Anthocyanins: Possible role as Multitarget therapeutic agents for prevention and therapy of chronic diseases

Swathi Putta[1,+], Nagendra Sastry Yarla[2,#], Ilaria Peluso[3,+], Dinesh Kumar Tiwari[4,+], GorlaV.Reddy[4], , Priyanka Voori Giri[4], Naresh Kumar[4], Ramarao Malla[2], Veera Brahma Chari[5], Rama Sekhara Reddy D[5], Ramesh Bade[2], Mastan Mannarapu[6], George Barretto[7], Da-Yong Lu[8], Vadim V. Tarasov[9], Vladimir N. Chubarev[9], Frederico Fávaro Ribeiro[10] , Luciana Scotti*[11], Marcus T. Scotti[11], M.A.Kamal[12], Gjumrakch Aliev[13,$], Chinthalapally V. Rao[14], Anupam Bishayee[15,!]

[1]*Department of Pharmaceutical Sciences, University College of Pharmaceutical Sciences, Andhra University, Visakhapatnam-530003, A.P., India*

[2] *Institute of Science, GITAM University, Visakhapatnam-530045, A .P., India*

[3]*Centre for Food and Nutrition, Council for Agricultural Research and Economics, Rome, Italy*

[4]*Department of Animal Biology, School of Life Sciences, University of Hyderabad, Hyderabad- 500 046, India*

[5] *Krishna University, Machilipatnam, Krishna District, A.P., India*

[6]*Department of Biotechnology, Dravidian University Kuppam – 517 426. Chaittoor dist., A.P., India*

[7]*Departamento de Nutrición y Bioquímica, Facultad de Ciencias, Pontificia Universidad Javeriana, Bogotá D.C., Colombia.*

[8]*School of Life Sciences, Shanghai University, Shanghai200444, China*

[9] *I.M. Sechenov First Moscow State Medical University, Moscow, Russia*

[10] *Federal University of Pernambuco, Brazil*

[11]*Federal University of Paraiba, Campus I, 58051-970, João Pessoa, PB, Brazil*

[12]*King Abdulaziz University, P. O. Box 80216, Jeddah 21589, Saudi Arabia*

[13]*"GALLY" International Biomedical Research Consulting LLC, San Antonio, TX 78229, USA*

[14] *Center for Cancer Prevention and Drug Development Medical Oncology/Stephenson Cancer Center*

975 NE 10th Street, BRC 1203, OUHSC, Oklahoma City, OK 73104, USA

[16]*Department of Pharmaceutical Sciences, College of Pharmacy, Larkin Health Sciences Institute, Miami, FL 33169, USA*

[+]*Equal contribution*

*Corresponding author:

L. Scotti, Health Sciences Center, Federal University of Paraíba, Campus I58051-970, João Pessoa, PB, Brazil

Fax 55-83-3291-1528 E-mail: luciana.scotti@gmail.com

#Co-corresponding author

$ Co-corresponding author

! Co-corresponding author

Abstract:

Anthocyanins belong to the flavonoids class of polyphenols and they are water soluble dark colored natural pigments from fruits and vegetables. Dietary consumption of anthocyanins is high compared to other flavonoids, owing to their wide distribution in plant materials. Anthocyanins are the active component in several herbal folk medicines due to its multifaceted medicinal properties. *Method:* This review discusses the anthocyanins as multitarget drugs, which posses antioxidant, antidiabetic, antihyperlipidemic, anti inflammatory, anticarcinogenic, antiulcer, cardioprotective, hepatoprotective, neuroprotective role. *Results:* Several chemotherapeutic activities were observed *in vitro* and *in vivo* experimentation on cell-line studies, animal models, and clinical trials. This property of anthocyanins could be promising in providing health benefits against chronic diseases.

Key words: Anthocyanins, Antioxidant, Anti-inflammatory, Anticarcinogenic, Cardioprotective, Hepatoprotective, Neuroprotective.

Introduction:

Vegetable, fruit, and cereal consumption in the diet has been promoted because of its reported benefit to human health, especially in the prevention of degenerative diseases. Plant tissues, especially fruits and vegetables, contain many different chemical compounds with different biological and pharmacological capacities and properties. Growing interest in the role of antioxidants in human health has triggered with intense of phytochemical research and pharmacology.

Interests in dietary polyphenols, including anthocyanins, drastically intensified after the recognition of their potential health benefits (1)

Anthocyanin rich foods are becoming more popular. Epidemiologic studies suggest that the consumption of anthocyanins lowers the risk of cardiovascular disease, diabetes, cognitive function disorders and cancer, due to their antioxidant anti-inflammatory properties (2,3)

The aim of the present work was to review the current literature of anthocyanins and particularly their health promoting properties such as chemotherapeutic, cardioprotective, Neuroprotective, hepatoprotective and antidiabetic properties by *in vitro*, *in vivo* and clinical studies as related to their multiple proposed mechanisms of action.

Chemistry and biosynthesis of anthocyanins:

The chemical structure of Anthocyanin is based on 2-phenyl-1-benzopyrilium, also called flavylium (4). The molecule contains a positive charge which makes it to absorb light and thus contain colour which spectrum depends on degree of methylation and hydroxylation of 3 rings and their surrounding

environment such as variations pH. Anthocyanidins are sugar free molecules which undergo hydroxylation and/or methoxylation and give rise to 6 common anthocyanin found in vegetables and fruits (Figure 1). Like other flavonoids anthocyanins also present in plants in the form of glycosides. Sugar molecules mostly attached to C3, C3', C5, C5' and C7 position of parental ring (5). Glucose, arabinose, galactose , Xylose, rhamnose and fruction are common sugar linked to these natural pigment while glucose is most common (6) .

Figure1: Basic structure of anthocyanins

The biosynthesis of anthocyanin takes place by cell membrane associated enzymes in a sequential phenomenon. Acetic acid and Phenylalanin are two building blocks in the pigment biosynthetic pathways accomplished by a chain of enzymes by various chemical process in two different pathways. In Shikimic acid pathways, acetic acid synthesized by photosynthesis catalysed into phenylalanine while in another pathway, it catalysed into malonyl CoA (7). After series of enzymatic and chemical process both pathways end up with a common intermediate pigment- Chalcones. Chalconeisomerase catalyse chalcones into Naringenin which further oxidized into Anthocyanins (8) .

Natural sources of anthocyanins:

The word anthocyanin is derived from two Greek words, anthos and kyanos, meaning flower and dark blue, respectively (9). Anthocyanins are members of the flavonoids group of phytochemicals, a group predominant in teas, honey, wines, fruits, vegetables, nuts, olive oil, cocoa, and cereals. Although most

commonly accumulated in flowers and fruits, they are also present in leaves, stems, and storage organs (9) .

Anthocyanins are mostly present in higher plant but also reported in few plants such as fens and mosses. These pigments are present in all fruits and flower but the major source are strawberries, plums, pomegranate, cherries, red cabbage, blueberries, purple grapes, black currants, black beans, kidney beans, raspberries, and banana (10,11) .

There are approximately 17 anthocyanidins found in nature, only 6 of which are widely distributed: cyanidin, delphinidin, petunidin, peonidin, pelargonidin and malvidin (12) .

Figure 1: Anthocyanins

Anthocyanins have been known to confer different colors (bright red, blue and purple) to various fruits, vegetables and as well as to the autumn foliage of deciduous trees owing to conjugated bonds in their structures, which absorbe light at about 500nm (13).

Food sources of anthocyanins (cyanidin-3-glucoside, cyanidin-3-rutinoside, cyanidin-3-rhamnoside, cyanidin-3-xyloglucoside, delphinidine -3-glucoside and delphinidine -3- rutinoside) are berries (14,15), acerola cherry (16), litchi (17), plums (18) and pomegranate (19). The later contains also pelargonidin-3-glucoside, pelargonidin-3,5-glucoside (19). Other foods containing anthocyanins are black carrots and purple or black rice (20). Anthocyanins in food are generally ingested as constituents of composite mixtures of flavonoid components. It is estimated that routine intake of anthocyanins is from 500 mg to

1 g, but it could be several g/d if an individual is consuming flavonoid rich supplements (21).

The dietary intake of anthocyanins varies among gender and different age groups. The dietary reference intake (DRIs) of anthocyanins and other flavonoids is not available in Europe, USA or Canada (22). In USA, based on USDA Nutrient Database of flavonoids and NHANES, the intake of anthocyanins has been estimated to 11.6 $\pm$ 1.1mg/d (individual $\geq$ 20 years). However their dietary intake in women has more (12.6$\pm$ 1.3mg/d) than man (10.5$\pm$ 0.8mg/d (10, 22).

On the contrary, in the European Prospective Investigation into Cancer and Nutrition (EPIC) study, the reported total anthocyanidin mean intake ranged from 19.83 mg/d to 64.88 mg/d in men, whereas for women the range was 18.73 mg/d to 44.08 mg/d (23).

