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Blueberry Bioactive Properties and Their Benefits for Health: A Review

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Abstract— **Research intended to elucidate the biochemical role of dietary antioxidant bioactive substances, such as blueberry constituents, particularly anthocyanins, associated with their functional properties, has been conducted. The purpose was to identify the effect of these substances on specific biomarkers and the biological occurrence of these correlations, by reducing the risk of developing degenerative diseases, such as diabetes mellitus, cancer, coronary heart disease, hypertension, hypercholesterolemia, and obesity. In view of the above, the aim with this literature review was to gather information about the antioxidant bioactive substances from blueberries, showing how they acted to their antioxidant power, in relation to reducing the risk of developing degenerative chronic diseases. These substances were observed as significant variations of the bioactive composition in the blueberries, influenced by soil and climate conditions. Blueberries, through the biological function of their bioactive substances, would have shown positive effects in reducing the risk of developing several non-transferable chronic diseases.**

Keywords: **antioxidants, anthocyanins, chronic degenerative diseases, free radical.**

I. INTRODUCTION

Some foods, especially fruit berries provide plenty of antioxidants with their specific biochemical functions, and are beneficial to health.

Research both in vitro and in vivo demonstrated that foods of this nature, including blueberries, contained antioxidants in their important bioactive composition, and thus play roles to act as aids in reducing the risk of developing certain diseases, contributing to the health of the body [1].

Blueberries, also known as the blueberry, belong to the genus Vaccinium species, and are characterized as a small fruit-shaped berry, blue-black in color, originating from the northern Europe and North America [2],[3]. Blueberries have been examined especially for being a great source of antioxidants, since they include a varied amount of bioactive substances, coming from these large groups, flavonoids and phenolic acids [4],[5],[6], with potential functional properties.

Blueberries are consumed as fresh fruit and versatile as ingredients in processed foods, fruit pulp, yogurt, candy, ice cream, jams, liqueurs, preserves, and juices [7]; these are still encapsulated in the form of concentrated extracts[8].

This review provides an updated and comprehensive overview of bioactive blueberry compounds; as well as the effect of their antioxidant power and biological mechanisms of these compounds on health, they act as an adjuvant to reduce the risk of developing non-communicable chronic diseases.

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II. BLUEBERRY BIOACTIVE COMPOUNDS

The blueberry *(Vaccinium sp.)* is a world-researched fruit, due to its rich source of natural phenolic compounds [9].If this contribution was seen in their cultivation, then blueberries would spread more and more in several countries [2].

The bioactive compounds are from a biochemical pathway of secondary metabolites of plants and fruit in general [10] which are chemically divided into terpenes, nitrogen compounds, and phenolic compounds [11]. The phenolic compounds of different foods, as well as blueberries, are characterized by substances which have an aromatic ring containing at least one hydroxyl [11], (Fig.1).

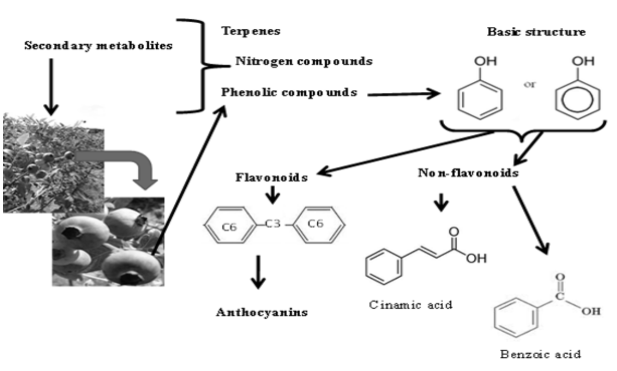

Figure 1:Origin and basic structure of the phenolic compounds in the blueberry

In the blueberry, phenolic acids, flavonoids, anthocyanins, procyanidins, proanthocyanidins, polyphenols, tannins, antioxidant vitamins such as vitamin C, chlorogenic acid, quercetin, kaempferol, mirecitina, catechin, epicatechin, chlorogenic acid, p - coumaric acid, and hydroxycinnamic acids, inclusive, among others, comprise the bioactive fruit [9],[12].

