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Prevention and Treatment Effects of Edible Berries for Three Deadly Diseases: Cardiovascular Disease, Cancer and Diabetes

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Abstract

Cardiovascular disease (CVD), cancer and diabetes are serious threat to human health and more and more aroused people's attention. It is important to find the safe and effective prevention and treatment methods for the three deadly diseases. At present, a generally attention in the possible positive effects of edible berries for the three deadly diseases has been noted. Berry phytochemical compounds regulate different signaling pathways about cell survival, growth and differentiation. They contribute to the prevention and treatment of CVD, cancer and diabetes. This article reviews previous experimental evidence, several common berry phytochemical compounds and their possible mechanisms involved in three deadly diseases were summarized.

Key words: prevention; treatment; berries; three deadly diseases

Introduction

CVD refers to heart, brain and systemic tissue of ischemic or hemorrhagic disease caused by the hyperlipidemia, blood viscosity, atherosclerosis and high blood pressure. Each year due to CVD deaths accounted for 30% of the total number of deaths in the world(Wightman et al., 2015). Cancer is one of the major chronic diseases, the incidence of cancer is increasing, greatly threatening the health and social development of citizens. In 2012, an estimated 14.1 million new cancer cases and 8.2 million cancer deaths occurred worldwide. Mortality rates in the 50 selected countries range from over 200 deaths per 100,000 males and over 100 deaths per 100,000 females (Ferlay et al., 2010). With people's living standards improve, dietary patterns and lifestyles change, the diseases associated with glucose-lipid metabolism disorders is rapid increased. Diabetes, especially type 2 diabetes (T2D) has become a global health threat. T2D incidence rates in the United States have increased from 5.6 million cases in 1980 to 15.8 million in 2005(Kellogg et al., 2010). CVD, cancer and diabetes become the three major threatening diseases for human health. Nowadays berries are becoming part of the diet, not only for their appealing aroma and appearance, but also because of their health benefits. Berries are important functional food and supplement to the diet. Blueberry, mulberry, bilberry, cranberry, raspberry, blackberry, currants etc are the common berry crops all over the world. They have both commercial and nutritional value because of their treatment and prevention for some chronic diseases.

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The recent experimental and epidemiological evidence have shown that berries have the therapeutic and preventive effect for CVD, cancer and diabetes. High levels of anthocyanins and flavonols confer antioxidant capacity of berries. CVD and cancer are all due to long-term exposure to oxidative stress (OS) (Joseph et al., 1999). Reactive oxygen species (ROS) induced OS leads to apoptosis and even necrosis, so ROS play an important role in the development of CVD and cancer(Takasawa et al., 2010), anthocyanins have significantly ROS scavenging and reducing activity(Fernandes et al., 2013), they also can decrease DNA damage to protect the body(Liu et al., 2013). Some studies have found that berry phytochemical play an important role in the regulation of blood pressure, platelet aggregation, atherosclerosis and whole-body metabolism (De et al., 2010). In addition, anthocyanins not only inhibit the proliferation of cancer cells by regulating the expression of related proteins and genes, but also prompt cancer cell apoptosis by inducing the expression of related genes(H. P. Huang et al., 2011; Kausar et al., 2012). The inadequate insulin secretion results in diabetic patients with a long-term damage and causes the failure of various organs. Inhibition of postprandial hyperglycemia may be one of the most effective ways to control diabetes(Bailey et al., 2004). Berries rich in bioactive phytochemicals, particularly anthocyanins and proanthocyanidins may inhibit the increase of blood glucose to improve diabetes and other metabolic disorders (Kellogg et al., 2010).

The prevention and treatment mechanism of berries and berry bioactive compounds for CVD

At present, many epidemiological studies have shown that consumption of berries product and the decrease of CVD risk are closely related (Hjartåker et al., 2015). Some articles showed that berries through restrained platelet aggregation, effected blood lipids, lowered OS, improved endothelial function, regulated the metabolism protect the body from cardiovascular disease (Wightman et al., 2015).

Berries and berry bioactive compounds effect on inhibition of platelet aggregation

Normal platelet activation aggregation is a necessary defense mechanism, but excessive platelet aggregation causes thrombosis, hinder blood flow, severe or even cause acute myocardial infarction, stroke or some other thrombotic diseases (Nurden, 2011). Therefore, anti-platelet aggregation is one of the important directions in the treatment of thrombotic diseases (Michelson, 2010). The studies of Johansson have shown that sea buckthorn berry oil had a significant inhibitory effect on adenosine-5'-diphosphate-induced platelet aggregation, sea buckthorn berry oil was very beneficial for blood clotting(Johansson et al., 2000), and ate berries for eight weeks could reduce platelet aggregation in vivo in a middle-aged population at risk of CVD (Erlund et al., 2008).

Phenolic substances inhibit platelet aggregation is due to phenols affect thrombin activity. Thrombin is one of the strongest platelet agonists in the body(Covic et al., 2000; Licari et al., 2010; Traynelis et al., 2007; Wu et al., 2010). Black chokeberry extracts through inhibited thrombin activity to inhibit human plasma coagulation. Pre-culture of thrombin with blackberry

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extract resulted in a change in its ability to induce fibrinogen polymerization, when the blackberry extract concentration was 50 mg/mL, the extract had almost complete inhibition of thrombin-induced polymerization (Bijak et al., 2011). Flavonoids inserted into the catalytic site of thrombin, they interacted (H-bond) with His57 of the thrombin catalytic triad, pomegranate polyphenols induced similar inhibitory effects (Cuccioloni et al., 2009). So the mechanism of flavonoids inhibit thrombin activity is that they bind to thrombin activity centers and inhibit enzyme activity. Phenolic fusions may be the most promising dietary supplements to prevent thrombosis(Cuccioloni et al., 2009; Mozzicafreddo et al., 2006).