Bioavailability of Anthocyanins:

After dietary intake, anthocyanins undergo rearrangement reaction in presence of different pH and temperature. Human physiological temperature is suitable for rearrangement of anthocyanins into different isomers (24). In acidic environment of stomach, anthocyanins are present in flavylium form (positive charged) while all other flavonoids present in neutral form ((24).

After consumption of anthocyanins is rapidly absorbed, appearing in the bloodstream within 6 to 20 min and maximum blood levels were reached after 15 to 60 min (25,26). The absorption of anthocyanins by passive diffusion was limited due to their higher water soluble nature and large molecular structure (27). The absorption of anthocyanins requires active transport mechanism across the

intestine or need to be hydrolyzed by β-glucosidase, β-glucuronidase, and α-rhamnosidase in small intestine (28). But in contrast anthocyanidins, aglycones from anthocyanins are transported across the intestinal epithelium by passive diffusion due to their hydrophobic nature (29). ANTS are rapidly taken up from blood into tissues and reached T1/2 at 0.36 min and readily cross the blood brain barrier and blood retinal barrier (30). Most anthocyanins have been detected as intact glycosides which rapidly reach the circulatory system within 6 to 20 min and to the urine, so that they do not appear to undergo extensive metabolism both in animals and in humans (31,32). After reaching to the blood stream, ANTs are subjected to phase II metabolism and later detoxified by phase II enzymes located in liver and also in the intestine epithelium and kidneys (33). The anthocyanins undergo biotransformation by methylation, glucuronidation, and/or sulfation following ingestion, (34). The clearance of anthocyanins was found to be rapid and after 6 h of ingestion in humans (35). Intact glycosylated forms and some methylated forms, but no aglycones or glucuronide forms, were detected in urine (36,37) and metabolized forms are rapidly excreted into bile and in urine (38). The plasma concentrations of anthocyanins have been found to be low and efficient passage is vital for their availability to tissues (39). Anthocyanins can cross the blood brain barrier. The bioavailability of anthocyanins depends significantly on their chemical structure, being influenced by the nature of the sugar moiety and also by the structure of the anthocyanins aglycone.

A work performed on healthy volunteers showed that after intake of black raspberry in the oral cavity, anthocyanins were detected in their hydrolysed form

aglycone and glucuronidated anthocyanin conjugated form. The hydrolysis of anthocyanins is resultant catalysis of b-glycosidase might be either from epithelial cells or bacterial origin (40). The local effects of such transformation of anthocyanins is difficult of analyse because of very less residence time. The anthocyanins are generally detected in plasm in the native form might be because of their absorption through gastric membrane. The stomach showed only parental anthocyanins while the other organs such as jejunum, kidney and liver showed parental, conjugated as well as methylated anthocyanins (41). In small intestine, anthocyanins inters into more basic pH where carbinol pseudo base become more predominate and anthocyanin glycosides efficiently and rapidly get absorbed (42,43). After that anthocyanins rapidly metabolized and appear in circulation or excreted out from body either in intact and/or their metabolized forms such as methylated, sulphated or glucuronidated forms.

Gut microorganism has been shown vital role in carbohydrate metabolisms, vitamins B12 synthesis and several other functions and thus considered as microbial organ. In anthocyanins metabolism, apart from conjugation, addition of sulphate and methylation, it also includes anthocyanins heterocycle cleavage and breakage of glycoside linkages (44-46). Gut microorganisms play vital role in anthocyanins metabolism by expressing and releasing the enzymes such as β-D-glucosidases, β-D-glucuronidases and α-L-rhamnosidases which are needed to release glucuronidate and glycoside from anthocyanins derivatives.

Oral administration of anthocyanin-rich fruits, extracts or pure compounds has proved to be effective in preventing or suppressing diseased states (47). A recent study revealed that feeding mice with a diet supplemented with transgenic tomatoes rich in anthocyanins prolonged life span (48).

Molecular targets of Anthocyanins:

Oxidative stress is a state of imbalance of reactive oxygen species (ROS) and reactive nitrogen species (RNS) generation and their detoxifying system. The antioxidant properties of anthocyanins are due to their chemical structure which contains three rings (two aromatic rings and one non-aromatic ring) and one free electron for delocalization. The presence of conjugated groups, position and degree of derivatization by glycosylation, and number and position of hydroxyl groups further enhance its anti-oxidant properties (49). The antioxidant property of anthocyanins can be mediated by several mechanisms such as inhibiting capturing free radicals and/or anions, chelating metal ions but also targeting ROS generated pathways, such as xanthine oxidase and arachidonic acid pathways. Anthocyanins directly remove reactive oxygen molecules such as singlet oxygen, H_2O_2, superoxide, hydroxyl and peroxyl molecules (50,51). The anthocyanins molecules chelate metal ions and forms stable anthocyanins metal complex either by presence of 3', 4' dihydeoxy group and/or presence of catechol group.

On the other hand anthocyanins induce the ---------- pathway. Nrf-2 is a transcription factor associated to regulation of antioxidant and protective defence including γ-glutamylcysteine synthase (GCS), glucose 6-phosphate dehydrogenase (G-6PDH), hemeoxygenase-1(HO-1), quinoneoxidoreductas-

1(NQO-1), glutathione S-transferase (GST) and glutamate cysteine ligase (GCL). A cytosolic protein, Keap-1 form complex with Nrf-2 thus inhibits its translocation into nucleus. In nucleus, Nrf-2 binds to anti-oxidant response element (ARE) and thus induce the expression of anti-oxidant enzymes and other targeted genes (52-54). In several studied, anthocyanins and their derivatives has shown increase level of Nrf-2 and HO-1 (55,56). Therefore, the anti-oxidant activities of anthocyanins could be due to the combined effects on ROS and on the Nrf-2 translocation and activation of their targeted genes.

The anthocyanins also show anti-inflammatory and anti-cancer properties by targeting phospholipase A_2 (PLA2) pathways at different sites. The derivatives of anthocyanins are more potent inhibitors of PLA_2 (57). The $^{\bullet}OH$ radicle of anthocyanins inhibit the enzymatic activity of cyclooxygenase-1 (COX1) and cyclooxygenase-2 (COX2) pathways (58-62). The anthocyanins also inhibits the lipoxygenase pathways due to both the scavenging properties and to the binding to the enzyme at hydrophobic site and/or interference with the lipoxygenase substrates (63).

Anthocyanins has also shown to inhibit the translocation of transcription factor Nf-κB by reducing the degradation of IκB (64,65). Anthocyanins has also shown the inhibition of TNF-α and thus block the expression of tnf alpha induced adhesion molecules such as ICAM, MCP and VCAM (64).

In vitro and animal studies:

Anti-carcinogenic activity of Anthocyanins:

Epidemiological studies suggest a reduced risk of cancer at various sites with regular intake of a diet rich in fruits and vegetables (66). Cancer therapy predominantly involves cytotoxic chemotherapeutic agents, is often accompanied by several adverse effects. New strategy for cancer therapy is by targeting apoptosis or angiogenesis as therapeutic approaches. Anthocyanins display a wide range of biological activities, including antioxidant, anti-inflammatory, anti-cell proliferative, anti-angiogenic, and anti-invasive activities, as well as the induction of apoptosis and chemopreventive effects (67) (Table 1). Anthocyanins inhibit cancer progress and metastasis through cell signal cancer (68), lung cancer (69), colon cancer (70), prostate cancer (71) and esophageal cancer (72) Anthocyanins from Purple fleshed sweet potato P40 cultivar have been reported to block the cell cycle at G1 phase in human colon SW480 cancer cells (73). Human epidermal growth factor receptor 2 (HER2) overexpression is responsible for 30% of breast cancer cases (74). RAS/RAF/MAPK pathway transduces HER2 signaling and thus plays crucial role in the development of breast cancer. In several studies, it has been shown that anthocyanins inhibit metastasis in breast cancer cells by targeting the RAS/RAF/MAPK pathway. Several i*n vivo* studies also claim for anthoccynain to be a potential cancer preventing agent. Anthocyanin rich grape extract has been demonstrated to suppress adenoma development in the Apcmin mouse by decreasing adenoma cell proliferation and down regulation of PI3 pathway componene Akt. Which reinforces cell proliferation (75). In another

study anthocyanins in black raspberries have been found to arrest esophageal tumors in N-nitrosomethylbenzylamine (NMBA)-induced tumors in the F344 rats (76).

