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Review article
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Pigmented Maize (*Zea mays* L.) Contains Anthocyanins with Potential Therapeutic Action Against Oxidative Stress – A Review

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Different maize (*Zea mays* L.) varieties have been used for thousands of years as a healthy food source in Mesoamerica including pigmented maize. Maize ingestion could contribute to the reduction in the rate of non-communicable diseases and, in turn, to its function as an adjuvant in their management. These diseases are mainly associated with oxidative stress, which is characterized by a redox cell imbalance produced due to pro-oxidant molecules accumulation, inducing irreversible damages. Although the endogenous antioxidant defense system is efficient, exogenous antioxidants are necessary to help to prevent this damage. Bioactive compounds, like anthocyanins, contained in dietary plants exert a major activity against oxidative stress. Could the maize anthocyanins play a curative, preventive or complementary role in the treatment of chronic diseases? Here, we describe the occurrence of anthocyanins from pigmented maize and their chemical structures. Furthermore, the biosynthesis, bioavailability, and stability are also summarized. Finally, many *in vitro* and *in vivo* studies of maize anthocyanins are discussed that demonstrated their nutraceutical potential, antioxidant capacity, and other biological effects. Given the importance of the biological properties of maize anthocyanins, it is necessary to understand the current knowledge and propose further research or clinical studies which allows us to better elucidate the biological mechanism of maize anthocyanins derivatives of several varieties and processes of cooking and combination with other ingredients to enhance their nutritional and health benefits.

INTRODUCTION

Oxidative stress is a condition that begins when the redox balance of living organisms is altered by an excessive formation of radical molecules, which exceeds the endogenous antioxidant capacity [Lobo *et al*., 2010]. Usually, the electron transport chains in the mitochondria utilize oxygen to convert nutrients into adenosine triphosphate (ATP) and through this process generate radicals, which are used to carry out cellular signaling processes. However, various environmental, physical, and chemical factors can cause the excessive generation of these radicals, resulting in the chemical imbalance of biomolecules and cellular stress [McCord, 2000].

The main feature of this condition is an increase in free radicals and reactive species such as hydrogen peroxide (H_2O_2), superoxide (O_2^-), hydroxyl radical (HO^-), singlet oxygen ($^1O_2$), alkoxy radical (RO), and peroxyl radical ($ROO^•$). These compounds cause necrosis, apoptosis, damage, and cell death due to modification in the structure and function of macromolecules such as lipids, proteins (in biological membranes and tissues), and deoxyribonucleic acid (DNA) [Birben *et al*., 2012].

Although the endogenous antioxidant defense system is efficient, sometimes it is overwhelmed and needs exogenous antioxidants. Plant and animal reducing compounds such as vitamin C, vitamin E, carotenoids (xanthophylls and carotenes), anthocyanins, chalcones, isoflavones, tannins, flavandiols, and flavonols can restore the oxidative balance [Kasote *et al*., 2015]. Several epidemiological studies have demonstrated that individuals who consumed fruits, vegetables, and whole grains with anthocyanins, were at a lower risk to develop chronic diseases such as cancer, diabetes, and cardiovascular disease (CVD) [Pandey & Rizvi, 2009]. Most of these beneficial health effects are attributed to exogenous antioxidant compounds ingested from plant sources at different concentrations. Anthocyanins are among the bioactive compounds that stand out for their beneficial properties [He & Giusti, 2010].

Maize is widely distributed and consumed around the world, especially in developing countries. Because of this, some researchers have focused their efforts on the generation of new varieties of pigmented maize through cross-hybridization to obtain new varieties of grains with a greater

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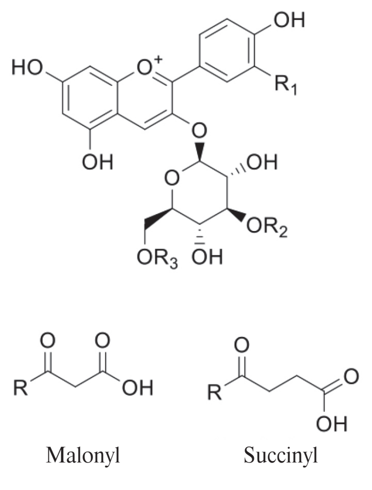
antioxidant capacity [Tiessen *et al.*, 2017]. Therefore, such improved maize varieties could function as bioactive agents and potential candidates to be included in the prevention and integral management of chronic degenerative diseases, and in reducing their incidence [Chander *et al.*, 2008]. This review aimed to collect data on the effect of anthocyanins present in pigmented maize. They were considered regarding their metabolism, as well as their intervention in the antioxidant and modulating capacity of several cellular processes involved in oxidative stress such as cell growth, cell proliferation and cell death.

OCCURRENCE OF ANTHOCYANINS AND THEIR CHEMICAL STRUCTURES

Anthocyanins are responsible for many colors (blue, blue-black, red, and purple) of leaves, flowers, fruits, seeds, roots, and stems. In cereal grain (a kind of single-seed fruit), the anthocyanins are localized mainly in the cells of pericarp, testa, and aleurone layer, which depends on many structural and regulatory genes [Fan *et al*., 2016; Li *et al*., 2018]. Several plant foods contain different concentrations of anthocyanins including: berries (*Morus* and *Rubus* gender), grapes (*Vitis*), plums and cherries (*Prunus*), red pear (*Pyrus*), red apple (*Malus*), pomegranate (*Punica*), blackcurrants (*Ribes*), raspberry (*Rubus*), strawberries (*Fragaria*), chili (*Capsicum*) [Aza-Gonzalez & Ochoa-Alejo, 2012], camu-camu (*Myrciaria dubia*) [Langley *et al.*, 2015], açaí (*Euterpe oleracea*) [Peixoto *et al.*, 2016], cacao (*Theobroma)* [Chavez-Rivera & Ordoñez-Gomez, 2013], and calyces of *Hibiscus sabdariffa* L. (Jamaica) [Gurrola-Diaz *et al.*, 2010], as well as such red radishes, red peppers, tomatoes, red onions, purple and red-fleshed potatoes (*Solanum Tuberosum* L.) [Jansen & Flamme, 2006], purple cabbage (*Brassica oleracea* var. *capitate*), and eggplant (*Solanum melongena* L.) [Sadilova *et al.*, 2006]. Anthocyanins are also present in grains such as in the color-varieties of corn (*Zea*), wheat (*Triticum*), rice (*Oryza*) [Goufo & Trindale, 2014], and bean (*Phaseolus)* [Takeoka *et al.*, 1997]. These foods (seeds, fruits, and vegetables) are the main source of natural pigments, which providing them unique colors and flavors and make them attractive for consumption, and eventually may serve in a complementary natural treatment of chronic diseases. In maize, they accumulate in structures such as stem, pod, leaves and inflorescences; in the cob, they are found in bracts, rachis, and kernels [Cui *et al.*, 2012]. Chemically, the anthocyanins are polyhydroxy/polymethoxy glycosides derived from the anthocyanidins. They are formed by an anthocyanidin molecule, that is the aglycone, to which a sugar moiety is bound by a β-glycosidic bond or, in some cases, by α-glycosidic bond. There are approximately 20 types of anthocyanidins in nature, but only six: pelargonidin (Pl), cyanidin (Cy), peonidin (Peo), delphinidin (Dp), petunidin (Pt) and malvidin (Mv), are widely distributed [Tsuda, 2012]. The name of these compounds is derived from the plant source from which they were first isolated. The basic chemical structure of aglycones is the flavylium ion, also called 2-phenyl-1-benzopyrylium (2-phenylchromenyl; IUPAC). It consists of a 15-carbon skeleton (C6-C3-C6) organized into two aromatic groups: benzopyrylium/chromenium, and phenolic (also known as hydroxycinnamoyl) (see Figure 1). Because of the trivalent character of oxygen, flavylium typically functions as a cation (oxonium ion) or flavylium salt [De Rosso *et al*., 2008].