Phenolic compounds in the blueberry can be classified into two major groups: non-flavonoids and flavonoids. Flavonoids with a 15-carbon skeleton arranged in a common basic chemical structure, with two aromatic rings linked by a chain of three carbons, form a C6-C3-C6 system (Fig.1). From these, there is a variation with combinations of methyl and hydroxyl groups that form numerous compounds. The different classes of flavonoids include flavanones, flavones, flavanols, isoflavones, anthocyanins, and flavans that differ from each other with respect to the degree of oxidation around the heterocyclic ring oxygen [13].

Non flavonoids, phenolic or simple acids ,are characterized by having a benzene ring, a carboxylic acid grouping ,and one or more hydroxyl groups and / or methoxyl in the molecule. These also consist of two groups: those derived from hydroxybenzoic acid, and derivatives of hydroxycinnamic acid [13], [14], (Fig.1).

III. ANTHOCYANINS

Polyphenols, natural pigments, are more abundant in blueberries, evidenced by the purplish blue coloring of the fruit [15]. This is the color of both the anthocyanins since the anthocyanidins are controlled by three basic pigments: pelargonidin (red), cyanidin (red) and delphinidin (violet). In addition to their dye properties, anthocyanins have been explored for their good source of antioxidants [16] and potential functionality for use as food, or by a pharmacy.

Anthocyanins are present in the blueberry fruit in the glycosylated form of aciloglicosilada and anthocyanidins [10], and present with a sugar residue attached mostly at the 3-position on the ring, or less often, to the position of 5 or 7. They differ in the number of hydroxyl groups, the degree of methylation of these groups, the amount and position of the molecules of sugars, and aliphatic or aromatic acids [17], [18]. The carbohydrates commonly connected to mono, di or trisaccharide forms of anthocyanidins are galactose, glucose, arabinose, xylose, and rhamnose [19], (Fig.2).

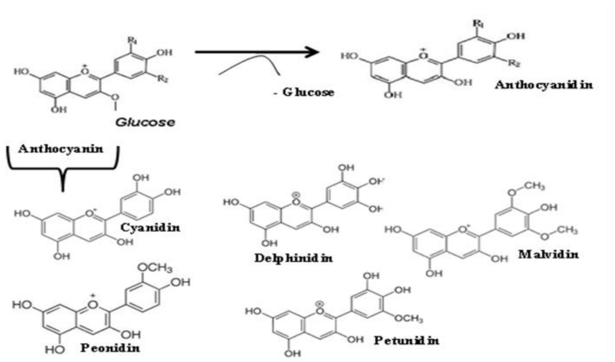

Figure 2: Chemical structure of anthocyanin, anthocyanidin and the main anthocyanins blueberry.

The quality, quantity and prevalence of these bioactive blueberry compounds depend on the type of crop, soil composition, climate characteristics, genetics of the fruit harvest season, the maturation phase, sun exposure, and the post-harvest [4],[18]. In all these the quantity of the blueberry anthocyanin is interfered by the presence of a high pH, oxygen, light, heat, and the extraction method; yet this also influences the determination of the amount of anthocyanin in the fruit, since these compounds are unstable [20],[21].

A wide range of studies identified and quantified anthocyanins and the phenolic acids of the blueberry. In [5], when 42 different cultivars of blueberries were compared and showed that the most common anthocyanins were found to delphinidin, cyanidin, and malvidin petunidin; however we observed significant quantitative differences between cultivars, where the rabbiteye variety was the one with a greater amount of malvidin anthocyanins, followed by delphinidin and cyanidin. The study [18] found that among the total anthocyanins in certain blueberries, delphinidin (56.6%) was expressed as the largest amount in the fruit, followed by malvidin (30.6%), petunidin (7.9%), cyanidin (4 , 2%), and peonidin (0.6%).