Antidiabetic activity of Anthocyanins:

Fruit and vegetables may reduce the risk of obesity and decrease the incidence of type-2 diabetes associated with insulin resistance. Anthocyanins reported to have insulin secretion activity. Cyanidine 3-glucoside-rich purple corn anthocyanins have been suggested to ameliorate the high fat diet-induced obesity and hyperglycemia in mice. It is likely that the delphinidin-3-O-glucoside is contributing significantly less to the hypoglycemic activity of the anthocyanin-enriched extract since it is not active when delivered as a pure compound (77). Cyanidine 3-glucoside has also been given an account to improve hyperglycemia and insulin sensitivity due to downregulation of retinol binding protein 4 (RBP4) expressions in diabetic mouse. Dietary rich anthocyanin bilberry extract reported to improve hyperglycemia and insulin sensitivity via activation of AMP-activated protein kinase in diabetic mice. Investigation on cell lines and animal models and clinical trials in humans propose that ANTs do display antidiabetic properties (Table 2). Available data recommend that ANTs may lower blood glucose by improving insulin resistance, protecting β cells, increasing excretion of insulin and decreasing digestion of sugars in the small intestine (78), however, it is still mysterious whether anthocyanins induce apoptotic cell death and how insulin secretion is activated.

Cardio protective activity of Anthocyanins:

At present, high cholesterol rich foods, obesity, hypertension, physical inactivity have exacerbated the risk of cardiovascular diseases several fold. It is estimated that 17.1 million people died from cardiovascular diseases (CVDs) in 2004, representing 29% of all global deaths. It has been hypothesized that by 2030, almost 23.6 million people will die from CVDs, mainly from heart disease and stroke (79). Consumption of fruits and vegetables has been associated with a decreased risk of CVD due to the presence of large variety of bioactive compounds present in it (80). Researchers showed considerable interest on natural bioactive components due to their contribution to maintaining or improving cardiovascular health as an alternative to pharmaceutical medications. Bilberries (*Vaccinium myrtillus L.*) are one of the richest dietary sources of anthocyanins, which are also considered the most pharmacologically active constituents. Anthocyanins have been reported to be cardioprotective at low concentrations, but cardiotoxic at high concentrations (81). In general it is considered that the cardioprotective activity of anthocyanins is owed to their antioxidant properties. Cardiovascular disease development is due to platelet aggregation, hypertension, hyperlipidemia, and vascular endothelium dysfunction, significant reduction of ischemia and inflammatory condition, DNA cleavage, estrogenic activity, enzyme inhibition, increased cytokine production, capillary permeability and fragility, and membrane strengthening (82). Anthocyanins may regulate different signaling pathways involved in the development of CVD (Table 3) (83, 84)

Hepatoprotective activity of Anthocyanins:

The liver plays vital functions in the maintenance, performance and regulating homeostasis of the body. It is involved with many biochemical pathways to growth, fight against disease, nutrient storage and supply. In recent years, chemical liver injury incidents augmented significantly in Asian countries and lack in the proper balance of the redox system was supposed to be the main source. A study exploiting chronic liver injury model has demonstrated that anthocyanins could be used as a potential oral hepatoprotective agent against chemical induced liver injury from food plant. ACNs acts by reducing hepatic lipid accumulation, inhibition of lipogenesis by reducing SERBp1c, promotion of lipolysis by induction of PPARα activity and reduction of oxidative stress (Table 4). Most of the hepatotoxic chemicals damage hepatic cells by producing ROS/RNS. Several anthocyanins have been studied for their role in the modulation of lipid metabolism and fat deposition in different tissues, including the liver (85). An anthocyanin fraction (AF) obtained from purple-fleshed sweet potato has shown hepatoprotective activity in acetaminophen-induced liver damage in mice by preventing hepatic glutathione (GSH) depletion by paraceptamol (APAP) and hepatic GSH levels (86). Anthocyanins have been found to decrease the levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) in carbon tetrachloride (CCl_4) induced liver injury in mice (87). Elevated levels of COX-2 and iNOS are involved in several physiological aberrations including inflammation. Nrf2 is a transcription factor that regulates the expression of antioxidant proteins that protect against oxidative damage triggered by injury and inflammation. Several drugs that stimulate Nrf2

pathway have been studied for treatment of oxidative-stress-associated diseases. Anthocyanins from purple sweet potato have been shown to reduce dimethylnitrosamine-induced liver injury in rats by inducing nuclear erythroid 2-related factor 2 (Nrf2)-mediated antioxidant enzymes and reducing COX-2 and iNOS expression (88).

Neuroprotective activity of Anthocyanins:

Anthocyanin rich fruit diets may also have beneficial effects in combating cognitive decline and neurodegeneration associated with ageing. Any aberrations in the dopaminergic neurons results into detrimental neurodegenerative disorders including Parkinson's disease owing to their pivotal roles in executive functions such as motor control, motivation, arousal, reinforcement, and reward, as well as lower-level functions including lactation, sexual gratification, and nausea. Anthocyanin and proanthocyanidin-rich extracts have been shown to rescue dopaminergic cell death elicited by rotenone, thus shows that anthocyanin- and proanthocyanidin-rich herbal extracts could alleviate neurodegeneration in Parkinson's disease via augmentation of mitochondrial function (Table 5). Oxidative stress is believed to play a major role in ethanol induced neurotoxicity. Targeting ethanol-induced oxidative stress using natural antioxidants is a striking approach. In a study (89), it has been demonstrated that anthocyanins could potentially alleviate ethanol induced neural toxicity that could be an imperative footstep for developing preventive/therapeutic strategies. These physiological functions of anthocyanins are largely based on their anti-oxidant function as a free radical scavenger but recent studies have revealed that anthocyanins regulate the

expression of several genes related to atherosclerosis, and induce apoptosis or autophagy (90). These observations suggest that anthocyanins may play a role in the in reversing age-related neuronal and behavioral changes, modulation of signal pathways involved in cell death and inflammation upon exposure to oxidative stress.

Human evidence:

A search for literature on human evidence was conducted on electronic databases (Pubmed, Google Scholar and research gate) with the search terms: anthocyanins AND [subjects OR patients]. In addition to the well-known beneficial effects on eyes' healthy (91-94), it has been suggestd a role of anthocyanins in the prevention and management of some multifactorial diseases (95-99). Table 6 resumes the major publications reporting potential benefit in cancer, cognitive decline, hepatic and cardiovascular diseases (CVD) risk factors, such as hyperglycemia, hypertension and dyslipidaemia, including 49 intervention studies (8 on cancer, 5 on cognitive function, 23 on CVD risk markers on patients, 10 on CVD risk markers on healthy subjects).

It has been reported that higher intakes of anthocyanins, anthocyanidins or anthocyanin-rich foods were significantly associated with a lower risk of type 2 diabetes (100), myocardial infarction (101) and esophageal cancer (102), whereas no association was found with CVD (103) and ovarian cancer risk (104) (Table 6).

Despite the first study that investigated the effect of anthocyanins on cancer reported no significant effects (105), anthocyanins decreased radiation dermatitis during therapy for breast malignancy (106) and a supplement containing

resveratrol, lycopene, vitamin C and anthocyanins has been suggested for counteracting the adverse effects of radiation with or without the adjuvant chemotherapy (107) (Table 6). Besides, improvement of cancer progression has been reported after the consumption of strawberries (108), black raspberry beverage (109), bilberry extract (mirtocyan) (110) and black raspberries powder (111) or gel (111) (Table 6). In particular, in colorectal cancer patients, after mirtocyan (an anthocyanin-rich standardized bilberry extract) daily for 7 days before surgery, anthocyanin concentrations in plasma and urine were detected and reached about 179 ng/gr in tumor tissue at the highest dose, inducing a decrease of 7% in tumor tissue proliferation (110). Concerning the mechanisms, strawberries reduced the histologic grade of dysplastic premalignant lesions of the esophagus, by inhibiting the iNOS, COX-2 and NFκB pathways (108). On the other hand, the cognitive benefit after blackcurrant extract supplementation has been associated to the inhibition of monoamine oxidase-B and monoamine oxidase-A (112). Cognitive improvements have been observed also in children after consumption of a blueberry drink (113) and in elderlies after concord grape (114), blueberry (115) or cherry (116) juices' intake (Table 6). In some studies, cognitive improvement was observed concomitantly with anti-hypertensive (116) or glucose-lowering (115) effects.

In this context, many intervention studies investigated the effects of anthocyanins or anthocyanin-rich foods and extracts on markers or factors associated with cardiovascular diseases and characterizing Metabolic Syndrome (hyperglycaemia, hypertension, dyslipidaemia, obesity) (Table 6). In patients (with

CVD, diabetes, dyslipidemia or overweight/obesity), in the majority of the interventions (78.26%, 18/23) improvements have been reported of at least one of the following CVD risk factors: blood pressure or lipid and glucose metabolism (Table 6). In some studies these effects associated with improvements of antioxidant (117-120) or anti-inflammatory (121, 118, 120) markers. Results from two meta-analyses confirm the lipid lowering effects of anthocyanins (122,123). In particular, Liu et al.(123) reported that anthocyanin supplementation significantly reduces serum total cholesterol (TC, -24.06 mg/dL), triglycerides (TG, -26.14 mg/dL) and low density lipoprotein cholesterol (LDL-C, 22.10 mg/dL) levels and increases high density lipoprotein cholesterol (HDL-C, 5.58 mg/dL), in patients with dyslipidemia. On the contrary, in healthy subjects, improvement of CVD risk markers were reported only in 20% (2/10) of cases after the consumption of anthocyanin-rich food or extract (Table 6). Probably supplementation could be more beneficial for subjects suffering from CVD or with increased risk. In agreement with this hypothesis McAnulty et al. (124) reported improvement in blood pressure in a subset of subjects (9/13) with prehypertension (≥120/80 mm Hg) after 6 weeks of blueberry powder consumption.