Berries and berry bioactive compounds effect on blood lipids

Commonly used indicators of lipid metabolism are: total cholesterol (TC), triglyceride (TG), high density lipoprotein cholesterol (HDL-C), low-density lipoprotein (LDL) and low-density lipoprotein cholesterol (LDL-C).Abnormal blood lipids are the major risk factor for CVD, dyslipidemia and TC, LDL, TG are too high may cause CVD and atherosclerosis (Z. D. Zhao et al., 2016), hypercholesterolemia also is a risk factor for CVD in the elderly (Davidson et al., 2010). Lin's study found that the activity of LPL in the liver of mice was increased in each anthocyanin dose group (Lin et al., 2012). Increasing LPL activity affect serum TC, LDL-C, HDL-C, TG levels, thereby regulating the body's lipid metabolism, resisting to the occurrence of hyperlipidemia(Shan et al., 2006; Tsutsumi, 2003). The main underlying cause of CVD is atherosclerosis and it is expected to become the main cause of global mortality by 2050(Libby et al., 2010; Sorelle, 1999). Anthocyanins have the effect of lowering blood lipids and anti-atherosclerosis (Liao et al., 2007), pathological examination found that anthocyanins significantly reduce the area of atherosclerotic plaque, mitigating the damage to endothelial cells and elastic plate, reducing the number of foam cells and vascular wall proliferation(Lin et al., 2012). TC/HDL-C ratio of 5.0 or more is a risk factor for CVD(Listed, 1995). Lycium ruthenicum pigment (PLR) was added into the feed, the ICR male mice were treated by intragastric administration, the results showed that the appropriate dose of PLR significantly inhibited the weight gain ($P < 0.05$) of high-fat diet mice. The levels of serum, TC, TG ,LDL-C and arteriosclerosis index (LDL/HDL) were significantly decreased, and the level of HDL-C/TC was significantly increased, indicated the PLR had the effect of regulating blood lipids and preventing atherosclerosis(Jin et al., 2007).

The LDL is closely related to the occurrence of CVD , oxidized LDL(OX-LDL) plays a key role in the development of arteriosclerosis(Berliner et al., 1995), grape polyphenols enhanced flow-mediated vasodilation, promoted endothelial nitric oxide synthetase (eNOS), inducted endothelin-1 inhibition and reduced LDL oxidation that against atherosclerosis(Fernandez et al., 2016). The hypolipidemic activity of flavonoids and phenolic compounds from grape skin and acai puree were determined in vivo used zebrafish, the compounds inhibited LDL oxidation at a final concentration of 0.1 mg/mL (J. Y. Kim et al., 2012). OX-LDL is associated with the occurrence of atherosclerotic CVD. Grape seed proanthocyanidin extract (GSPE) was used to conduct a series of studies to demonstrate its ability to protect hearts in animals, GSPE inhibited LDL oxidative modification (Baiges et al., 2010; Sano et al., 2007). Researchers provided troche containing 0, 200 or 400 mg proanthocyanidin from grape seed extract to 61 healthy subjects. After the start of administration, at 6 and 12 week , the malondialdehyde-modified LDL (MDA-LDL) content of the 400mg dose group decreased significantly compared to the basal level. At 12 week after the start of administration, In the 200 mg group (MDA-LDL/ApoB of subjects were high relatively), a significant decrease in MDA-LDL level was found (Sano et al., 2007). Dining with consumption of grape seed extract at the same time enhanced the plasma antioxidant substances, reduced the oxidation of substances, proved resistance effect of LDL regard to oxidative modification(Natella et al., 2001; Ventura et al., 2004).

For overweight and obese women, sea buckthorn berries reduced very LDL-C, the result was more pronounced in groups with higher CVD risk. In all subjects, sea buckthorn had a tendency to reduce total and LDL cholesterol, significantly reduced serum-free cholesterol. 2-month mix of berry products supplements increased significantly HDL levels (5.2%) and had a greater impact on person with higher CVD risk (Larmo et al., 2013). The lipid-lowering effects of anthocyanins extracted from Lycium ruthenicum were decreased the weight, TC, TG and LDL-C content of mice, and increased the content of HDL-C(Lin et al., 2012). HDL-C is generally considered to be the good cholesterol because it can transport fat molecules (including

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triacylglycerol and cholesterol) to the arterial wall. However, HDL-C-deficient mice still can transport cholesterol to bile, so probably because of the presence of alternative mechanisms of cholesterol removal(Amigo et al., 2011; D. W. Zhang et al., 2008). Mulberry polyphenol extracts (MPEs) initially activated JNK/p38 and p53, which in turn activated both Fas-ligand and mitochondrial pathways, thereby caused mitochondrial translocation of Bax and a reduction in Bcl-2. It then triggered the cleavage of procaspases, finally resulted in apoptosis of vascular smooth muscle cells (VSMCs). Apoptosis of VSMCs is the key determine the number of VSMCs in remodeling, the effect of MPEs on the apoptosis of VSMCs prevent the occurrence of atherosclerosis(Chan et al., 2016).