The monosaccharides commonly bound by *O*-glycosylation to the anthocyanidins, are glucose and rhamnose followed by galactose, xylose, arabinose, and occasionally, gentiobiose and raffinose [Horbowicz *et al*., 2008; Yonekura-Sakakibara *et al*., 2012; Fang, 2014]. All of them bind to anthocyanidin primarily by the hydroxyl group at the 3-position and secondarily at the 5 or 7-position but can also be found at positions 3', 5', or 6', but rarely at the 4' position. When two sugars are present in the same molecule, they are located in the 3 and 5 hydroxyl groups, producing a more stable structure than when a molecule contains only a single monosac-



R_1	Anthocyanidin
-H	Pelargonidin
-OH	Cyanidin
-OMe	Peonidin

R_2	R_3	Name
H	H	Anthocyanidin-3-O-β-glucopyranoside
H	Malonyl	Anthocyanidin-3-O-(6”-malonyl-glucoside)
Malonyl	Malonyl	Anthocyanidin-3-O-(3”, 6”-dimalonyl-glucoside)
H	Malonyl	Anthocyanidin-3-O-(6”-succinyl-glucoside)
Succinyl	Succinyl	Anthocyanidin-3-O-(3”, 6”-disuccinyl-glucoside)
Malonyl	Succinyl	Anthocyanidin-3-O-(malonyl, succinylglucoside)

FIGURE 1. The structure of anthocyanin compounds isolated from maize. The enzymatic system of maize permits to yield three different anthocyanidins: pelargonidin, cyanidin, and peonidin, as well as their acylated derivatives: malonylated and succinylated ones [Abdel-Aal *et al*., 2006; Fossen *et al*., 2001].

charide. The combination of the anthocyanidins with the different sugars generates more than 700 different anthocyanins [Wallace & Giusti, 2015]. The degree of glycosylation has a significant impact on the biological activity of the anthocyanin, depending on the chemical nature (type of carbohydrate) as well as the number and position of the glycosylation sites [Zhao *et al*., 2014]. Cereals like maize produce anthocyanins monoglycosylated with glucose, and later do acylation with one or two malonyl-CoA or succinyl-CoA [Fossen *et al*., 2001; Abdel-Aal *et al*., 2006] (see Figure 1).

Cyanidin is the major constituent of the pigmented maize grain and exhibits a significant antioxidant activity in comparison with that of the non-pigmented maize. In fact, its phytochemical composition and concentration of bioactive compounds vary depending on grain color, with a wide variety of tones ranging from black, blue, purple, red, yellow to white. Because it is a staple food providing a high anthocyanin content, there has been scientific interest in the study of pigmented maize and its health benefits [Lopez-Martinez *et al*., 2009]. Particularly, a similar profile of anthocyanin has been identified with different extraction methods (microwave, ultrasound, and maceration) like in the case of: cyanidin-3-(6''malonyl)-glucoside, cyanidin-3-*O*-glucoside and mainly peonidin-3-*O*-glucoside, pelargonidin-3-*O*-glucoside, pelargonidin-3-(6''malonyl)-glucoside, and peonidin-3-(6''malonyl)-glucoside [Salinas-Moreno *et al*., 2005a; Yang & Zhai, 2010; Camelo-Méndez *et al*., 2016; Li *et al*., 2017; Chen *et al*., 2018; Fernandez-Aulis *et al*., 2019], however some differences in the anthocyanin profile are due to the environmental factors, maturity stages, and parts of the plant (husk, cob, and leaf) [Fossen *et al*., 2001; Li *et al*., 2008].

STABILITY OF ANTHOCYANINS

Anthocyanins are unstable and susceptible to degradation upon the effects of temperature, light, enzymes, pH, and oxygen radicals. All these factors can affect their stability as well as their coloration intensity [Cevallos-Casals *et al*., 2004]. In aqueous solutions, anthocyanins suffer structure intramolecular adjustment mainly caused by the electronic deficiency (positive charge) of the flavylium nuclei. In vacuolar pH (4–6), the principal red flavylium (stable at <3) undergoes a proton loss, a water molecule addition, and an intramolecular rearrangement, generating the quinoid form with blue/violet coloration (at pH = 4), the colorless carbinol (at pH = 5), and chalcones with yellow coloration (at pH = 6), respectively [Kallam *et al*., 2017]. If pH keeps rising, the anionic forms start to accumulate, shifting the color of medium to green, when the ionized chalcone and ionized quinoid are in the equilibrium state at pH 8–10 [Levi *et al*., 2004]. At pH values greater than 12, dianion chalcone is the major compound, producing a yellow color in the solution [Petrov *et al*., 2013] (see Figure 2).

Two processes which can affect the stability and color of anthocyanins from maize are: the co-pigmentation, and the acylation [Cooper-Driver, 2001]. The co-pigmentation effect is a non-covalent intermolecular interaction with other phenolic compounds through a type π-stacking interaction (a property of aromatic rings), which enables the hy-