On the other hand, Kusunoki et al. (125) reported that black soybean extract alone had no effect on the blood lipids of type 2 diabetics (complicated by postprandial hyperlipidemia), but enhanced the antihyperlipidemic action of fenofibrate, suggesting a potential food-drug interaction. In this context, food-drug interactions have been reported for pomegranate (126) and chanberry (127). However, only the aglycons anthocyanidins, but not the glycosides anthocyanins, are substrate of P-

glycoprotein (P-gp)(128) suggesting that anthocyanins could be safe in disease patients.

In agreement with this hypothesis is the improvement of transaminases in patients with nonalcoholic fatty liver disease (NALFD)(129) and in subjects with borderline hepatitis (130,131) (Table 6). In particular, Zhang et al. (129) conducted a CONSORT-compliant, randomized, double-blind, placebo-controlled pilot trial of purified anthocyanin in patients with NALFD. Patients received either purified anthocyanin (320mg/d) derived from bilberry and black currant or placebo for 12 weeks and exhibited improvement in transaminases and insulin resistance (129). Similar doses are efficacious also in metabolic diseases. Studies in subjects with dyslipidemia (132,133,121) and with type 2 diabetes (134,135) indicated an improvement in glycemic control and a reduction of dyslipidemia by anthocyanins purified with an effective dose included in 300-320mg- range day (150-160mg twice/day of anthocyanins).

Summary:

Anthocyanins, since ages, were known to provide bright red orange to blue-violet colors to plant fruits and vegetables particularly due to absorbance in visible range. These compounds are most abundant in berries (eg, black currants, elderberries, blueberries, strawberries) and their juices, and in red and purple grapes, red wine, sweet cherries, eggplants, black plums, blood oranges, and red cabbage.

Plants produce anthocyanins as a defensive mechanism against plentiful of environmental stressors, such as ultraviolet light, cold temperatures, and drought.

It is considered that this production of anthocyanins in roots, stems, and especially leaf tissues is to offer resistance against these environmental perils.

Furthermore, anthocyanins are the most effortlessly familiar and prominent flavonoid in the diet; the consumption of these compounds is assessed to be as much as nine fold higher than that of other nutritional flavonoids. The quantity of anthocyanins in foods can differ significantly. For example, red delicious apples provide more anthocyanins than Fuji apples; black raspberries are a far richer source than red raspberries; and Concord grapes are a much more concentrated source than red grapes.

While the answers to how and why anthocyanins may help prevent disease remain unsolved or unexplained, the literature to date is ambiguous, and utmost researchers are looking for more revisions to explore the potential health benefits of these naturally occurring compounds in plants. Anthocyanins are the potential natural phytochemicals due to their wide range of biological activities. The specific bioactivities of the anthocyanins are related to the molecular structures of the anthocyanins. The reported data demonstrates that the activity of anthocyanins particularly depends on the type of anthocyanins compound present in the source. The present review particularly focused on the chemotherapeutic, neuroprotective, cardioprotective, hepatoprotective and antidiabetic activities of anthocyanins and their analogues with multiple mechanisms of actions through *in vitro* models, *in vivo* animal models and several clinical investigations. Anthocyanins are rapidly absorbed from the stomach due to abundance in the gastrointestinal tract and attain low concentrations in serum. The More emphasis is needed for food

industry and pharmaceutical industry to isolate and standardize active principles of anthocyanins. Anthocyanins from elderberries have long been used in herbal medicine to combat colds and influenza. Several studies reported that elderberry anthocyanins were found to bind to H1N1 swine flu virus, hindering its ability to infect host cells. The researchers have noted that the elderberry anthocyanins acted in a way analogous to that of the pharmaceutical drug oseltamivir (Tamiflu). So, people have supported the notion that anthocyanins could be provided in the form of medicinal pills for the treatment of myriad of diseases. However, it needs more studies in order to establish pharmacokinetic and pharmacodynamic aspects and to improve the stability of anthocyanins.

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Table 1. Anti-carcinogenic activity of Anthocyanins:

Plant	Compound	Cancer, Model	Mechanism	Effects	References
	Cyanidin	Cisplatin-induced apoptosis in HK-2 proximal tubular cells	Cleavage of caspases and PARP, Activation of p53 and mitochondrial-mediated apoptosis pathways, ERK and AKT pathways Suppressed the overproduction of ROS	Antioxidant activity Proapoptotic activity	136
	Anthocyanin	Benzo[a]pyrene Induced lung cancer in BALB/c mice.	Decreased lipid peroxidation, Carcinoembryonic antigen aryl hydrocarbon hydroxylase and alanine transaminase Increased SOD, CAT, GPx and GSH	Antioxidant activity, Chemoprotective in nature	137
	Delphinidin and Cyanidin	MCF7-GFP-Tubulin breast cancer cells, Sulforhodamine B colorimetric cytotoxicity assay	DPPH radical scavenging activity, Inhibition of growth of MCF7 cells, Morphologically damaging MCF7 cells rounding-up of cells, chromatin condensation	Antioxidant activity, Proapoptotic activity Antiproliferative activity	138

Berry extract	Anthocyaninn	H_20_2 and TNF α induced carcinogenesis	Inhibition of VEGF expression by human keratinocytes, Inhibition of basal MCP-1 and inducible NF-kB transcriptions, Decreased tumor growth	Antioxidant activity, Antiangiogenic activity, Anticarcinogenic activity	139
Black currant	Cyanidin-3-O-glucoside, Cyanidin-3-O-rutinoside, Delphinidin-3-O-glucoside and Delphinidin-3-O-rutinoside	Diethylnitrosamine-induced hepatocellular carcinogenesis in rats	Decreased the incidence, total number, multiplicity, size and volume of preneoplastic hepatic nodules, Inhibition of abnormal cell proliferation and induction of apoptosis, Up-regulation of Bax and down-regulation of Bcl-2 expression at the translational level.	Antioxidant activity, Anti inflammatory activity	140
Black Raspberries	Cyanidin-3-O-glucoside, Cyanidin-3-O-rutinoside, Cyanidin-3-O-(2G-xylosylrutinoside)	NMBA induced esophageal tumors	Down regulation of NF-κB expression, Decreased Ki-67 expression, COX-2 expression, and Bcl-2 expression, Increasing Bax protein expression	Antiproliferative activity, Anti inflammatory activity, Proapoptotic activity, Anticarcinogenic activity	141
Black rice	Peonidin 3-glucoside, Cyanidin 3-glucoside	SCC-4, Huh-7, HeLa SKHep-1 cancer cells	Reduced expression of matrix metalloproteinase (MMP)-9 and urokinase-type plasminogen activator (u-PA), Inhibition of of cell invasion, DNA	Anticarcinogenic activity	142

			binding activity and the nuclear translocation of AP-1		
	Anthocyanin	Breast cancer cell lines MCF-7, HER2, MDA-MB-231	Activating caspase cascade, Cleaving poly (ADP-ribose) polymerase (PARP), depolarizing mitochondrial membrane potential and releasing cytochrome C, Inhibiting the expression of angiogenesis factors MMP-9, MMP-2 and uPA in tumor tissue	Proapoptotic activity, Antiangiogenic activity	143
		ErbB2 Positive Breast Cancer Cell Line BALB/c nude mice	Reduced transplanted tumor growth, Inhibited pulmonary metastasis, Decreased lung tumor nodules, Inhibited capacity for migration, adhesion, motility and invasion. Decreased activity of a transfer promoting factor, urokinase-type plasminogen activator (u-PA).	Antimetastasic activity	144
Black soya bean		Intestinal cancer	Decreased expression of Cytosolic and nuclear β-catenin, mucosa expression of cyclooxygenase-2 and cytosolic phospholipase A2 and Serum PGE2	Antioxidant activity, Anti inflammatory activity	145
Blueberry and	Malvidin-3-*O*-galactoside,	Human ovarian tumor cell line,	DPPH radical and ORAC radical scavenging activity,	Antioxidant activity Antiproliferative effect	146