The fractions of malvidin and delphinidin were described in several studies as the main anthocyanin found in blueberries [21]. For the phenolic compounds of blueberries, indicated by the main research, included gallic acid, caffeic, coumaric, and ferulic acids were found [22].

The amount of anthocyanins found in blueberries is used as a marker for assessing the quality of these fruits and their derivatives, as this is the main substance responsible for the antioxidant function of the fruit. Analyzed the anthocyanins in bilberries (*Vaccinium myrtillus L.*), and blueberries (*Vaccinium corymbosum L.*), [23] determined at 1210 mg / 100 g 212 mg / 100 g of fresh weight, respectively. Evaluated the blueberry by determining an average of 1242.4 mg / L of anthocyanin in the fruit [24]. Determined a variation in the amount of blueberry anthocyanins in various cultivars of 137 mg / kg to 272 mg / kg [4].

Anthocyanins are found mainly in the outer layers of the hypodermis (skin), while the rest of the fruit contains little or no anthocyanins, namely the pulp of the fruit, which is a common by-product of juice processing consisting of a source of polyphenols [4]. This has been explored as an ingredient in the development of products with health benefits, as well as the extraction of isolated compounds in particular anthocyanins [8].

Studies have evaluated the bioactive microencapsulation of the blueberry, in order to preserve the compounds, and to facilitate the targeted release of these in the body [8].

Increasing evidence has shown a significant role of anthocyanins in lowering the risk of the onset of various diseases by their antioxidant properties, attributed to the OH group and their ability to bind free radicals [18],[25],[26].

IV. BLUEBERRY ANTIOXIDANT POTENTIAL

The human body utilizes a two-way antioxidant protection: physiological endogenous antioxidant mechanisms that occur naturally and exogenous antioxidants; a diet consumed by both mechanisms minimize oxidation and oxidative stress induced by reactive free radical species [27].

The blueberry bioactive compounds are exogenous antioxidants, which act when consumed, slowing or preventing oxidation by inhibiting the initiation or propagation of a chain of oxidation reactions [25]. They also act on the inactivation of hepatic detoxification enzymes, blocking the activity of viral or bacterial toxins, promoting the elimination of free radicals, inhibiting cholesterol absorption, regulating the gene expression in cell proliferation, reducing platelet aggregation, inducing apoptosis, and stimulating the immune system [26], [18].

The bioactive compounds of the anthocyanins and other flavonoids of the blueberry generally act as free radical scavenger peroxides, singlet and triplet oxygen suppressors, by eliminating superoxide radicals generated chemically [18]. According to [28], anthocyanins showed a potent antioxidant effect on a model of oxidative stress induced by H_2O_2 on endothelial cells; and this action was observed at a concentration of 15-100 g / mL of an isolated anthocyanin fraction. In research conducted by [29], we observed a high correlation of coefficients between the in vitro antioxidant activity (DPPH, ABTS, FRAP) and the antioxidant constituents of the fruit (total phenolics, total flavonoids and proanthocyanidins content). These results suggest that the antioxidant in blueberries and the radicals of cleaning properties might be attributed to the high level of these antioxidant compounds [29].

The analysis of the many cultivars of blueberries showed that, in general, the antioxidant activity of these fruits was given in the following order of action of substances as quantity: chlorogenic acid, mirecitina derived from quercetin and delphinidin, cyanidin, and malvidin petunidin [5]. In another study, the results showed that cyanidin-3-glucoside, delphinidin 3-rutinoside and malvidin-3-galactoside were determined in the major anthocyanins of blueberries [30].

In addition to anthocyanins, flavonoids are important in the composition of blueberry polyphenols, including quercetin, kaempferol, mirecitina, catechin, epicatechin, vitamin C, and several proanthocyanidins, all contributing to the antioxidant activity of the fruit [31]. Despite its low bioavailability and variable instability in the plasma, the anthocyanin pigment contained in fruits and vegetables demonstrated biological efficacy in a variety of clinical conditions.