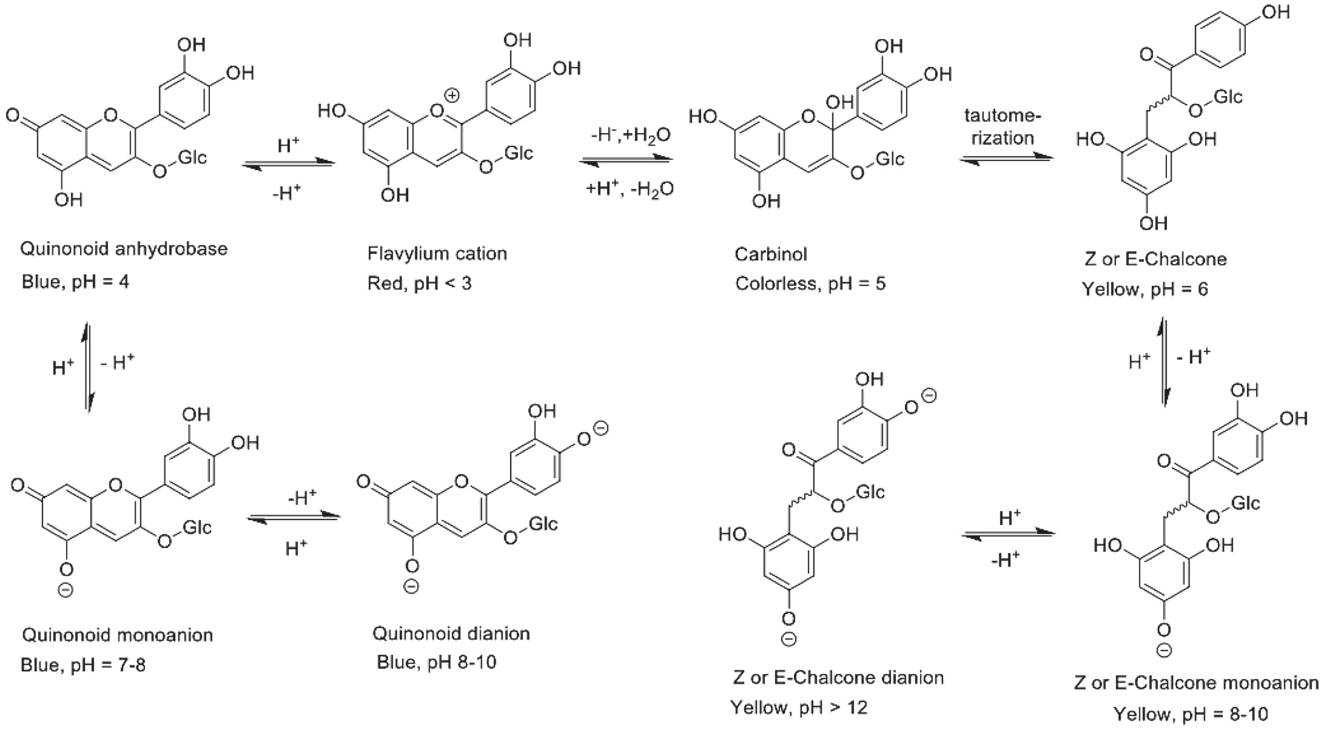


FIGURE 2. Anthocyanin structural changes in aqueous medium at different pH. Cyanidin-3-*O*-glucoside is the structure shown; contains the most abundant aglycone in purple maize. In low pH (<3), the flavylium cation is the major chemical species, quinoid form with blue/violet coloration (pH = 4), colorless carbinol (pH = 5), and chalcones with yellow coloration (pH = 6). The ionized chalcone and quinoid forms are in the equilibrium state at pH 8–10. At pH values greater than 12, the yellow dianion chalcone is the major compound.

perchromic shift in mildly acidic conditions through stabilizing blue quinoid species instead of carbinol compound in an aqueous medium [Mazza & Brouillard, 1990]. The acylation with hydroxyl cinnamic acids (HCAs) can increase the number of interactions due to an extra phenyl ring [Gläßgen & Seitz, 1992]. In the case of maize, the acylation occurs with malonyl and succinyl moieties, which cannot stabilize further the co-pigmentation, as happens for the acylation with HCAs [Harakotr *et al*., 2014]. Most of the aliphatic acylations are lost under an alkaline pH, such as the nixtamalization process [Mora-Rochín *et al*., 2016].

ANTHOCYANINS IN PIGMENTED MAIZE (*ZEA MAYS* L.)

The prehispanic cultures named the maize cob "*centli*" and the kernel "*tlaolli*" in their Nahuatl language. The earlier evidence for maize (*Zea mays* L.) domestication was estimated 8,700 calendrical years ago, found in Xihuatoxtla Shelter in Guerrero, Mexico [Piperno *et al*., 2009]. This grain constitutes one of the main sources of calories, proteins, and vitamins for the rural inhabitants of many regions including Mexico, central and north America. People in these regions have incorporated pigmented maize into their regular diets [Betrán *et al.*, 2000]. There are many varieties of maize with different nutritional values, of which four varieties stand out: blue, red, yellow, and white [de la Parra *et al*., 2007]. Maize is commonly consumed in the form of dry mass flour to make "tortillas", chips, tamales, "gorditas", and many other basic foodstuffs of the Mexican and Latin American (*e.g.* different types of beverages).

Pigmented maize is a major source of starch, proteins, fats, sugars, anthocyanins, salicylic acid, resins, saponins, potassium, sodium salts, sulfur, phosphorus, and other phenolic compounds [Pedreschi & Cisneros-Zevallos, 2007]. High concentrations of anthocyanins and phenolic compounds are distributed in the aleurone and pericarp monolayer of the grain, which provides the characteristic blue, red, purple, and black color to the maize varieties [Espinosa Trujillo *et al.*, 2009]. Red and blue/purple beads are the most common [Salinas *et al.*, 1999] and due to genetic variations, at least 59 races have been described in Mexico, many of them corresponding to variants of pigmented grains [Sanchez *et al.*, 2000; Salinas-Moreno *et al.*, 2013]. Žilić *et al*. [2012] reported differences in the anthocyanins content in several varieties of pigmented maize ranging from 2.50 to 696.07 mg CGE/kg d.m. (cyanidin-3-*O*-glucoside equivalent per kilogram of dry mass). In this work, cyanidin-3-*O*-glucoside was the most abundant anthocyanin contained in the light blue maize variety. In another study conducted on blue maize planted in some regions of Mexico (Querétaro and Chihuahua States), Urias-Lugo *et al.* [2015a] confirmed the highest concentration at 1052 mg Cy3glu/kg (cyanidin-3-*O*-glucoside for each kg of sample) of anthocyanins in the grain.