Berries and berry bioactive compounds effect on OS

In pathophysiology, OS may be critical for the production of some diseases (Ramana et al., 2017; Sultana et al., 2013). The imbalance of systemic production of ROS and reactive nitrogen substances (RNS) and biological system detoxification capacity or repair ROS/RNS-induced damage are common underlying mechanisms of OS generation (Mazzoni et al., 2016). The study of monitoring ROS/RNS production and antioxidant defense systems has shown that OS with subsequent mitochondrial respiratory injury and mitochondrial damage associated with the pathophysiology of these diseases (cancer, CVD and other senile recessive diseases) (Ramalingam et al., 2012). The positive effects of berries in OS have been demonstrated (Iff et al., 2011). Phenols are the most representative compounds of berry bioactive compounds,

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different berry species have different profiles of polyphenols, while anthocyanins are the most effective antioxidants of phenolic compounds in berries(Bornsek et al., 2012; Braga et al., 2013). Blackcurrants mainly include glucosylated and rutinosylated cyanidin and delphinidin, delphinidin glycosides(belong to phenols) are the prevailing form of anthocyanins in bilberry(Veberic et al., 2015). The free radical scavenging capacity of anthocyanins depends on the number and position of methyl and hydroxyl groups in the skeleton, the B ring of delphinidin containing 3 hydroxylation makes it has a strong antioxidant capacity(Kähkönen et al., 2003; Noda et al., 2005).

In vitro and in vivo studies have found that polyphenol-rich berries inhibited OS and inhibited the occurrence of some diseases(Giampieri et al., 2015; Nile et al., 2014). Compared with the baseline, content of F2-isoprostanes (8-iso-prostaglandin F2a) decreased at 4 weeks in the maqui berry extract (standardized by Delphinol) -supplemented group ($p < 0.05$) in urinary. In healthy adults, overweight adults and smoking adults, maqui berry extract diet intervention affected the content of F2-isoprostanes(Davinelli et al., 2015). Superoxide and F2-isoprostanes are two recognized markers of OS (Wightman et al., 2015).Chokeberry (Aronia melanocarpa) contains anthocyanins, phenolic acids and quercetin glycosides, the consumption of chokeberry may reduce CVD risk, chokeberry as interventions have reduced OS in humans and rodents(B. Kim et al., 2013; Kujawska et al., 2011). Extract of chokeberry reduced OS in blood platelets from the healthy subject group (B et al., 2008; Kedzierska et al., 2009). Dosed with carbon

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tetrachloride(CCl_4) and N-nitrosodiethylamine (NDEA) in mice increased the thiobarbituric acid reactive substances (TBARS, expressed the level of hepatic microsomal lipid peroxidation) content of the mice. Chokeberry juice pretreatment reduced the increase in TBARS caused by NDEA and CCl_4, the reduction rates were 45% and 56%, respectively. The rate of decline of TBARS was 50% in rats administered juice alone, chokeberry juice pretreatment was effective in inhibiting chemical-induced OS (Kujawska et al., 2011). The experimenter injected lipopolysaccharide (LPS) (200 μg per kg bw) into the Male Sprague-Dawley rats for 4 weeks, with or without Lonicera caerulea berry extract (LCBE) co-administration (50, 100 and 200 mg per kg bw intragastrically once daily). Supplementation of LCBE inhibited the increase of LPS induced Toll-like receptor (TLR) TLR2 and TLR4 expression, while prevented the generation of ROS which cause OS. LCBE supplement inhibited TLR and MAPK(mitogen-activated protein kinase) signaling and OS pathways(Y. Wang et al., 2016), supplemented with blueberry extract, the ROS level was also reduced in acrylamide-stimulated rats(M. Zhao et al., 2015), thus they play a defensive role for the occurrence of some diseases.

ORAC (oxygen radical absorbance capacity) and FRAP (ferric reducing antioxidant capacity) analyses showed that berries have a high resistance to OS in vitro (Hurst et al., 2010; White et al., 2010). However, in vivo some research found that berries effects were not through their antioxidant cleared capabilities. Some studies suggested that polyphenols of berries work through activated or restrained signaling processes of various cells. For example, the phenolic modulated the activity of kinase and caused activation of the transcription factor (e.g., Nrf-2, NF-κB), changed activation of receptor (PRR dimerization) and activity of possible direct ligand (e.g., PPAR-γ) (Scalbert et al., 2005; Tangney et al., 2013).

Berries and Berry bioactive compounds effect on endothelial function

Regularly intake of some berries or berries products may improve the endothelial function, several berries were effective inducers of endothelium-dependent relaxations in the porcine coronary artery (Auger et al., 2011). Vascular endothelium normal function damage leads to endothelial dysfunction, endothelial dysfunction is an independent predictor in CVD patients for morbidity and mortality (Cornelissen et al., 2014). At present, there are two main methods of endothelial function measurement, respectively, flow-mediated dilation (FMD) and digital pulse amplitude tonometry (PAT) (Hamburg et al., 2009). FMD and PAT were not significantly correlated, and they showed independent information for vasoreactivity. Long-term consumption of grape juice refrained the smoking-induced reduce in FMD. The research of Clifton also indicated that complemented with grape seed extract in individuals with above average vascular risk, the FMD is enhanced(Clifton, 2004).