Blackcurrant	petunidin-3-*O*-dalactoside, Deldelphinidin-3-*O*-glucoside, Delphinidin-3-*O*-rutinoside, Cyanidin-3-*O*-glucoside, Cyanidin-3-*O*-rutinoside, Delphinidin-3-*O*-galactoside	MTT assay	inhibit cell proliferation on HeLa, A2780 and B16F10 tumor cells		
Brown rice		Human colorectal cancer, HCT116 cells	Elevation of Bax protein and Reduction of Bcl2 protein levels, Activation of caspase-3 activity	Antioxidant activity Proapoptotic activity	147
		H_2O_2-induced apoptosis in human SH-SY5Y neuronal cells.	Induction of transcriptional changes in SOD 1, SOD 2 and catalase Induction of apoptotic of transcriptional changes in AKT, NF-Kβ, ERK1/2, JNK, p53 and p38 MAPK	Antioxidant activity	148
Chokeberries		Benzo(*a*)pyrene and 2-amino fluorene in the Ames test, Sister Chromatid Exchanges (SCEs) test with human blood-derived lymphocytes cultured *in vitro*	Free-radicals scavenging action, Inhibition of enzymes activating promutagens and converting mutagens to the DNA-reacting derivatives	Antioxidant activity, Antimutagenic activity, Anticarcinogenic activity	149
		HT-29 Colon Cancer	Inhibition in the mRNA	Anticarcinogenic activity	150

		Cells	levels of cyclin B1 and cyclin A genes, Increased Expression of p21WAF1 and p27 KIP1 Genes in HT-29 Cells, Inhibited COX-1 and COX-2 gene expression		
Elder berry	Cyanidin-3-*O*-sambubioside, Cyanidin-3-*O*-glucoside, Cyanidin-3,5-*O*-diglucoside, Cyanidin-3-*O*-rhamnoglucoside Cyanidin-3-*O*-xyloglucoside	Carcinogenesis	Inhibition of COX-1and ODC, Induction of quinone reductase, cyclooxygenase-2, and ornithine decarboxylase	Anti initiation activity Antipromotion activity	151
Litchi	Cyanindin-3-rutinside, Cyanidin-3-glucoside, Quercetin-3-rutinosde Quercetin-3-glucoside	Breast cancer	Up-regulated expressions of CYP1A1 and ADPRTL1, Down-regulated expression of BIRC genes, Ability to stabilize DNA triple-helical complexes	Anti proliferative activity, Proapoptotic activity	152
Mulberry	Cyanidin-3-rutinoside Cyanidin 3-glucoside	Metastatic A549 human lung carcinoma cells	Decreased expressions of matrix matalloprotinase-2 (MMP-2) and urokinase-plasminogen activator (u-PA) enhance the expression of tissue inhibitor of matrix	Anti migration activity Anti initiation activity	142

			matalloprotinase-2 (TIMP-2) and plasminogen activator inhibitor (PAI)		
	Cyanidine-3-rutinoside	Human gastric carcinoma AGS cells, TUNEL assay	Activation of p-p38, p-c-jun, and p-p53induced apoptosis in AGS cells through extrinsic (p38/Fas/FasL/caspase 8 signaling) and intrinsic (p38/p53/ Bax signaling) apoptotic pathways	Anti proliferative activity	153
Rice	Peonidin 3-Glucoside, Cyanidin 3-Glucoside	Human ductal breast carcinoma HS578T cells line	Induces activation of caspase-3, chromatin condensation, and cell death, Peonidin 3-Glucoside down-regulates protein levels of cyclin-dependent kinase (CDK)-1, CDK-2, cyclin B1 and cyclin, Cyanidin 3-glucoside decreases the protein levels of CDK-1, CDK-2, cyclin B1, and cyclin D1.	Chemopreventive activity Antimetastasic activity	74
		Colon adenocarcinoma (Caco-2), Lung carcinoma (A549), Breast adenocarcinoma (MCF-7), Bladder carcinoma (5637) and Prostate carcinoma (LNCaP) cell lines	Decreased cell number in the G(2)/M phase, Increased sub-G1 phase, Induced mRNA expression	Antimetastasic activity	154

Plums and Peaches	Cyanidin-3-glucoside	Human colon cancer cells	Increased activity of alkaline phosphatase and dipeptidyl peptidase, Inhibition of growth of Caco-2, SW1116, HT29 and NCM460 cells	Growth inhibitory activity	155
Pomegranate	Pelargonidin 3-glucoside Cyanidin 3-glucoside Delphinidin 3-glucoside Pelargonidin 3,5-diglucoside Cyanidin 3,5-diglucoside Delphinidin 3,5-diglucoside	TPA-mediated cutaneous edema in CD-1 mouse MALDI-TOF MS	Inhibition ODC protein expression, Increased COX-2 expression, Inhibition of TPA developed skin edema, epidermal ODC activity, phosphorylation of MAPKs protein such as ERK1/2, JNK1/2 and p38, TPA-induced degradation of IκBα, IKKα protein, NF-!B/p65 activation, Reduced tumor incidence and lower tumor body burden	Antitumor activity Chemopreventive activity	156
Potato		Prostate cancer cells. LNCaP and PC-3, Cell proliferation assay TUNEL assay DNA fragmentation assay	Inhibition of cell proliferation, Increased cyclin-dependent kinase inhibitor p27 Levels, mitogen-activated protein kinaseand c-jun, Activation of N-terminal kinase, caspase-independent apoptosis through nuclear	Proapoptotic activity	157

			translocation of endonuclease G (Endo G)		
Purple rice	Cyanidin 3-glucoside, Cyanidin 3-galactoside, Cyanidin 3-rutinoside, Cyanidin 3, 5-diglucoside, Malvidin 3-galactoside, Peonidin 3-glucoside,	MTT assay in human hepatocellular carcinoma HepG2, prostate cancer LNCaP and murine normal fibroblast NIH3T3 cells.	Loss of MTP and activation of caspase-3 and -9.	Proapoptotic activity	158
Ras berry	Cyanidin-3-O-glucoside, Cyanidin-3-O-rutinoside,	NMBA induced esophageal tumors	Up regulation of Ki-67, COX-2 and CD45	Anti proliferative activity, Antiangiogenic activity, Anti inflammatory activity, Proapoptotic activity	141
Sorghum Bicolor	3 - deoxyanthocyanidins	Human Epithelial larynx cell line (Hep 2), MTT assay	*In vitro* antiproliferative property against Hep – 2 cancer cell line. the morphological changes of Hep – 2 cells	Anti proliferative activity	159

Table 2. Neuroprotective activity with Anthocyanins:

Plant	Compound	Model	Mechanism	Effects	References
	Anthocyanins	Kainic acid (KA)-induced excitotoxicity, Mouse hippocampal cell line (HT22) and primary prenatal rat hippocampal neurons	Increased cell viability, Attenuation of KA-induced dysregulation of Ca(2+), ROS accumulation and activation of AMPK, Diminished KA-induced activation of AMPK and caspase-3	Anti oxidant activity Anti inflammatory activity	160
	Anthocyanins	Ethidium bromide induced demyelination	Reduced Na^+,K^+-ATPase and Ca^{2+}-ATPase activities and decreased 4-hydroxynonenal, malondialdehyde, protein carbonyl and NO_2 *plus* NO_3 levels, Reduction myeloperoxidase activity, interleukin (IL)-1β, IL-6, tumor necrosis factor-α and interferon-γ levels.	Anti oxidant activity Anti inflammatory activity	161
	Anthocyanins	Ethanol in the hippocampus of brain in postnatal day-7 rat	Activation of glutamatergic neurotransmission, synaptic dysfunction, GABAB1R activation, neuronal apoptosis inhibited expression of phosphorylated c-Jun N terminal kinase (p-JNK), phospho-nuclear factor kappa B (p-NF-κB), cyclooxygenase 2 (COX-2), attenuation of neuronal apoptosis in the hippocampal CA1, CA3 and	Anti oxidant activity Anti inflammatory activity	162

			DG regions of the developing rat brain.		
	Anthocyanins	Acrolein-Induced Toxicity in SK-N-SH Cells	Reduction in reactive oxygen species and protein carbonyl levels, glutathione depletion. Modulation of transcription factors NF-κB and Nrf2 and the proteins γ-GCS and GSK3β, and the protein adaptator p66Shc.	Acts on oxidative stress and cognitive impairment	163
	Anthocyanins	D-Galactos induced cognitive impairment in adult rats.	Improved behavioral performance in Morris water maze and Y-maze tests. Decreased expression of the receptor for advance glycation end product, reduced level of reactive oxygen species (ROS) lipid peroxidation. Inhibited activated astrocytes Suppression of v p-NF- $_{K}$ B, inducible nitric oxide synthase (iNOS), and tumor necrosis factor-alpha (TNF-α) in the hippocampus and cortex regions. Suppression of C-jun N-terminal kinase (p-JNK) and Improved deregulation of synaptosomal-associated protein (SNAP)-23, SNAP-25, and phosphorylated CREB	Anti oxidant activity Anti inflammatory activity	164
	Anthocyanins	Scopolamine induced	Decreased AChE activity	Anxiolytic activity	165

		amnesia in rats.	Increased Na^{+},K^{+}-ATPase and Ca^{2+}-ATPase activities in hippocampus		
	Anthocyanins	Scopolamine induced memory impairment in adult rats	Decreased the step-down latency prevented memory impairment, Increase of NTPDase activity Decrease in 5′-nucleotidase activity Increase in adenosine deaminase activity Decrease in ATP levels in the cerebral cortex and hippocampus	Neuroprotective activity	166
	Anthocyanins	Streptozotocin induced sporadic dementia of Alzheimer's in rats	Decreased AChE, Ca+-ATPase activities and Decreased NOx levels in cerebral cortex and hippocampus. Increased Na+,K+-ATPase activity	Anxiolytic activity	165
	Cyanidin-3-O-*β*-glucoside	Induction of cerebral ischemia by bilateral clamping of common carotid arteries	Increased levels of nonproteic thiol groups, Reduced lipid hydroperoxides, Increased the expression of heme oxygenase and *γ*-glutamyl cysteine synthase, Reduced expression of neuronal and inducible nitric oxide synthases.	Acts against Postischemic Reperfusion brain damage.	167
Berry	Cyanidin-3-glycosides,	Luminometric MAO assay	*In vitro* inhibitory effect on both	Competitive interaction	168