Anthocyanins in pigmented grains hold the promise of being functional food compounds due to their antioxidant and anti-inflammatory activity, phase II enzyme activators, anti-cell proliferation, and hypoglycemic effect [Tsuda *et al.*, 2003; Urias-Peraldi *et al*., 2013]. Generally, the seeds have a high proportion of pigments in the aleurone layer and, to a lesser extent, in the starchy endosperm [Betrán *et al.*, 2000]. The diversity of the varieties of pigmented maize is due to the physical characteristics such as the variability in the size, density, hardness, and chemical composition of the grain as well as environmental factors such as the climatic conditions where it grows, soil type, cultivation practices and finally, to specific genetic factors of each variety. The interaction of these factors provides to each variety of pigmented maize a unique observable characteristic such as coloration; but also, a different biological activity based on the quantity and profile of secondary metabolites, which enhances its functional food potential. For example, in light red-colored grains, the most abundant anthocyanidin is the pelargonidin [Salinas *et al.*, 1999; Abdel-Aal *et al.*, 2006], while in the blue grains (blue, purple, and black) the cyanidin derivatives prevail [Pedreschi & Cisneros-Zeballos, 2007; Zhao *et al.*, 2009]. In magenta red kernels, cyanidin derivatives predominate but they also contain derivatives of pelargonidin and peonidin [Salinas-Moreno *et al*., 2005a]. Specifically, the main anthocyanins reported in maize are cyanidin 3-*O*-glucoside and pelargonidin 3-*O*-glucoside that have been described in a relatively high proportion (about 40%) as malonylated *i.e.*, cyanidin 3-*O*-(6''-malonyl-glucoside) and cyanidin 3-*O*-(3'',6''-dimalonyl-glucoside). The cobs of some landraces may contain kernels with up to three colors [Barrientos-Ramírez *et al*., 2018]. In the blue-grain varieties, the pigment is found in the aleurone layer, in those having light red grain – in the pericarp, and in those with magenta/red grain – it is located in both, the pericarp and aleurone layer [Salinas-Moreno *et al.*, 2012]. There are both acylated and non-acylated anthocyanins in pigmented maize grains. Compared to other cereals, pigmented maize from Mexico exhibits a high concentration of anthocyanins of acylated type, which increases its chemical stability at extreme conditions of pH and temperature [de Pascual-Teresa *et al.*, 2002; Salinas-Moreno *et al.*, 2005a]. The acylated anthocyanins identified in the maize grain were cyanidin-3-*O*-glucoside, pelargonidin-3-*O*-glucoside, and peonidin 3-*O*-glucoside [Styles & Ceska, 1972]. The sugar moiety might bind to one or more acyls (aliphatic acids such as malic, malonic, or succinic acid). In some cases, the acyl radicals can also come from cinnamic acids (*p*-coumaric, caffeic, ferulic or synaptic) acting on glucose and rhamnose [Wang *et al*., 1997].

Several studies support the role of anthocyanins in suppressing free radicals and thereby in helping prevent and/or treat certain diseases such as atherosclerosis, diabetes, hypertension, inflammation, cancer, and also aging [Liu *et al*., 2012]. In addition, there is evidence that hybrid maize may contain high levels of nutraceutical compounds and could be considered an advantage for commercial production of tortillas and related food products with added value [Urias-Peraldi *et al.*, 2013]. Currently in the food industry, maize anthocyanins have been used as dyes of many food products [Salinas-Moreno *et al*., 2005b]. However, the stability and function of maize anthocyanins depends on the type of cooking method, pretreatment, and combinations with other ingredients [Bello-Pérez *et al*., 2016].

"Nixtamalization" is the main process of transformation of maize for consumption that was developed by the Mexicas before the Precolumbian era. The word derives from the Nahuatl – *nextli*, ashes, and *tamalli* – cooked maize dough. This technology is still widely used in the American continent to obtain a wide variety of food products. The "nixtamalization" process involves chemical, structural, and nutritional changes in the various constituents of the grain [Rojas-Molina *et al.*, 2007]. Because the nixtamalization process is a thermal-alkaline treatment that produces a decrease in anthocyanin content in pigmented maize, techniques such as fractional nixtamalization have been developed, which allows recovering approximately 58% of anthocyanins of pigmented maize probably because the endosperm and embryo layers are removed and nixtamalized separately. However, the nixtamalization by extrusion allows obtaining a greater quantity of anthocyanins in the blue maize (cyanidin 3-*O*-glucoside, equivalent to 620.9 mg/kg) than in those of red, yellow, and white colors. Additionally, different anthocyanin derivatives are formed or even increased during the process, which modifies the anthocyanin profile [Escalante-Aburto *et al.*, 2013a,b]. Besides, the nixtamalization processing of Mexican blue maize landraces has been found to increase the relative percentage of non-acylated anthocyanins (cyanidin-3-*O*-glucoside and peonidin-3-*O*-glucoside) and to decrease the relative percentage of acylated anthocyanins, such as cyanidin 3-*O*-(succinyl-glucoside) and cyanidine-3-*O*-(disuccinyl-glucoside), when compared to the raw kernels [Mora-Rochin *et al.*, 2016]. All this can be useful in the selection of varieties of pigmented maize and their use as food products with a nutraceutical potential; which makes it necessary to search for methods that would improve grain processing and enable retaining a higher concentration of phenolic compounds, and subsequently evaluating the potential benefits to health through daily consumption under a controlled trial.

BIOSYNTHESIS OF ANTHOCYANINS IN PIGMENTED MAIZE

The characteristic coloration of each variety of pigmented maize grain is contained into genes related to the biosynthetic pathway of anthocyanins. This also includes maize varieties with white and yellow grains. The regulation of this pathway is directed by three families of transcriptional factors: *r1*(*red1*)/*b1*(*booster1*) family that belongs to the class of transcription factors type bHLH (basic helix-loop-helix), *c1*(*colorless1*)/*pl1* (*purple plant1*)/*p1*(*pericarp color1*) family corresponding to the MYB-like transcription factors, and WD40 factor PAC1 (*pale aleurone color 1*) [Sharma *et al.*, 2011; Hu *et al.*, 2016]. The expression of each member of this family occurs in a tissue-specific manner or during plant development. The pigmentation patterns of maize depend to a large extent on the allelic combination of the MYB and bHLH loci [Shen & Petonilo, 2006]. For example, the dark blue color, typical of some grains of maize that develop in tropical climates, is generated by the allelic combination of the regulatory *pl1*/*B1* genes [Lago *et al.*, 2013, 2014]. This allelic combination can activate mainly the synthesis of cyanidin-3-*O*-glucoside in the pericarp and some tissues of the maize plant. Whereas *r1*/*c1* combination is required for the accumulation of pelargonidin-3-*O*-glucoside in the aleurone layer [Cone, 2007; Sharma *et al.*, 2011; Li *et al.*, 2019].

BIOAVAILABILITY OF ANTHOCYANINS

In animal and human studies, it has been reported that anthocyanins are rapidly absorbed as glycosides in the stomach and small intestine, mainly in the jejunum section so that they can reach many peripheric tissues and modulate metabolic changes in the organism [Talavéra *et al.*, 2004; Kay *et al.*, 2005]. On the other hand, despite the intake of anthocyanin-rich foods, the plasma concentration of these compounds remains very low [Manach *et al.*, 2005]. It is suggested that they have a low rate of bioavailability [Bitsch *et al.*, 2004; Felgines *et al.*, 2005; Tian *et al.*, 2006]. Some causes of low bioavailability are due to their chemical structure, excretion with feces, instability at neutral pH [Mullen *et al.*, 2006; Bub *et al.*, 2001], metabolism of the intestinal microbiota [Aura *et al.*, 2005], effect of the intestinal mucosa, and hepatic metabolism. Despite the low bioavailability, some beneficial effects may be caused by the metabolites such as protocatechuic acid (a major metabolite of anthocyanins in humans with antimicrobial and antioxidant effects) [Wang *et al.*, 2010].