V BIOLOGICAL ACTION OF ANTIOXIDANTS IN BLUEBERRY COMPOUNDS

The antioxidant activity of blueberries has been evaluated in in vivo studies with the fruit administrated in various forms, as a beverage, blueberry extracts, with lyophilized and isolated anthocyanins. The bioactive compounds acted individually or synergistically, contributing to the protection the body from the occurrence of various chronic degenerative pathologies, as they acted on glucose metabolism as an anti-diabetic, and anti-cancer deterrent; cardiovascular disease, hypertension, and obesity were also deterred [16], [9].

The bioactive properties from the bioactive compounds of the blueberry initially acted by neutralizing free radicals, and acted in other ways as reported in the literature for each type of pathology. For example, in diabetes, according to [13], a diet rich in fruits and vegetables is inversely correlated with the incidence of type 2 diabetes; these beneficial effects are largely attributed to their phenolic compounds. One explanation of this protection is the fact that the bioactive polyphenol compounds may interfere with the metabolism of carbohydrates, lowering fasting hyperglycemia and the postprandial state by the action of inhibiting disaccharidases (amylase and glucosidase) in the intestinal lumen; this restricts the digestion mechanism of the polysaccharide constituents in the diet, thus reducing the absorption of simple sugars [32]. Some other mechanisms are involved in the antidiabetic action of bioactive compounds; among them the polyphenols contribute to improved glucose uptake in the muscle and adipocytes; this increased hepatic glucokinase activity allows the glucose user to promote more energy storage in the form of glycogen, and suppresses the hepatic glucose output [32].

The literature contains research indicating that blueberry extracts are inhibitors of α-glucosidase enzymes responsible for catalysing the uptake of glucose. In this way, they act as an effective measure for the regulation of type II diabetes (characterized by insulin resistance and deficiency of their production in the body), controlling glucose uptake and contributing to improve insulin sensitivity [33].

As chemopreventive agents, the desempenhan polyphenols of the blueberry have a protective role in many types of cell cultures, by inhibiting the growth of tumor cells. In a study developed by [6], the purified bilberry anthocyanins acted to inhibit the proliferation of murine melanoma cells and induced apoptosis. In research conducted by [34], blueberry aqueous extracts showed anti-proliferative effects in three cell lines (Caco-2 HT-29 and HCT 116), and human colon cancer. According to [35], blueberry consumption daily for six weeks acted by increasing the number of NK (Natural Killer) cells that act by killing tumor cells through the induction of apoptosis. Anthocyanins, even when applied in very low concentrations (<1 mg / L) provide protective effects for health. One of the mechanisms which explain the chemo protection of phenolic compounds is based on the assumption that anthocyanins act as absorbing oxygen radicals; thus they inhibit the generation of these free radicals by stimulating an expression of detoxification enzymes and a decrease in lipid peroxidation, besides inducing apoptosis [6]. Research conducted by [22] suggest that the preventive properties of bioactive compounds of the blueberry imply reduced levels of free radicals, increased levels of glutathione in human cells of colon tumor, providing protection from the oxidative stress in the colon.

In cardiovascular diseases such as atherosclerosis, research infers that blueberry bioactive compounds increase the production of nitric oxide. Since these are more bioavailable, they improve the endothelial function and vascular tone, because they act to inhibit the contraction of vascular smooth muscle growth and platelet aggregation, as well as leukocyte adhesion, thereby contributing to the maintenance of a functional endothelium. Therefore, control of the endothelial tissue relaxation directly influences the vasomotricity, by reducing the lipid antioxidant activity of the bioactive compounds,[36],[37], contributing to the prevention of heart diseases. According to [38], their study evaluated the association between the total antioxidant capacity of the diet and the incidence of heart failure among middle-aged women and the elderly, for 11.3 years. It was possible to assess the total dietary antioxidant capacity, which reflects all the antioxidants that have been associated with a lower risk of heart failure. These results indicate that a healthy diet rich in antioxidants is a preventive factor for heart failure.