	Cyanidin-3,5-diglucosides, Proanthocyanidins		MAO A and MAO B		
Black soybean	Anthocyanins	Ethanol-induced neuronal apoptosis and morphological studies	Reverse the effects of ethanol on cellular levels of Bax, Bcl-2, active caspase-3, cleaved PARP-1, GABAB1R, and CaMKII were abrogated in cells transfected with GABAB1R siRNA, Inhibited the ability of ethanol to elevate intracellular free Ca(2+) level	Proapoptotic activity	169
Black soybean	Anthocyanins	Oxygen Glucose Deprivation by Promoting Autophagy	Increased the viability of U87 Cells in dose-dependent manner in of U87 glioma cells. Promotes autophagy induction under OGD stress, Decrease levels of reactive oxygen species, Silencing the Atg5 expression	Antioxidant activity, Cytoprotective activity	170
Black soybean	anthocyanins + vitamin C	Ethanol induced neurodegeneration in the adult rat brain	Decreased the expression of poly (ADP ribose) polymerase-1 Decreased expression of GABAB1R, phospho-cAMP response element binding protein. Alterations to the Bax/Bcl-2 ratio, release of cytochrome C and activation of caspase-3 and	Antioxidant activity Neuroprotective activity	171

			caspase-9.		
Blue berry	Cyanidin-3-O-β-galactoside, Cyanidin-3-O- β -glucoside, Cyanidin-3-O- β -arabinose, Malvidin-3-O- β -galactoside, Malvidin-3-O- β -glucoside, Malvidin-3-O- β -arabinose, Peonidin-3-O- β -arabinose Delphinidin-3-O- β -galactoside	19 month old F344 rats 8 weeks study period Morris water maze (MWM), a measure of spatial learning and memory.	Reversing age-related deficits in neuronal signaling and behavioral parameters	Neuroprotective activity	172
Blue berry		LPS induced neuronal inflammation	Increased protein levels in HSP70	Anti oxidant activity Anti inflammatory activity	173
Palm	Cyanidin, Delphinidin, Malvidin, Pelargonidin, Peonidin	Lipopolysaccharide induced oxidative stress, Inflammation in Mouse Brain BV-2 Microglial Cells	Decreased nitrite production, Reduction expression of iNOS, COX-2, p38-MAPK, TNFα, and NF-κB	Anti oxidant activity, Anti inflammatory activity	174
		Manganese-Induced Oxidative Stress in Rat Primary Astrocyte Cultures	Scavenging DPPH• radical Restoration of GSH/GSSG ratio and net glutamate uptake, Protecting astrocytic membranes from lipid peroxidation, decreased expression of erythroid 2-related factor (Nrf2) protein	Neuroprotectiing activity	175

Grape		AAPH induced erythrocyte hemolysis and oxidative DNA damage. female BALB/c mice	Scavenging both DPPH and ABTS radicals, inhibiting 2',-7'-dichlorofluorescin (DCFH) oxidation. Elevated the levels of antioxidant enzymes in mice sera, livers, and brains, Inhibition of acetylcholinesterase	Antioxidant activity acetylcholinesterase inhibitory activity	176

Table 3. Cardio protective activity of Anthocyanins:

Plant	Compound	Model	Mechanism	Effects	References
	Cyanidin-3-glucoside	Bovine artery endothelial cells (BAECs)	Increased eNOS expression, Increased nitric oxide output, Phosphorylation of Src and extracellular signal-regulated kinase 1/2 (ERK1/2), Sp1	Cardioprotective activity	177
Anthocyanins	Delphinidin-3 glucoside, Cyanidin-3-glucoside, Pelargonidin-3 glucoside, Malvinidin-3-glucoside Peonidin-3-glucoside	Ischemia-induced apoptosis in the perfused heart	Prevented caspase activation Increase in the routine respiration, Block apoptosis by reducing cytosolic cytochrome C.	Cardioprotective activity Proapoptotic activity	178
Artichoke	Cynarin	Human coronary artery smooth muscle cells (HCASMC)	Inhibited iNOS induction, Reduced cytokine-induced iNOS promoter activation and	Cardioprotective activity	179

			iNOS protein expression.		
Berries	Anthocyanins	*In vitro* and *In vivo* models	Inhibited basal MCP-1, inducible NF-κβ transcriptions and IL-8, Reduced ability to form hemangioma, Decreased EOMA cell-induced tumor growth	Antiangiogenic activity Antiatherosclerotic activity	180
Blueberries		Coronary Artery Ligation	Reduced TUNEL(+) cardiomyocytes and reduced inflammatory cells were observed in the myocardial area	Development of post myocardial infracted chronic heart failure.	181
		Exploratory pilot study in healthy subjects	Increased Insulin and Decreased triglyceride levels Increased HDL-cholesterol	Anti oxidant activity Cardio protective activity	182
	Anthocyanins	Cyclophosphamide induced cardiac injury in rats	Attenuated mean arterial blood pressure, heart rate and activities of heart enzymes, Improved cardiac dysfunction, left ventricular hypertrophy and fibrosis Attenuated LV leukocyte infiltration and inflammatory cytokines expression.	Anti oxidant activity Cardio protective activity Proapoptotic activity	183
		Murine macrophage cell line, LPS-induced atherogenesis	Decreased mRNA expression and protein levels of scavenger receptor CD36 Increased expression and protein levels of ATP-binding cassette	Atheroprotective activity	184

			transporter A1		
Pomagranate	Anthocyanins	High fat diet induced hypercholesterolemic rabbits	Decreased TC, TG, LDL, VLDL levels and increased HDL and serum antioxidant capacity, Decreased atherosclerotic plaque thickness, sizes of plaques in renal arteries	Antioxidant activity Antihyperlipidemic activity	185
Red wine	Delphinidin Cyanidin	Human aortic vascular smooth muscle cells (VSMCs)	Prevented the platelet derived growth factorAB -induced formation of ROS in VSMCs, Inhibited phosphorylation of p38 MAPK and JNK.	Antioxidant activity Cardio protective activity	186
Sour cherry		Ischemia and reperfusion in Isolated hearts from Sprague-Dawley rats	Induced heme oxygenase-1 (HO-1), Suppression of infarct size, Enhanced postischemic ventricular function includes HR, AF, CF, AOP, AOdP/dt, CO and SV. Enhancement of p-(473)Akt/Akt ratio Upregulates Bcl-2 expression in the heart	Cardio protective activity	187
Sour cherry		Ischemia-reperfusion-induced damage in isolated rat hearts	Reduce the incidence of VF and VT during reperfusion, Improved the postischemic recovery of cardiac function (coronary flow, aortic flow, and left ventricular developed pressure) Reduction of infarct size	Cardio protective activity	188

			Reduction in caspase-3 activity		

Table 4. Hepatoprotective activity of Anthocyanins:

Plant	Compound	Model	Mechanism	Effects	References
	Cyanidin-3-glucoside	CCl_4 induced liver injury in mice	Reduction in serum SHOT, SGPT, and liver MDA Reduced the incidence of liver lesions. Prevented DNA damage and Decreased the protein levels of γ-H2AX Increased SOD, CAT, GPx and GSH levels, Inhibited IL-6 and iNOS expression	Antioxidant activity, Anti inflammatory activity	189
	Cyanidin-3-O-β-glucoside	High glucose-induced apoptosis	Decrease in cell viability, Increase in apoptotic cell death, Reduction in reactive species generation, Improvement of mitochondrial membrane potential, Inactivation of caspase-3 and -9, Down-regulation of the pro-apoptotic Bax protein, phosphatidylinositol 3-kinase (PI3K)/Akt and mitogen-activated protein kinases (MAPKs).	Antioxidant activity, Hepatoprotective ativity	190
Acerola cherry	Cyanidin-3-O-rhamnoglucoside	D-galactosamine-induced liver injury in rats	DPPH radical scavenging activity, Decreased serum levels of AST, ALT, and GGT, Reduction MDA levels.	Antioxidant activity, Anti inflammatory activity	191