The relative composition of the different molecular structures of the anthocyanins coexisting in an aqueous solution at any given time depends on the pH, temperature, concentration, and time. This is particularly important since anthocyanins are exposed to different pH conditions throughout the gastrointestinal tract, which affects their bioavailability and therefore their bioactivity and/or pharmacodynamics [McGhie & Walton, 2007]. Intake of foods rich in anthocyanins for a prolonged time favored the accumulation of these compounds in several tissues but not in the plasma and urine [Kalt *et al.*, 2008].

In addition, the type of food matrix significantly affected the absorption of anthocyanins [Yang *et al.*, 2011]. *In vitro* and *in vivo* studies have shown that the properties of aglycone, sugar, and the presence of acyl radicals can influence the absorption and metabolism of anthocyanins, being biotransformed mainly by conjugation with glucoronic acid and also by methylation reactions [de Ferrars *et al.*, 2014].

On other hand, the microbiota plays a special role in the metabolism of anthocyanins, which reach the colon in two ways. In the first one, they cannot be absorbed by the stomach and small intestine whereas in the second, the anthocyanins are excreted in the bile after absorption in the stomach and duodenum. Subsequently, after reaching the colon, the anthocyanins are hydrolyzed to liberate the glycosylated fraction of the aglycone and consequently degrade into phenolic acids, which are more susceptible to reabsorption [Kay, 2006].

In regard to their elimination, the number of anthocyanins excreted by urine is low and the mechanism of excretion depends on how and where anthocyanins are biotransformed. Studies with oral administration of purple maize in broilers showed that the anthocyanins did not affect the biochemical parameters and histopathology characteristics although they were presented in the skin, urine, and feces [Nabae *et al.*, 2008; Amnueysit *et al.*, 2010]. In most reports, the mechanism describing the elimination of anthocyanins through feces is limited because anthocyanins are converted in other compounds by microbiota action [Couteau *et al*., 2001]. For example, glucose-bound aglycones are less stable to the action of the β-glucosidase enzyme of the small intestine compared to galactose-binding aglycones. This instability upon intestinal enzymes action can probably be attributed to the action of the microbiota. It should be also noted that acylated anthocyanins with *p*-coumaric acid or a second sugar in their structure are resistant to degradation and render them susceptible to reabsorption in the small intestine [He *et al*., 2005]. Although the bioavailability studies of anthocyanins from other plants could be applied to pigmented maize, not enough *in vitro* and *in vivo* studies have been reported to provide pharmacokinetic data about their bioavailability.

EFFECT OF THE NUTRACEUTICAL POTENTIAL OF ANTHOCYANINS FROM PIGMENTED MAIZE ON OXIDATIVE STRESS

The antioxidant capacity of the extracts of pigmented maize is mainly due to the phenolic compounds that they contain. Of these, the aglycones have a superior activity to that of anthocyanins because of a greater number of sugars in the molecule [Serna-Saldivar *et al*., 2013]. The *in vitro* and *in vivo* studies of anthocyanins have shown a wide spectrum of their antioxidant effects. Among those, stands out the reduction of free radical absorption capacity, the stimulation of phase II enzymes for the detoxification, as well as the reduction of oxidative products formation in the DNA and lipids peroxidation. For example, sheep fed with diets based on anthocyanin-rich maize silage showed no significant change in the plasma total antioxidant status (TAS) in comparison to these administered the control diet [Hosoda *et al*., 2012]. However, it has been reported that the intake of anthocyanins *in vivo* increases plasma/serum antioxidant capacity (PAC) in golden Syrian hamsters and human subjects, respectively [Mazza *et al*., 2002; Auger *et al*., 2004].

Besides, anthocyanins have been found to offer the protection against mutagenesis caused by environmental and carcinogenic toxins and the modulation of specific signaling pathways for cell proliferation [Wang & Stoner, 2008]. Some of these effects are summarized in Table 1, highlighting results from extraction protocols (aqueous or hydroalcoholic). The general biological responses involve the upregulation of enzymes and the activation of mechanisms that protect cells and organisms from oxidant agents (radicals) and from oxidative stress damage (due to the redox imbalance), which is a common feature in the development of non-communicable diseases.

ANTIOXIDANT CAPACITY OF ANTHOCYANINS

The scientific interest in food anthocyanins has increased because they have been shown capable of preventing cellular oxidative stress [Prior, 2003]. The antioxidant activity of anthocyanins depends mainly on the aglycone molecule but may also be affected by covalently bound sugars altering solubility and membrane permeability. Anthocyanins have an adequate chemical structure to act as antioxidants, which allows them to donate hydrogens [Rice-Evans *et al*., 1997; Wang *et al.*, 1999] or electrons to free radicals or to trap them and move them in their aromatic structure [Ramírez-Tortosa *et al.*, 2001]. Optimal antioxidant activity is related to the presence of hydroxyl groups in the 3’ and 4’ positions of the B ring, which confer molecular stability to the formed radical [Kongpichitchoke *et al*., 2015]. While the free hydroxyl group in the 3 position of the C ring and the 5 position of the ring A, are electron donors [Rice-Evans *et al.*, 1996]. In the same sense, the antioxidant capacity of anthocyanins is due to their flat structure, which allows a greater delocalization of electrons through the rings [Dangles & Elhajji, 1994]. In the maize, it has been reported that maize cyanidin derivatives are more potent antioxidant agents than those of delphinidin. In addition, cyanidin has a greater antioxidant power if the glycosylated sugar is a rhamnose rather than glucose [Abdel-Aal *et al*., 2008].

Furthermore, glucosides identified in the rose variety of maize, like cyanidin, pelargonidin and peonidin, being cyanidin-3-(6-malonyl-glucoside) a malonic derivative cyanidin, are probably responsible for its grain color as well as its nutraceutical value [Barrientos-Ramírez *et al*., 2018]. Accordingly, in one study with waxy corn a significant ($r = 0.70$) correlation was reported between TAC (total anthocyanin content) and DPPH (2,2-diphenyl-1-picryl-hydrazyl-hydrate) assay and a moderate correlation between TPC (total phenolic content), DPPH, and TEAC (Trolox equivalent antioxidant capacity) ($r = 0.60$ and $r = 0.76$, respectively). These results confirm that the antioxidant capacity of anthocyanins depends largely on the type and amount of cyanidin glucosides and not only on the quantity of total polyphenols of the maize kernel [Duangpapeng *et al*., 2019]. On the other hand, in blue maize, the anthocyanin profile showed primarily acylated cyanidins and pro-anthocyanidins in raw and nixtamalized extracts. Results from the DPPH assay showed that the antioxidant capacity in the blue maize tortilla extract had slightly lower values (45.1 μM ET/g fresh weight) than raw blue maize extract (49.2 μM ET/g fresh weight). It can be explained because of the nixtamalization process in the tortilla’s manufacturing which modifies the type and content of anthocyanins in the grain. Nevertheless, both extracts reduced the TBARS production in homogenized rat brains (IC_{50} = 792 mg/mL and IC_{50} = 750 mg/mL, respectively). These findings suggest that the nixtamalization process improves the biological anthocyanin’s properties [Herrera-Sotero *et al*., 2017]. Finally, these results show also that the antioxidant activity of anthocyanins depends on the type, number, and glycosylation site in the molecule of anthocyanidins contained in the maize kernel as well as methodology used to evaluate the antioxidant capacity of these compounds [Zhao *et al.*, 2014].