Some short-term intervention research have found that intake of flavonoids or flavonoid-rich foods had advantageous effects for endothelial dysfunction biomarkers (Dalgard et al., 2009; Freese et al., 2004; Hooper et al., 2008). Endothelial cells lining the luminal surface of all blood vessels is a key role in the control of vascular tone in part via the release of potent vasodilators

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including nitric oxide (NO) and endothelium-derived hyperpolarizing factor (EDHF).Polyphenol-rich sources such as berries and berry products induce beneficial endothelium-dependent relaxations by raising the NO composition and the EDHF composition of the relaxation. So polyphenols stimulate the endothelial formation of major vasoprotective factors NO and EDHF and polyphenols are potent for cardiovascular system (Auger et al., 2011). The research of Youdim also showed that blueberry anthocyanins reduced H_2O_2-induced ROS in endothelial cells in rats. Polyphenols from blueberry and cranberry localized into endothelial cells then decreased vulnerability of endothelial cells at both the membrane and cytosol level. Blueberry and cranberry polyphenols also decreased TNFα induced several inflammatory mediators (IL-8, MCP-1 and ICAM-1) up-regulation involved in the leukocytes recruitment to sites of damage or inflammation along the endothelium (Youdim et al., 2002). Overweight and obese women consumed air-dried whole sea buckthorn berries reduced circulating TNFα concentrations (Lehtonen et al., 2011). So blueberry, cranberry and sea buckthorn berries have a protective effect on endothelial cells (Youdim et al., 2002). Endothelial production of adhesion molecules is stimulated by TNF-a, IL-6, and CRP (Proinflammatory cytokines),for example, E-selectin and ICAM-1 (inter-cellular adhesion molecule 1) are mediators of endothelial dysfunction in capillary and arteriolar endothelium(Landberg et al., 2011).

Polyphenol-rich berries through a redox-sensitive mechanism modulate migration of endothelial cell and formation of capillary-like tube. Improving plasma glucose and free fatty

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acids (FFA) concentrations are related to damaging endothelial function. Jackson through experiments found that compared to the PBS control ($p<0.05$), used high FFA and combinations of glucose and FFA handled human umbilical vein endothelial cells (HUVECs) ,cell migration and capillary-like tube formation were significantly reduced. In cells treated with FFA or a combination of FFA and glucose compared to cells exposed to the same nutrients/combinations alone, HUVECs pre-treated with strawberry or wild blueberry extracts, cell migration and capillary-like tube formation were significantly increased. In high blood glucose and/or FFA levels human, strawberry or wild blueberry extracts were protective for endothelial function (Jackson, 2014).

The prevention and treatment mechanism of berries and berry bioactive compounds for cancer

At present, cancer radiotherapy, surgery and chemotherapy management methods are limited, for some cancer patients, cytotoxic drugs are not easily affordable or available. In addition, radiotherapy, surgery and chemotherapy management methods are associated with adverse effects (Chidambaram et al., 2011). The chemopreventive and chemotherapeutic properties of some berries can against cancer (Kleihues et al., 2003). Healthy diet has been long proposed as an alternative strategy to reduce the risk of cancer (H. Zhang et al., 2014), 10%–70% of all cancers was correlated with diet (Bishayee et al., 2015). Most berries are rich in bioactive substances (Szajdek et al., 2008), the antioxidant activity of berry bioactive substances involved

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in scavenging ROS and preventing the generation of ROS(Tulipani et al., 2014), regulating cell cycle, participating in the genes transduction and expression about apoptosis, stimulating antioxidant enzymes, inhibiting carcinogen-induced DNA adduct formation and enhancing DNA repair (G. D. Stoner et al., 2008). For cancer prevention, berries ability to decrease DNA damage (the first step of cancer begins to generate) is seen as a good way. Bioactive compounds of berries regulate the expression of genes about DNA damage (Paredeslópez et al., 2010). These genes include XPA, DNL3, ERCC5, CYP450, CYP3A4, MAPK14 and MAPKK (H. S. Aiyer et al., 2008; Harini S Aiyer et al., 2008). Berries also had preventive effects against colon cancer through modulated multiple signaling pathways such as NF-κB, Wnt/β-catenin, PI3K/AKT/PKB/mTOR, and ERK/MAPK(Afrin et al., 2016). In healthy female volunteers, supplementation with 1L/d of a mixture of blueberry and apple juices for 4 weeks, the levels of H_2O_2-induced DNA damage was significantly reduced(Wilms et al., 2007).