Blueberry consumption has been associated positively with the control of hypertension; pathology usually associated with other chronic degenerative diseases from the group is not transferable. According [39], the bioactive blueberries act as an adrenergic agonist contraction receptor, thereby improving the vascular tone through an endothelium-dependent vasodilation. In research conducted by [35], the continuous consumption of blueberries for pre hypertensive patients with an average blood pressure ≥ 120/80 mmHg, caused a significant reduction in the diastolic pressure. In general research attributes this benefit to the specific biological actions in the arterial walls, such as an excessive reduction of reactive oxygen species in the blood vessels, and changes in the nitric oxide synthesis, with an increase in the dilation of vessels [37].

Some researchers undermine the fact that in a study conducted in rats, where one group received the entire blueberry in lyophilized form and another group only the isolated anthocyanin, only the latter, which lacked the other blueberry components (sugars and lipids), showed an effective reduction in body weight gain, dyslipidemia correction, or a reduction of the blood glucose. Thus, it is understood that the data presented suggests that the sugar and lipid components of the whole blueberry cannot perform protective physiological functions. Blueberry extracts exhibit a good amount of purified anthocyanins, and are more effective than whole berries in the action to prevent the development of obesity [36], and to reduce low density lipoproteins (LDL) in the serum of individuals diagnosed with a metabolic syndrome [37]. Studies suggest that the consumption of a diet rich in fat, accompanied by a good supply of polyphenolic compounds, such as those found in blueberries, can minimize the occurrence of complications, and metabolic disorders [40]. In studies of humans, it was observed that the consumption of whole blueberries improved insulin sensitivity and cardiovascular risk factors in obese, non-diabetic and insulin resistant persons [41], [33].

Thus, with this broad overview about the polyphenol composition, the bioactive properties of bilberry fruit, as well as the mechanisms from the action of these compounds on biological markers, one can infer that the chemical nature of this fruit could become a dietary potential mechanism in reducing the risk of diseases; in the long term this would contribute to a healthier population and a reduction in the amount spent on health both by individuals and government bodies responsible for public health.

VI. CONCLUSIONS

Based on the consulted literature, polyphenolic compounds in blueberries have been increasingly studied for their health benefits. Among these, those with a greater emphasis on quantity are derived from the group of the flavonoids, in particular anthocyanins from this group. Analysis of the constitution, the content definition, and class antioxidants in blueberries are dependent on environmental conditions and varieties of the fruit. Much of the research shows a high variability in the fruit polyphenol concentration, as well as the in the amount of aglycone and sugar attached to them. The absorption of bioactive compounds in the blueberry, even in minute fractions, acts by neutralizing free radicals and demonstrates positive actions on biological biomarkers, showing help to reduce the risk of chronic degenerative pathologies. In diabetes, blueberry polyphenols inhibit the action of glucosidase and amylase in the intestine, which reverses the decrease in fasting hyperglycemia and the postprandial state. As a chemoprevention, this inhibits the proliferation of cells through the stimulation of the production of natural killer cells that induce apoptosis. In cardiovascular diseases the production of nitric oxide increases the maintenance of the functional endothelium. This increases the pressure of the acting adrenergic agonist receptor and contraction, and an improved vascular tone. In obesity, the blueberry anthocyanins extracted act to decrease the body weight gain and to reduce low density lipoproteins. More and more research has elucidated the mechanisms through which the blueberry polyphenols act in the body, highlighting their importance in food as an aid to maintain health. We should also encourage production of this fruit, as well as continue research aimed by ace analysis to show the efficiency of bioactive compounds in reducing the risk of chronic degenerative pathologies.

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