Choke berry		CCl4 -induced acute liver damage in rats	Decreased plasma AST and ALT, Reduction in liver MDA and depletion of GSH content. Inhibition of necrosis, fatty change, ballooning degeneration and inflammatory infiltration of lymphocytes	Antioxidant activity, Anti inflammatory activity.	192
Black rice	Cyanidin-3-glucoside Peonidin-3-glucoside	CCl4-induced hepatotoxicity in mice	Reduced aminotransferase, enhanced superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) Decreased tiobarbituric acid reactive substances (TBARS), and 8-hydroxy-2′-deoxyguanosine (8-OHdG) levels	Antioxidant activity, Hepatoprotective activity	193
Cherry		CCl4-induced hepatotoxicity in mice	DPPH free radical scavenging activity, Trolex Equivalent Antioxidants Capacity (TEAC) and Ferric Reducing Antioxidant Power (FRAP), Reduction in AST, ALT, ALP, Total Bilirubin (TB) and albumin.	Antioxidant activity hepatoprotective activity	194
Chestnut bee pollen	Total anthocyanins	CCl4-induced hepatotoxicity in rats	Ferric reducing/antioxidant power, and DPPH radical activity, Reduction in AST and ALT, Protects the hepatocytes.	Antioxidant activity Hepatoprotective activity	195
Cornelian Cherry	anthocyanins	CCl4-induced hepatotoxicity in mice	Reduction in Aspartate Transaminase (AST), Alanine Transaminase (ALT), Alkaline Phosphatase (ALP), Total Bilirubin (TB), albumin and MDA content	Hepatoprotective activity	196

Colocasia antiquorum	Cyanidin 3-glucoside, Pelargonidin 3-glucoside Cyanidin 3-rhamnoside	Alcohol induced liver injury	Reduction in SGPT, SGOT, ALP, Cholesterol and Triglyceride levels Histopathological protection of liver, Reduction in Bilirubin (TB) and albumin.	Hepatoprotective activity	197
Golden berry	Anthocyanins	CCl4-induced hepatotoxicity in rats	Reduction in serum markers like ALT, AST, ALP, LDH, creatinine, urea and bilirubin, Protection against hepatic cell damage.	Hepatoprotective activity	198
China rose	Anthocyanins	CCl4-induced hepatotoxicity in rats	Reduction in serum aspartate and alanine aminotransferase activities	Antioxidant activity	199
Roselle	Anthocyanins	CCl4-induced hepatotoxicity in rats	Reduction in plasma alanine transferase, Prevention in hepatic nacrosis	Hepatoprotective activity	200
	Anthocyanins	Tert-butyl hydroperoxide-induced hepatic toxicity in rats	DPPH radical scavenging activity, Decreased the leakage of lactate dehydrogenase and formation of malondialdehyde, Decreased AST and ALT, Decreased incidence of liver lesions including inflammatory, leucocyte infiltration, and necrosis.	Antioxidant activity Hepatoprotective activity	201
	Anthocyanins	Paracetamol induced hepatotoxicity in rats	Lowering of ALT and AST Marked amelioration of necrosis	Antioxidant activity	202
	Anthocyanins	CCl4-induced hepatotoxicity in rats	Decreased AST and ALT. Restoration of glutathione content Inhibited MDA, Inhibited the activation of the hepatic stellate cells	Antioxidant activity Hepatoprotective activity	203
	Anthocyanins	Acetaminophen (AAP)-induced	Decreased lipid peroxidation and Increased catalase activity and	Antioxidant activity	204

		hepatotoxicity in rats	glutathione level Decreased expression of pJNK, Bax and tBid in the liver *In vitro*, protected BALB/c normal liver cells	Hepatoprotective activity	
Purple sweet potato	Anthocyanins	Tert-butyl hydroperoxide-induced hepatotoxicity in HepG2 cell line and in rat liver	Decreased ALT and AST Reduced malondialdehyde and glutathione. Reduced the incidence of liver lesions Up-regulated heme oxygenase-1 (HO-1), NAD(P)H:quinone reductase and glutathione S-transferase Induced Nrf2 nuclear translocation and Akt and ERK1/2 activation	Antioxidant activity Anti inflammatory activity Hepatoprotective activity	88
	Anthocyanins	Dimethylnitrosamine-induced liver injury in rats	Inducing nuclear erythroid 2-related factor 2 (Nrf2), Decreased increased serum alanine aminotransferase and aspartate aminotransferase, Depletion of malondialdehyde and glutathione, Increased the expression of Nrf2, NADPH:quinine oxidoreductase-1, heme oxygenase-1, and GSTα Decreased the expression of COX-2, iNOS and NF-κB	Antioxidant activity Anti inflammatory activity Hepatoprotective activity	205
	Anthocyanins	D-galactose-induced hepatotoxicity in rats	Decreased MDA and Protein carbonyl contrent and GSH levels, Decreased SOD1 and GPx1 activities, No change in hepatic mRNA	Pro oxidant and antioxidant activity	206

			expressions of SOD2 and GPx1, Decreased SOD1 and GPx4 expressions, Decreases in serum ALT and AST		
	Anthocyanins	Acetaminophen induced hepatotoxicity in mice	Prevented hepatic GSH depletion, Up regulation of hepatic GSH levels and GSH S-transferase activities, Reduced CYP2E1-dependent aniline hydroxylation and CYP2E1 protein levels. Scavenging FeCl(2)/ascorbate-induced lipid peroxidation superoxide radical.	Antioxidant activity Hepatoprotectibve activity	207
Red radish	Anthocyanins	CCl4-induced hepatotoxicity in rats	Decreased ALT, AST, ALP, TB, DB, MDA and GSH level Amelioration in necrotic zones and hepatocellular degeneration.	Antioxidant activity Hepatoprotectibve activity	208
Poison berry	Anthocyanins	CCl4-induced hepatotoxicity in rats	Decreased ALT, AST, ALP, acid phosphatase (ACP) and lactate dehydrogenase (LDH). Reduction in total protein, total bilirubin, total cholesterol, triglycerides and Urea.	Antioxidant activity Hepatoprotectibve activity	209

Table 5. Antidiabetic activity of anthocyanins:

Plant	Compound	Model	Mechanism	Effects	References
	Cyanidin-3-rutinoside	*In Vitro* Study	Inhibitory activity on pancreatic α-amylase, intestinal α-glucosidase (maltase and sucrose), Retarded absorption of carbohydrates	Antidiabetic activity	210
	Delphinidin 3-rutinoside	GLUTag L cells	Potent enhancer of GLP-1 secretion, activation of CaMKI	Incretin mimetic activity	211
	Cyanidin-3-O-β-glucoside	Diabetic apolipoprotein E–deficient (apoE2/2) mice	Significant amelioration of the adhesion to fibronectin, migration, and tube formation and enhances endothelial repair	Antidiabetic activity, Anti atherogenic activity	212
	Pelargonidin	STZ induced diabetic neuropathic rat	Decreased TBA formation, Non-significantly reversed elevation of nitrite level, Increased SOD levels, Ameliorated the alteration in hyperalgesia,	Antioxidant activity	213
Chilean wineberry	Quercetin-3-orutinoside	Alloxan induced diabetic rats	Reduced fasting blood sugar, cholesterol, LDL and triglycerides. Improved nitric oxide bioavailability and endothelium dependent relaxations.	Antidiabetic activity, Antihyperlipidemic activity	214

Aronia berries	Cyanidin 3-galactoside, Cyanidin 3-glucoside, Cyanidin 3-arabinoside Cyanidin 3-xyloside	*In vitro* models	DPPH radical scavenging activity, Inhibition of 15-lipoxygenase (15-LO), Xanthine oxidase (XO) and α-glucosidase	Antioxidant activity	215
Bilberry	Anthocyanins	Type 2 diabetic mice	Reduced the blood glucose levels, Increased insulin sensitivity, Upregulation of glucose transporter 4, Inactivated acetyl-CoA carboxylase. Upregulated PPAR ɣ, acyl-CoA oxidase, and carnitine palmitoyltransferase-1A in the liver	Antidiabetic activity	216
Black carrots	Cyanidin-3-rutinosides Malvidin-3,5-diglycosides Delphine-3-glucoside Cyanidin Malvidin	Estrogen-deficient animals with Diet-induced obesity	Normalized HOMA-IR, Decreased hepatic triglyceride levels Increased gene expressions of CPT-1 and PPAR-ɣ Decreasing mRNA expressions of FAS and SREBP-1c, Decreased fat accumulation in 3T3-L1 adipocytes	Antidiabetic activity Antihyperlipidemic activity	217
Blue berry	Anthocyanins	Zucker Fatty and Zucker Lean rats were fed a higher-fat diet (45% of kcal) or a lower-fat diet (10% of kcal) containing 2% (wt/wt)	Reduced triglycerides, fasting insulin, homeostasis model index of insulin resistance and glucose area under the curve, Reduced abdominal fat mass,	Antidiabetic activity Antihyperlipidemic activity	Liu, J., 2015