Stoner et al used carcinogen N-nitrosomethylbenzylamine (NMBA) treated rats for 5 weeks, then added 5% berries (black raspberries, red raspberries, strawberries, blueberries, noni, açaí or wolfberry) to the diet until the end of the study. The researchers determined tumor incidence, multiplicity and size to investigate the antitumor effect of berries. All berries had equally effective in inhibit tumorigenesis induced by NMBA in the rat esophagus. The levels of the serum cytokines, interleukin 5 (IL-5) and GRO/KC were also reduced in the study, which was the prediction of the inhibitory effect of chemopreventive agents on rat esophageal carcinogenesis(Gary D. Stoner et al., 2010). Black raspberries have the potential to prevent cancer, it rich in ellagitannins and anthocyanins, which have chemopreventive potential (Cerdá et al., 2005; L. S. Wang et al., 2009). Dietary freeze-dried powder of black raspberries prevented carcinogen-induced esophagus and colon tumors in rat (Kresty et al., 2001) and estrogen-induced tumors in the rat mammary gland (Harini S. Aiyer et al., 2008). Angiogenesis is critical to tumor growth and metastasis .The black raspberry powder (BRB) down-regulated the expression of c-Jun, cyclooxygenase-2(COX-2), and inducible nitric oxide synthase (iNOS). The down-regulation of vascular endothelial growth factor (VEGF) was correlated with inhibition of COX-2 and iNOS. VEGF was a crucial angiogenic activator, the VEGF expression was obviously inhibited by BRB from a (2.38±0.34)-fold increase in animals treated with NMBA alone to a (1.08 ±0.22)-fold increase in animals treated with NMBA plus BRB ($p < 0.005$) (T. Chen, Rose, et al., 2006). The extracts of black raspberry induced cytotoxic effects in colon cancer HT-29 and HCT-116 cells, exerted important pro-apoptotic functions of the COX-2 expressing HT-29 cells (Seeram et al., 2006). The chemopreventive activity of ellagitannins and their derivatives from black raspberry seeds acted on HT-29 cells were investigated. Ellagitannins, hydrolyzed to ellagic acid and further metabolized to urolithin A and urolithin B, showed anti-cancer activity by: (i) suppressing cell proliferation; (ii) preventing the cell cycle at G1 and G2/M phase (iii) inducing apoptosis by external and inner apoptotic pathways(Cho et al., 2015). The ethanol extract isolated from Goji berry(EEGB) extremely reduced human T47D cell proliferation. At the concentration of 1 mg/mL, after 24 h, 48 h and 96 h, the extract decreased cell proliferation for 70%, 55.7% and 51.4% of control cells respectively. IC50 was 0.75 mg/mL (96 h). The most significant effect appeared when T47D cells were treated with 1 mg/mL EEGB, which inhibited proliferation up for 75%(Wawruszak et al., 2015). The anticancer mechanism of Goji berry may be attributed to the reduced expression of cell cycle-regulated proteins, including $p21^{waf1}$, cyclins A, B, D, CDK's and p53(Mao et al., 2011). The p53 is a tumor suppressor (transcriptional factor) that controls cell cycle, apoptosis and DNA repair mechanisms (Rodrigues et al., 1990). In recent years, berries have received a high degree of attention because of their ability to inhibit chemically-induced colon and esophageal cancers in animal models (Harris et al., 2001; Gary D. Stoner et al., 2010). The raspberry extract had great protective effects against H_2O_2 induced DNA damage in the colon cancer cells. Under the simulated intestinal physiochemical conditions, human HT-29 colon cancer cells treated by red raspberry extract in the G1 phase of the cell cycle were significantly reduced. In a matrigel invasion assay, raspberry extract also obviously repressed the invasion of HT-115 colon cancer cells(Coates et al., 2007). Blueberry and black raspberry had a very significant inhibitory effect for breast cancer in the rat model (Harini S. Aiyer et al., 2008; Ravoori et al., 2011). Lyophilized black raspberries (LBRs) inhibited AOM-induced colon carcinogenesis in rats, when fed rats at 2.5%, 5.0% and 10% LBRs of the diet, the incidence of tumor did not be reduced, but the total tumor (adenoma & adenocarcinoma) multiplicity was reduced by 42%, 45% and 71% ($P < 0.05$) relative to AOM

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controls respectively(Harris et al., 2001). In vitro and in vivo, berries and its phytochemicals have great therapeutic activity against lung cancer (Ho et al., 2010), breast cancer and prostate cancer (Adams et al., 2010; Hafeez et al., 2008; Nguyen et al., 2010).

Kausar et al used combination of suboptimal concentrations of equimolar anthocyanidins synergistically of berries suppressed growth of two aggressive non-small-cell lung cancer cell lines, found that a variety of berries mixture of diverse anthocyanidins had therapeutic effect for non-small-cell lung cancer and prevented its future recurrence and metastasis. The outstanding actions of the combinatorial therapy probably resulted from its effects on the oncogenic Notch and WNT pathways and their downstream targets (b-catenin, c-myc, cyclin D1, cyclin B1, pERK, MMP9 and VEGF proteins), increased cleavage of the apoptotic mediators Bcl-2 and PARP and increased suppression of TNF-a -induced NF-kappa B activation. The native mixture of anthocyanidins from bilberry with the concentration of 0.5 mg/mouse obviously suppressed the growth of H1299 xenografts in nude mice by about equal to 60% in vivo (Kausar et al., 2012).In preneoplastic tissues of NMBA-treated esophagus, the 5% black raspberry diet downregulated the mRNA and protein expression levels of COX-2 and c-Jun (a component of AP-1). The decrease of COX-2 and c-Jun expression correlated with the reduction of cell proliferation. The gene of c-Jun is a composition of the transcription activator(T. Chen, Hwang, et al., 2006).