OTHER BIOLOGICAL EFFECTS

Long-term ingestion of pigmented maize anthocyanins protected rat hearts against ischemia-reperfusion injury [Toufektsian *et al.*, 2008]. Besides, a study with mice reported that the anthocyanins from black rice, black soybean, and purple maize increased the fecal butyric acid content, as well as ameliorated diet-induced obesity by reducing both oxidative stress and inflammation [Wu *et al*., 2017]. Other properties of anthocyanins have been described as antimicrobial and antiproliferative activities [Cisowska *et al*., 2011]. These abilities been evaluated in extracts of anthocyanins from some types of native pigmented maize varieties in which the authors identified five anthocyanin compounds: cyanidin 3-*O*-glucoside, peonidin 3-*O*-glucoside, pelargonidin 3-*O*-glucoside, cyanidin 3-*O*-(6"-malonyl-glucoside), and cyanidin 3-*O*-(3", 6"-dimalonyl-glucoside), [Salinas-Moreno *et al.*, 2005a]. IC_{50} of Chinese purple maize extract was reported against pathological strains of *S. enteritidis* (5 mg/mL), *S. aureus* (10 mg/mL) and *C. albicans* (25 mg/mL) in a dose-dependent manner [Zhao *et al.*, 2009]. Moreover, another study determined the antimicrobial ability of anthocyanins isolated from the cob of purple maize. A significant antifungal activity of anthocyanins was observed in fluconazole-resistant strains of *C. glabrata*, *C. krusei*, and *C. parapsilosis* with MIC (Minimum Inhibitory Concentration) ranging from 0.625 to 2.5 mg/mL [Suket *et al*., 2014]. Furthermore, the antimicrobial activities of free and bound phenolic fractions from Peruvian purple maize were compatible with the survival of *L. helveticus* and *B. longum* (probiotic bacteria). Nonetheless, none of these fractions could inhibit the growth of pathogenic *H. pylori* [Galvez-Ranilla *et al*., 2017]. On the other hand, it has been reported that maize phenolic compounds could decrease starch digestibility by a specific anthocyanin-starch interaction [Hernández-Uribe *et al*., 2007; Camelo-Méndez *et al*., 2016], and also inhibit digestive enzymes involved in the absorption of carbohydrates. Moreover, it has been suggested that the use of pigmented maize flours might help in the formulation of gluten-free products with slowly digestible starches [Rocchetti *et al*., 2018].

Extracts of maize anthocyanins counteracted the proliferation of cancer cell lines. The antiproliferative capacity of anthocyanins was dose-dependent (IC_{50}=0.525 μg/mL) in HT-29 cells [Zhao *et al*., 2009]. Also, some authors [Urias-Lugo *et al*., 2015b] demonstrated that breast carcinoma (MCF7), hepatic (HepG2), colon carcinoma (Caco2 and HT29), and prostate carcinoma (PC3) cell lines treated with acidified extracts of anthocyanins of hybrid blue maize presented greater antiproliferative effect. The isomer cyanidin malonylglucoside I reduced the cell viability in Caco2, HepG2, MCF7, and PC3 cells, suggesting that acylated compounds inhibit the growth of cancer cells. Cyanidin 3-*O*-glucoside from purple maize suppressed Ras protein levels and inhibited 7,12-dimethylbenzo-anthracene [Guillen-Sanchez *et al.*, 2014], which induce mammary carcinogenesis in rats, suggesting that it may act as a potential chemotherapeutic agent [Fukamachi *et al*., 2008]. In addition, Navolokin *et al*. [2012] studied the effect of anthocyanin extracts from maize and observed reduced endogenous intoxication in rats with transplanted tumor suspension of liver cancer PC-1 cells.

Anthocyanins derived from the variety *Zea mays* var. *Kculli* (purple maize) improved insulin secretion of pancreatic beta cells in db/db mice compared to glimepiride (a sulfonylurea) but also protected pancreatic beta cells from apoptosis in cultures of the HIT-T15 cell line after treatment with the sulfonylurea, which increases the concentration of H_2O_2 [Hong *et al.*, 2013]. Interestingly, the mechanism of action of the anthocyanin extract of purple maize on insulin secretion differed from that of the GLP/GLP receptor/cAMP/PKA signal for insulin secretion. Extracts of purple maize (50 mg/kg purple maize extract) induced phosphorylation of AMP-activating protein kinase (AMPK), decreased expression of phosphoenolpyruvate carboxy kinase (PEPCK) and glucose-6-phosphatase (G6pase) in liver, and also increased the expression of the glucose transporter 4 (GLUT4) of skeletal muscle in C57BL/KsJ db/db mice. The authors suggested that the extracts exhibited antidiabetic activity through the protection of the pancreatic cells against ROS, increased the production and secretion of insulin, and activated the AMPK in the liver [Huang *et al.*, 2015]. In addition, other results indicate that the anthocyanin extract from the purple maize can be used in combination with the conventional treatment of type 2 diabetes and thus may improve the function of the pancreatic beta cells [Kang *et al.*, 2013]. Another study reported that purple maize anthocyanins, in particular cyanidin 3-*O*-glucoside and cyanidin-3-*O*-(6"-malonyl-glucoside), attenuated the proliferation of mesangial cells and protein accumulation of extracellular matrix "mesangium and glomerular basal membrane" (a diabetic glomerulosclerosis characteristic) in human mesangial cells stimulated by a high concentration of glucose through the inactivation of NF-κB translocation. This effect enhanced the signaling of transforming growth factor beta (TGF-β), as well as promoted the degradation of the extracellular matrix [Li *et al.*, 2012a]. Similarly, Roh *et al.* [2016] investigated the anti-inflammatory effects of *Zea mays* L. husk extracts and found a downregulation of the inducible nitric oxide synthase (iNOS) gene expression mediated by NF-κB and AP-1 signaling in RAW256.7 cells.