			Increased adipose and skeletal muscle PPAR activity		
Eggplant	Anthocyanins	*In vitro* assays and High fat diet induced hyperlipidemic rats	Decreased levels of serum total cholesterol, LDL, VLDL and triglyceride Increased HDL. DPPH radical and reducing power	Antioxidant activity Antihyperlipidemic activity	218
Litchi	Cyanidin-3-rutinoside, Cyanidin-3-glucoside,	*In vitro* study	Oxygen radical absorbance capacity activity and DPPH radical-scavenging activity	*In vitro* antioxidant activity	219
Morus alba	Anthocyanins	Male leptin receptor-deficient Zucker diabetic fatty (ZDF) rats	Ferric reducing ability power Reduction of blood glucose levels, Elevation of insulin levels Prevent islet degeneration	Antioxidant activity Antidiabetic activity	220
Purple corn		C57BL/KsJ *db/db* mice	Decreased blood glucose and HbA1C Levels, Increased C-peptide and adiponectin levels increased the phosphorylation of AMP-activated protein kinase (AMPK) Decreased phosphoenolpyruvate carboxykinase (PEPCK), glucose 6-phosphatase genes in liver, Increased GLUT4 expressions in skeletal muscle	Antidiabetic activity	221
		Human endothelial cells were cultured in	Enhanced platelet endothelial cell adhesion molecule	Antidiabetic activity Anti angiogenic activity	222

		conditioned media of mesangial cells exposed to 33 mM high glucose (HG-HRMC-CM), db/db mice	(PECAM)-1 and integrin b3 in HG-HRMC-CM, Attenuating the induction of VEGF and HIF-1α, Inhibition of the induction of vascular endothelium-cadherin, PECAM-1 and Ki-67 in db/db mice		
	Anthocyanins	Human mesangial cells exposed to 33 mM glucose (HG-HRMC) , db/db mice	Decreased the HG-HRMC-conditioned, media-induced expression of endothelial vascular cell adhesion molecule-1, E-selectin, and monocyte integrins-β1 and β2 through blocking the mesangial Tyk2 pathway Attenuated CXCR2 induction and the activation of Tyk2 and STAT1/3 in *db/db* mice, Attenuated the induction of intracellular cell adhesion molecule-1 and CD11b, Decreased monocyte chemoattractant protein-1 expression and macrophage inflammatory protein 2 transcription in the diabetic kidney, Inhibiting The induction of the macrophage markers CD68	Antidaibetic activity, Nephroprotective cativity	223

			and F4/80.		
Rice berry	Anthocyanins	Streptozotocin (STZ)-induced diabetes	Reduction in Blood glucose, HbA1C Elevation of insulin, GLUT4 levels and antioxidant enzymes SOD, CAT, and GPx, antioxidant capacity (ORAC), pro-inflammation cytokine TNF-a and IL-6	Antioxidant activity Anti inflammatory activity	224
Black soya bean	Anthocyanins	C57BLKS/J *db*/*m* and *db*/*db* mice	Decreased albuminuria Increased phosphorylation of AMPK and activation of PPA α and PPARγ, Inhibited the activity of acetyl-CoA carboxylase and sterol regulatory element-binding protein 1.	Anti oxidant activity Antidaibetic activity	225

Table 6. Human evidence on potential beneficial effects on cognitive decline, diabetes, hepatic and cardiovascular diseases markers.

Source	Publication type	Reported effects	Ref.
Anthocyanidins	Meta-analysis (Intake)	Subjects with highest-intake had lower risk of oesophageal cancer	102
Anthocyanins	Intervention (Cancer)	No effect on cancer progression	105
	Intervention (Cancer)	Reduced radiation dermatitis during therapy for breast cancer	106
	Intervention (Cancer)	Reduced radiation dermatitis during therapy for breast cancer with or without adjuvant chemotherapy with anthracyclines and taxanes.	107
	Intervention (Dyslipidemic)	Improvement of lipid profile	132
	Intervention (Healthy)	No effect on blood pressure	226
	Intervention (Hypercholesterolemia)	Improvement of lipid profile	133
	Intervention (Hypercholesterolemia)	Improvement of lipid profile	121
	Intervention (NAFLD)	Improvement of transaminases and glycaemic control	129
	Intervention (Type 2 diabetes)	Improvement of glycaemic control and lipid profile	117
	Meta-Analysis (RCT)	Improvement of lipid profile in subjects with dyslipidemia	122
	Nurses' Health Study (NHS) and NHS II (Intake)	No association with ovarian cancer risk	227

	Nurses' Health Study (NHS) and NHS II (Intake)	Subjects with highest-intake had lower risk of type 2 diabetes	100
Berry (Brazilian Myrciaria jaboticaba)	Intervention (Healthy)	Improvement of glycaemic control	228
Berry (maqui extract, Delphinol)	Intervention (Overweight, smokers)	No significant differences on blood pressure, and lipid profile.	229
Bilberry	Intervention (Cancer, extract mirtocyan)	In tumor tissue of patients with colorectal cancer the proliferation was decreased.	110
	Meta-analysis (RCT)	Improvement of lipid profile	123
Black raspberry	Intervention (Cancer, beverage)	Attenuated neoplastic changes in colorectal tissue of cancer patients.	109
	Intervention (Cancer, gel)	Improvement of oral cancer	230
	Intervention (Cancer, powder)	Improvement of oral cancer	111
Black soybean	Intervention (Type 2 diabetics, complicated by postprandial hyperlipidemia, extract)	No effect on glucose and lipid profile but enhancement of fenofibrate effect	125
Blackcurrant	Intervention (Healthy, extract)	Cognitive improvement	112
	Intervention (Healthy, juice)	No effects on blood pressure or lipid profile	231
Blueberry	Intervention (Children, drink)	Cognitive improvement	113
	Intervention (Elderlies, juice)	Cognitive improvement Improvement in glycaemic control	115
	Intervention (Healthy)	Anti-hypertensive only in prehypertensive subjects	124
	Intervention (Healthy)	Increased glucose	232

	Intervention (Healthy)	No significant differences on peripheral arterial function (Endo-PAT 2000)	232
	Intervention (Metabolic syndrome, beverage)	Anti-hypertensive No effects on glucose and lipid profile	234
	Nurses' Health Study (NHS) II (intake)	Decreased risk of Myocardial infarction	101
Cherry	Intervention (Elderlies, juice)	Cognitive improvement Anti-hypertensive	116
	Intervention (Type 2 diabetes, juice)	Anti-hypertensive Improvement of glycaemic and lipid profile	235
	Intervention (Type 2 diabtes, extract)	Improvement of glycaemic control	135
Chokeberry	Intervention (Healthy, juice)	No effect on blood pressure	236
	Intervention (Metabolic syndrome, extract)	Anti-hypertensive Improvement of lipid profile	118
	Intervention (Untreated grade I hypertension, juice)	Anti-hypertensive Improvement of lipid profile	237
Concord Grape	Intervention (Elderlies, juice)	Cognitive improvement	114
Cranberry	Intervention (CAD, juice)	No effect on blood pressure	238
	Intervention (Healthy, juice)	No effect on lipid profile	239
Pomegranate	Intervention (Atherosclerotic, juice)	Anti-hypertensive	119
	Intervention (CAD, juice)	No effect on blood pressure, glycaemic and lipid profile.	240
	Intervention (Hypertensive, juice)	Anti-hypertensive	241

		No effect on lipid profile	
Purple sweet potato	Intervention (Caucasian, borderline hepatitis, beverage)	Improvement of transaminases	130
	Intervention (Caucasian, hypertensive, beverage)	Anti-hypertensive	242
	Intervention (Japanese, borderline hepatitis, beverage)	Improvement of transaminases	131
Red grape	Intervention (Healthy, extract or red wine)	Improvement of HDL-C only with red wine No effects on other lipid profile or blood pressure	243
	Intervention (Mildly hypertensive, extract)	Anti-hypertensive	244
Red grapefruit	Intervention (Hyperlipidemic)	Improvement of lipid profile	245
Red orange	Intervention (Obese, juice)	Improvement of lipid profile No effects on glucose control and blood pressure	246
	Intervention (Type 2 diabetes, extract)	No effect on glycaemic control	247
Strawberry	Intervention (Cancer)	Reduced the histologic grade of dysplastic premalignant lesions of the esophagus	108
	Intervention (Healthy)	Improvement of lipid profile	248
	Intervention (Metabolic syndrome, beverage)	Decreased TC and LDL-C No effect on HDL-C, TG, glucose and blood pressure	249
	Nurses' Health Study (NHS) II (intake)	Decreased risk of Myocardial infarction	101
	Women’s Health Study (intake)	No reduction of CVD risk	103
Whortleberry	Intervention (Hyperlipidemic, extract)	Improvement of lipid profile	250

	Intervention (Hyperlipidemic, extract)	Improvement of lipid profile	120
	Meta-analysis (RCT)	Improvement of lipid profile	123