The prevention and treatment mechanism of berries and berry bioactive compounds for diabetes

Diabetes is one of the most serious public health problems. Including undiagnosed cases of diabetes, the number of diabetes patients is expected to reach 592 million by 2030(Aguiree et al., 2013; Wild et al., 2004). The WHO has reported that there were about 422 million diabetes patients in 2014(Roglic, 2016). It is more cost-effective that preventing the development of diabetes than treating its manifestation and complications (Thomas et al., 2012). Diabetes cannot be cured, only be prevented and managed. So stymieing the development of the disease is important to halt its progressively increasing morbidity(Pucel, 2013). Glucosidase inhibitor, insulin sensitizer, biguanides and other types of oral hypoglycemic agents have been synthesized to treat diabetes mellitus. However, their clinical applications are limited by side effects such as liver damage, diarrhea and lactic acidosis(M. Huang et al., 2015). In recent years, some natural agents have shown apparent therapeutic potential for diabetes mellitus because of their non-toxic and non-negative effects compared with synthetic drugs(Jiang et al., 2013), berries belongs to one of the natural agents.

Diabetes is a chronic metabolic disease associated with aging. In vivo, a study of mice has shown that dietary intake of cranberry can protect the islet cells from morphological and functional decline. Cranberry consumption inhibited two enzymes of starch digestion that converse maltodextrin into absorbable monosaccharides. The inhibitory of these enzymes improved the metabolic balance, delayed age-related recession in essential insulin, improved pancreatic cell glucose response and increased cell quality in normal elderly rats(Zhu et al.,

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2011). El-Baz treated rats with STZ and induced diabetes, the levels of TNF-α, IL-1β, TGF-β, apoptosis rates , alterations of the pro-apoptosis (eotaxin, caspase-1, and caspase-2) and inflammation , nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB1) and allograft inflammatory factor 1 (AIF-1) related genes were increased . While marked decrease in PON1 level was detected in STZ-induced diabetic rats. After used red and white berry extracts treated STZ-exposed rats, TNF-α, IL--1β, TGF-β levels, PON1 activity, low apoptosis rates were ameliorated, the alteration of the pro-apoptosis and inflammatory related genes were decreased (El-Baz et al., 2016). The mulberry extracts were administrated to diabetic rats in drinking water for five weeks, glucose level of diabetic rats had a significant decrease from the start day to the final of experiment, the value drops from 252 mg/dL to 155 mg/dL($p<0.05$) (Ştefãnuţ et al., 2013).

Hyperglycemia induces apoptosis of renal cells result in diabetic nephropathy (Krijnen et al., 2009). Dipeptidylpeptidase IV (DPP-IV) has incretin hormone regulatory effects, it is a serine aminopeptidase and a novel target for type 2 diabetes therapy. Berries were the most important contributors to reduce the risk of T2D (Knekt et al., 2002). Used a luminescence assay and computational modeling investigated inhibitory effects on DPP-IV of some well-characterized anthocyanins (ANC) isolated from berries, ANC isolated from blueberry-blackberry wine blends strongly inhibited DPP-IV activity (IC50, 0.07±0.02 to >300μM). Luteolin (0.12±0.01μM), apigenin (0.14±0.02μM), and flavone (0.17±0.01μM) were potent DPP-IV inhibitors, with IC 50 values lower than diprotin A (4.21±2.01μM) which is a reference standard inhibitory compound. Flavone was competitive inhibitor which docked directly into all three active sites of DPP-IV, while luteolin and apigenin docked in a noncompetitive manner. The main binding mode of all tested phenolic compounds with DPP-IV was Hydrogen bonding. Flavonoids, particularly luteolin, apigenin, and flavone act as naturally occurring DPP-IV inhibitors (Fan et al., 2013). Anthocyanins protect beta-cells that enhance the secretion of insulin, decreasing the digestion of sugars in the small intestine with multiple and simultaneous antidiabetic effects. Inhibitors of DPP-IV prevent pancreatic beta cell destruction in mice (Weber, 2004). The extracts enriched in flavonoids inhibited plasma DPP-IV (Bansal et al., 2012).

Polyphenols dietary effects of berries for diabetic patients include: protection of pancreatic-cells against glucose toxicity, anti-inflammatory and antioxidant effects, inhibition of starch digestion by inhibition of digestion enzymes, improvement of insulin resistance and inhibition of advanced glycation end products (AGEs) formation(S. Chen et al., 2016; Hui et al., 2015). The activity of glucosidase enzymes such as R-amylase was decreased by strawberry, blueberry, and raspberry extracts(Mcdougall et al., 2005), they reduced postprandial hyperglycemic episodes, stimulated glucose uptake in various cell models such as C2C12 myotubes and 3T3-L1 adipocytes (Martineau et al., 2006; Vuong et al., 2007). In addition, glycosylated anthocyanins actively regulated genetic markers associated with obesity(Tsuda et al., 2005). Anthocyanins suppressed the onset of obesity in high-fat diet rats, affected adipocyte gene

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expression level and adipocytokine secretion (Tsuda et al., 2003; Tsuda et al., 2004). Insulin sensitivity is associated with activation of AMP-activated protein kinase (AMPK). The AMPK pathway regulates energy homeostasis(Hardie, 2007), glucose uptake and insulin sensitivity. Choi et al evaluated the effect of mulberry fruit extract (MFE) on hyperglycemia and insulin sensitivity in an animal model of T2D, in the MFE-supplemented group, the blood levels of glucose and HbA1c were significantly lowered than in the diabetic control group. MFE treatment also increased insulin sensitivity. MFE dietary obviously adjusted the levels of phosphorylated (p)-AMP-activated protein kinase (pAMPK) and p-Akt substrate of 160kDa (pAS160) and enhanced the level of plasma membrane-glucose transporter 4 (GLUT4) in skeletal muscles, so MFE is a potential treatment for alleviating hyperglycemia in T2D (Choi et al., 2016).

