection infections (UTIs) which is mainly due to Asymptomatic bacteriuria (ASB), indicated by bacterias in the urine without manifestations of symptoms and signs[51]. Proanthrocyanidin (PACs), contained in cranberry fruit interacts with fimbria structures found in *Escherichia coli* generated an antiadhesion of *E. coli* binding in the bladder epithelium avoiding the colonization and replication and of *E. coli* avoid the appearance of urinary tract infections[51]. The Mechanism proposed for the effect of cranberry in the protection of UTIs is mainly due to interference with *E. coli* adherence in the urinary tract[52] avoiding uropathogenic P-fimbriated *Escherichia coli* from adherence to bladder cell receptors[53].

10. Radical-Scavenging Activity: Cranberry supplementation in rats fed (atherogenic diet) significantly decreased both TBARS level and serum protein carbonyl[54]. In other study in rats fed with an atherogenic diet and injected with LPS antioxidant defence system were evaluated. Further LPS injection level of total phenolics and superoxide dismutase (SOD), in plasma, were significantly diminished with cranberry supplementation[54].

11. Virucidal Activity: Different influenza virus (IV) infections were tested against *Vaccinium macrocarpon* (Aiton) extract. Considering anti-adhesive effect against several bacteria, was assumed that compounds cranberry be able to avoid viral linkage to target cells. Cranberry extract inhibits influenza A (IAV) and B (IBV) viruses replication in vitro due to content of proanthocyanidins (PAC-A). Virucidal mechanistic studies indicated that cranberry avoid linkage of (IAV) and (IBV) into target cells and cause a virucidal effect interacting with viral glycoprotein hemagglutinin (HA) and ectodomain showing disability of the HA-mediated adsorption and entry into host cells leading to loss of infectivity of IV particles[55].

6. CONCLUSION

The commonly consumed cranberry was picked for this review due to contain important number of phytochemicals, which can prevent some deadly disorders. The present review explored throughout of the literature, pharmacological and phytochemical researches of crude extracts as well as purified phenolic compounds from cranberry for the therapy of disorders supporting the possibility of developing new drugs and their clinical application.

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