In a model of *in vitro* inflammation of mono- or co-culture of macrophage or/and adipocyte cells treated with extracts rich in anthocyanins from purple and red maize, Zhang *et al.* [2019] showed an inhibition of NF-κB and JNK pathways *via* regulation of IκBα and JNK phosphorylation. Besides, these extracts decreased pro-inflammatory cytokine production and lipolysis, and enhanced the glucose transporter 4 membrane (GLUT4) translocation [Zhang *et al*., 2019]. Additionally, the anthocyanin-rich purple maize extract increased free fatty acid receptor-1 (FFAR1) and glucokinase (GK) activity in Caco-2, INS-1E, and HepG2 cells culture [Luna-Vital & de Mejía, 2018].

On the other hand, when an anthocyanin complex (prepared with dried petals of blue butterfly pea (*C. ternatea* L.), dried rhizomes of turmeric (*C. longa*) and dried purple waxy corn cobs (*Z. mays* L. ceritina Kulesh) was given to hamsters infected with *Opisthorchis viverrini* (an experimental model of inflammation and periductal fibrosis in liver), Intuyod *et al.* [2014] found reduced number of inflammatory cells and periductal fibrosis in this model. Besides, in the treated animals there were reduced the formation of 8-oxodG (an oxidative DNA damage marker), NF-κB expression, iNOS synthesis, and oxidative stress. Contrarily, the gene expression of CAT, SOD, and GPx was increased in the treated experimental group [Intuyod *et al.*, 2014].

TABLE 1. Antioxidant effect of pigmented maize anthocyanins on *in vivo* and *in vitro* models.

Author, year	Type of trial	Anthocyanin, origin	Extract/Dose/Period of the treatment	Results (main biological effects)
[Tsuda *et al*., 2000]	Rats with hepatic ischemia-reperfusion injury	Cyanidin 3-*O*-β-d-glucoside (C3G), *Zea mays* L.	0.2 g/kg body weight for 14 days	↓oxidative stress
[Ramos-Escudero *et al*., 2012]	*In vitro* cellular antioxidant response in isolated mouse organs (kidney, liver, and brain)	Total polyphenols, flavonoids, flavonols, flavanols, and anthocyanins of purple corn (*Zea Mays* L.)	Purple corn extract 100 mg/mL with or without H_2O_2 (100μM)	↓lipid peroxidation, ↑endogenous antioxidant enzyme activities (CAT, TPX – total peroxidases, and SOD)
[Tsuda *et al*., 2003]	Male C57BL/6J mice with obesity, hyperglycemia and hyperinsulinemia	Cyanidin 3-glucoside-rich purple corn color (PCC)	2 g/kg diet for 12 weeks	↓insulin resistance, suppressed mRNA levels of enzymes involved in fatty acid and triacylglycerol synthesis and lowered the sterol regulatory element binding protein-1 mRNA level in white adipose tissue
[Thiraphatthanavong *et al*., 2014]	Male Wistar rats, experimental diabetic cataract model	Hydroalcoholic extract of purple waxy corn	2, 10, and 50 mg/mL at room temperature for 72 h in enucleated rat lenses	↓lens opacity with MDA level and aldose reductase (AR) activity, ↑GPX activity
[Kang *et al*., 2013]	Adult male db/db mice (C57BLKS/+Lepr^{db} Iar) and their age-matched non-diabetic db/m littermates (C57BLKS/J)	Anthocyanins-rich purple corn extract (*Zea mays* L.)	10 µg/kg of BW PCE (purple corn extract) daily for 8 weeks	Retarded the endothelial proliferation in db/db mouse kidneys by induction of vascular endothelium-cadherin, PECAM-1 and Ki-67 and diminished the mesangial and endothelial induction of angiopoietin (Angpt) proteins
	Human renal mesangial cells (HRMC)		1–20 µg/mL in HRMC conditioned media	↓endothelial expression of vascular endothelial growth factor (VEGF) and hypoxia inducible factor (HIF)-1α induced by HG-HRMC-CM (high glucose-exposed mesangial conditioned media)
[Mamani-Choquepata *et al*., 2013]	Aortic rings of hypertensive rats stimulated with norepinephrine	Total anthocyanins of corncob without seeds of purple corn (*Zea mays* L.) in three extracts: aqueous, hydro alcoholic, and hydro alcoholic acidified	Increasing doses (0.05, 0.1, 0.5 and 1 mg/L of total anthocyanins) of the different extracts	Vasodilator effect of the purple corn is dependent on the concentration of anthocyanins. Greater vasodilation was the hydro alcoholic extract prepared in ethanol at 70%
[Villasante *et al*., 2015]	Rainbow trout, *Oncorhynchus mykiss*	Purple corn extract; PCE (containing cyanidin-3-glucoside, pelargonidin-3-glucoside, and peonidin-3-glucoside)	5% of PCE in diet for 8 weeks	↓adiposity and ↑percentage of total n-3 and total n-6 polyunsaturated fatty acids (PUFA) in the fish body, ↑expression of GPx1 in erythrocytes and ↓TAC in plasma
[Wattanathorn *et al*., 2015]	Streptozotocin diabetic Male Wistar rats with induction of diabetic neuropathy by chronic constriction	Extract of purple waxy corn (*Zea mays* L.) and ginger *Zingiber officinale* Roscoe (PWCG)	Doses of 100, 200, and 300 mg/kg of BW	↑SOD and GPx activity which in turn decreased oxidative stress status in the lesion nerve
[Hosoda *et al*., 2012]	Suffolk wethers fed a diet supplemented with purple corn pigment	Purple anthocyanin-rich corns (*Zea mays* L.) pigment in the diet	0.5% diet on dry matter basis for 14 days	Enhancement in plasma SOD activity, ↓oxidative stress
[Zhang *et al*., 2014]	Wistar rat fluorosis model	Maize purple plant pigment (MPPP) contains 45.96% cyaniding-3-glucoside and 12.99% 3',4'-dihydroxy anthocyanin-3-glucoside	Water containing 5 g/kg MPPP in the diet with 100 ppm fluoride	↓elevation of MDA levels in blood and liver, Bcl-2 protein expression, ↑Bax protein expression, SOD and GSH-Px activities in kidney and GSH level in liver and kidney
[Arroyo *et al*., 2008]	Male Holtzmann rats with hypertension by (Nitro-L-arginine methyl ester) L-NAME	Atomized hydro alcoholic extract of *Zea mays* L. (Andean purple corn)	Orally once a day for 25 days 500 and 1000 mg/kg of BW	↓in blood pressure and MDA

TABLE 1. Continued...