DISCUSSION

Berry bioactive ingredients has excellent medical and health care function, in vitro and in vivo studies suggested that most of them had effects of antioxidant effects, removed free radicals in the body, protected DNA, regulated cellular metabolism and apoptosis. They have significant prevention and treatment effect for CVD, cancer and diabetes. With the development of the economy, the change of people's lifestyles and the acceleration of the population aging, the major diseases that threaten human beings become chronic non-communicable diseases, while diet is closely related to chronic non-communicable diseases. The berries have the effect of protect or reduce the risk and the occurrence of several chronic pathologies, and it is considerable high

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nutritional value which could be developed for functional food benefits for human health. With the continuous improvement of people's living standards, people's attitude towards their own disease has been gradually turned to that prevention is equal important as treatment, berries because of its prevention effect is increasingly favored by mankind and becomes the most development potential health food. In addition, the techniques of extraction, separation, purification and material structure identification of various bioactive components in berries need to be improved to ensure the reliability and accuracy of the efficacy test. The study of the physiological function and bioactive substances of berries need to be further strengthened, not only limited to the study of the physiological effects of some berries, but also clarify the effective bioactive substances in berries and its structural characteristics and mechanism of action. With the further development of research at the molecular level, the specific physiological effects of each bioactive substance in each berry will be further revealed.

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Compliance with Ethical Standards

The authors declare that they have no conflict of interest to this work. This article does not contain any studies with human participants or animals performed by any of the authors. Informed consent was obtained from all individual participants included in the study.

References

Adams, L. S., Phung, S., Yee, N., Seeram, N. P., Li, L., and Chen, S. (2010). Blueberry phytochemicals inhibit growth and metastatic potential of MDA-MB-231 breast cancer cells through modulation of the phosphatidylinositol 3-kinase pathway. *Cancer Research.* **70**(9): 3594-3605.

Afrin, S., Giampieri, F., Gasparrini, M., Forbes-Hernandez, T. Y., Varela-López, A., Quiles, J. L., Mezzetti, B., and Battino, M. (2016). Chemopreventive and Therapeutic Effects of Edible Berries: A Focus on Colon Cancer Prevention and Treatment. *Molecules.* **21**(2): 169.

Aguiree, F., Brown, A., Cho, N. H., Dahlquist, G., Dodd, S., Dunning, T., Hirst, M., Hwang, C., Magliano, D., and Patterson, C. (2013). IDF Diabetes Atlas : sixth edition. *International Diabetes Federation.*

Aiyer, H. S., Kichambare, S., and Gupta, R. C. (2008). Prevention of oxidative DNA damage by bioactive berry components. *Nutrition & Cancer-an International Journal.* **60**(sup1):

36-42.

Aiyer, H. S., Srinivasan, C., and Gupta, R. C. (2008). Dietary berries and ellagic acid diminish estrogen-mediated mammary tumorigenesis in ACI rats. *Nutrition & Cancer.* **60**(2): 227-234.

Aiyer, H. S., Vadhanam, M. V., Radka, S., Caprio, G. D., Clapper, M. L., and Gupta, R. C. (2008). Dietary Berries and Ellagic Acid Prevent Oxidative DNA Damage and Modulate Expression of DNA Repair Genes. *International Journal of Molecular Sciences.* **9**(3): 327-341.

Amigo, L., Quiñones, V., Leiva, A., Busso, D., Zanlungo, S., Nervi, F., and Rigotti, A. (2011). Apolipoprotein A-I deficiency does not affect biliary lipid secretion and gallstone formation in mice. *Liver International.* **31**(2): 263-271.

Auger, C., Kim, J. H., Trinh, S., Chataigneau, T., Popken, A. M., and Schini-Kerth, V. B. (2011). Fruit juice-induced endothelium-dependent relaxations in isolated porcine coronary arteries: evaluation of different fruit juices and purees and optimization of a red fruit juice blend. *Food & Function.* **2**(5): 245-250.

B, O., B, W., P, N., M, K., A, T., A, S., W, O., A, J., and J, P. (2008). Studies on antioxidant properties of polyphenol-rich extract from berries of Aronia melanocarpa in blood platelets. *Journal of Physiology & Pharmacology An Official Journal of the Polish Physiological Society.* **59**(4): 823.

Baiges, I., Palmfeldt, J., Bladé, C., Gregersen, N., and Arola, L. (2010). Lipogenesis Is Decreased by Grape Seed Proanthocyanidins According to Liver Proteomics of Rats Fed a High Fat Diet. *Molecular & Cellular Proteomics Mcp.* **9**(7): 1499.

Bailey, C. J., and Day, C. (2004). Avandamet: combined metformin–rosiglitazone treatment for insulin resistance in type 2 diabetes. *International Journal of Clinical Practice.* **58**: 867-876.