Author, year	Type of trial	Anthocyanin, origin	Extract/Dose/Period of the treatment	Results (main biological effects)
[Moreno-Loaiza & Paz-Aliaga, 2010]	Male Swiss rat thoracic aortic rings	Extract by maceration of Andean purple corn cobs in 70% ethanol	Doses of the extract: 0.1, 0.5, and 1.0 mg/mL with L-NG-Nitroarginine methyl ester (L-NAME) to verify that the vasodilation depends on nitric oxide synthetase (NOs)	↓in maximum contraction. The vasodilation was inhibited by prior incubation with L-NAME
[Zhang *et al*., 2010]	Male Kunming mice with a cholesterol-rich diet comprising 1.0% cholesterol, 10.0% lard, 0.5% bile salt, and 88.5% commercial chow	Pigments extracted from black glutinous corncob (BGC)	Three cholesterol-rich diet groups were given 200, 500, and 800 mg/kg PBGC for 4 weeks	↓plasma total cholesterol (TC), low-density lipoprotein cholesterol (LDL-c), and triglyceride (TG). ↓lipid peroxidation and atherogenic index
[Guzman-Geronimo *et al*., 2017]	Male Wistar rat with high-sucrose (30%) diet-induced metabolic syndrome	Blue maize extract (*Zea mays* L.)	Total polyphenols and anthocyanins of 9.97 and 2.92 mg/kg of body weight for 4 weeks	Enhanced HDL-c (High-density lipoprotein cholesterol) and ↓systolic blood pressure, serum triglycerides, total cholesterol, and epididymal adipose tissue weight
[Mex-Alvarez *et al*., 2016]	Male albino mouse (*Mus musculus*) with high fat diet	Purple and red corn extracts (*Zea mays* L.)	Subcutaneous injection of maize extract at dose of 250 mg/kg for 60 days	↓total cholesterol, triglycerides, atherogenic index, and ↑HDL-c
[Li *et al*., 2012b]	Adult male db/db mice (C57BLKS/+Lepr^{db} Iar) and their age-matched non-diabetic db/m littermates (C57BLKS/J)	Anthocyanins-rich polyphenolic extracts of purple corn (PCE) (*Zea mays* L.)	10 mg/kg of BW PCE daily for 8 weeks	↓plasma glucose level, albuminuria, protein expression of nephrin and podocin were repressed, ↓collagen fiber accumulation in kidney glomeruli and CTGF expression *via* retarding TGF-β signaling
	Human renal mesangial cells (HRMC)	Anthocyanins-rich purple corn butanol fraction (PCB) (*Zea mays* L.)	PCB supplemented at concentration of 1–20 µg/mL for 3 days under the condition of high glucose and mannitol	↓production of fibrosis biomarkers of collagen IV and CTGF, promotes the activation via eliciting Tyk2-STAT signaling pathway, ↓expression of PDGF
[Foy Valencia, 2010]	Albino rats with high fat diet-induced hyperlipidemia	Anthocyanin extracts from the crown of *Zea mays L*. Starchy (purple maize)	5% powder and extract aqueous (*Chicha morada*) to 20% for 15 days	↓triglycerides, total cholesterol and LDL-c
[Toufektsian *et al*., 2008]	Male Wistar rats with *ex vivo* and *in vivo* models of ischemia-reperfusion injury	Maize lines nongenetically modified: ACR, Δ-D902, and F1	Maize seed powder replacing 20% from standard pellet for 8 weeks	↑ glutathione levels and infarct size were reduced
[Limsitthichaikoon *et al*., 2018]	Mucosal epithelium of porcine esophagus, male Wistar rats, and patients who were 18–25 years old	Purple waxy corn cobs (*Zea mays* L. var. *ceratina Kulesh*) and blue petals (*Clitoria ternatea* Linn)	Anthocyanin complex (AC), combined *Zea mays* and *Clitoria ternatea* extracts in a mucoadhesive gel for 7 days	Enhanced anthocyanin permeation *in vitro*. In humans and rats, mucoadhesive gel reduced erythema and sizes of oral wounds
[Flores Cortez *et al*., 2018]	Holtzman rats with experimental arthritis with pristane (PIA)	*Zea mays* L., purple variety	100 mg/kg and 1000 mg/kg extracts for 21 days	↓the inflammatory process and radiological modifications of PIA-induced arthritis
[Tian *et al*., 2019]	Lactating Saanen dairy goats	Anthocyanin-rich purple corn (*Zea mays* L.)	Dietary anthocyanin-rich 50% (DM) of purple corn silage for 8 weeks	↑ content of milk lactose, SOD level and TAC in plasma and milk
[Revilla *et al*., 2018]	Corn borer *S. nonagrioides* larvae with oxidative stress induced (H_2O_2)	Black maize kernels	Artificial diet with white and black maize flour for 28 weeks	Antioxidant activity has insecticide effect on young larvae and a positive effect on grown larvae

↓, Reduce;↑, Increase; SOD, superoxide dismutase; GPx, Glutathione peroxidase; ABTS, 2,2’-azino-bis (3-ethylbenzothiazoline-6-sulphonic acid); DPPH, 2,2-diphenyl-1-picrylhydrazyl; TC, total cholesterol; PBGC, pigment from black glutinous corncob; CTGF, connective tissue growth factor; PDGF, platelet-derived growth factor; BW, body weight; Bax, bcl-2-like protein 4; MDA, malondialdehyde; TAC, total antioxidant capacity; DM, dry mass.

CONCLUSION

Anthocyanins represent a promising class of antioxidants found naturally in plants that enhance their stress resistance and nutritional value through diverse biological mechanisms. Several studies *in vitro* and *in vivo* corroborate the antioxidant and biological effect of maize anthocyanins. The aging of the population and the exponential increase of governmental health expenses make it necessary to implement natural and cost-effective alternatives for the prevention and management of diseases caused by redox disequilibrium and cell aging. Maize is a staple crop widely accepted as food ingredient; therefore, it could be useful as a functional additive to prevent aging, obesity, and metabolic syndrome. Its permanent consumption could also reduce the increase of cases with chronic degenerative diseases such as diabetes, cancer, and cardiovascular diseases. Antioxidant efficacy of pigmented maize anthocyanins has been less documented in both *in vivo* and *in vitro* studies possibly due to the scarce knowledge of their bioavailability and pharmacokinetics. Besides, there is a wide diversity of anthocyanins that can be found in plants. This represents a methodological problem for reductionistic experimental approaches, since it requires the previous analysis of extracts for the exact chemical identification and characterization of the anthocyanins/polyphenols of each sample batch. There are equipment/infrastructure limitations for the determination of molecular structures and the antioxidant *in vitro* activity as well. Uniformity in the elaboration of the extracts, methodologies of quantification, and report of new results is also needed. Another important circumstance to be considered is the food manufacture process that simultaneously alters a large number of molecules. The process and secondary ingredients that best enhance the nutraceutical potential of colored maize are yet unknown, but we might learn the empirical lessons of centuries of the Mesoamerican culinary culture mixing for example, roasted maize, chili, chia seeds, and cacao beans. In conclusion, pigmented maize has properties that need to be exploited and thoroughly investigated. We expect that this review highlights the importance of anthocyanins from pigmented maize as well as its biological effects in order to promote further research in this field and increase the knowledge of the beneficial properties it offers to the health through its consumption.

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CONFLICT OF INTERESTS

Authors declare no conflict of interest.

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