Bansal, P., Paul, P., Mudgal, J., Nayak, P. G., Pannakal, S. T., Priyadarsini, K. I., and Unnikrishnana, M. K. (2012). Antidiabetic, antihyperlipidemic and antioxidant effects of the flavonoid rich fraction of Pilea microphylla (L.) in high fat diet/streptozotocin-induced diabetes in mice. *Experimental & Toxicologic Pathology Official Journal of the Gesellschaft Fur Toxikologische Pathologie.* **64**(6): 651-658.

Berliner, J. A., Navab, M., Fogelman, A. M., Frank, J. S., Demer, L. L., Edwards, P. A., Watson, A. D., and Lusis, A. J. (1995). Atherosclerosis: basic mechanisms. *Circulation.* **91**(9): 2488-2496.

Bijak, M., Bobrowski, M., Borowiecka, M., Podsędek, A., Golański, J., and Nowak, P. (2011). Anticoagulant effect of polyphenols-rich extracts from black chokeberry and grape seeds. *Phytotherapy Research.* **82**(6): 811-817.

Bishayee, A., Haskell, Y., Do, C., Siveen, K. S., Mohandas, N., Sethi, G., and Stoner, G. D. (2015). Potential Benefits of Edible Berries in the Management of Aerodigestive and

Gastrointestinal Tract Cancers: Preclinical and Clinical Evidence. *Critical Reviews in Food Science & Nutrition.* **56**(10): 1753.

Bornsek, S. M., Ziberna, L., Polak, T., Vanzo, A., Ulrih, N. P., Abram, V., Tramer, F., and Passamontib, S. (2012). Bilberry and blueberry anthocyanins act as powerful intracellular antioxidants in mammalian cells. *Food Chemistry.* **134**(4): 1878-1884.

Braga, P. C., Antonacci, R., Wang, Y. Y., Lattuada, N., Dal, S. M., Marabini, L., Fibiani, M., and Lo, S. R. (2013). Comparative antioxidant activity of cultivated and wild Vaccinium species investigated by EPR, human neutrophil burst and COMET assay. *European Review for Medical & Pharmacological Sciences.* **17**(15): 1987-1999.

Cerdá, B., Tomás-Barberán, F. A., and Espín, J. C. (2005). Metabolism of Antioxidant and Chemopreventive Ellagitannins from Strawberries, Raspberries, Walnuts, and Oak-Aged Wine in Humans: Identification of Biomarkers and Individual Variability. *Journal of Agricultural & Food Chemistry.* **53**(2): 227-235.

Chan, K. C., Ho, H. H., Lin, M. C., Huang, C. N., Huang, H. P., and Wang, C. J. (2016). Impact of polyphenolic components from mulberry on apoptosis of vascular smooth muscle cells. *Journal of the Science of Food & Agriculture.* **96**(2): 381-391.

Chen, S., Jiang, H., Wu, X., and Fang, J. (2016). Therapeutic Effects of Quercetin on Inflammation, Obesity, and Type 2 Diabetes. *Mediators of Inflammation,2016,(2016-11-28).* **2016**(3): 1-5.

Chen, T., Hwang, H., Rose, M. E., Nines, R. G., and Stoner, G. D. (2006). Chemopreventive properties of black raspberries in N-nitrosomethylbenzylamine-induced rat esophageal tumorigenesis: down-regulation of cyclooxygenase-2, inducible nitric oxide synthase, and c-Jun. *Cancer Research.* **66**(5): 2853-2859.

Chen, T., Rose, M. E., Hwang, H., Nines, R. G., and Stoner, G. D. (2006). Black raspberries inhibit N-nitrosomethylbenzylamine (NMBA)-induced angiogenesis in rat esophagus parallel to the suppression of COX-2 and iNOS. *Carcinogenesis.* **27**(11): 2301-2307.

Chidambaram, M., Manavalan, R., and Kathiresan, K. (2011). Nanotherapeutics to overcome conventional cancer chemotherapy limitations. *Journal of pharmacy & pharmaceutical sciences : a publication of the Canadian Society for Pharmaceutical Sciences, Societe canadienne des sciences pharmaceutiques.* **14**(1): 67.

Cho, H., Jung, H., Lee, H., Yi, H. C., Kwak, H. K., and Hwang, K. T. (2015). Correction: Chemopreventive activity of ellagitannins and their derivatives from black raspberry seeds on HT-29 colon cancer cells. *Food & Function.* **6**(8): 2861-2861.

Choi, K. H., Lee, H. A., Park, M. H., and Han, J. S. (2016). Mulberry (Morus alba L.) Fruit Extract Containing Anthocyanins Improves Glycemic Control and Insulin Sensitivity via Activation of AMP-Activated Protein Kinase in Diabetic C57BL/Ksj-db/db Mice. *Journal of Medicinal Food.* **19**(8): 737.

Clifton, P. M. (2004). Effect of Grape Seed Extract and Quercetin on Cardiovascular and

Endothelial Parameters in High-Risk Subjects. *Journal of Biomedicine & Biotechnology.* **2004**(5): 272-278.

Coates, E. M., Popa, G., Gill, C. I., Mccann, M. J., Mcdougall, G. J., Stewart, D., and Rowland, I. (2007). Colon-available raspberry polyphenols exhibit anti-cancer effects on in vitro models of colon cancer. *Journal of Carcinogenesis.* **6**(1): 4.

Cornelissen, V. A., Onkelinx, S., Goetschalckx, K., Thomaes, T., Janssens, S., Fagard, R., Verhamme, P., and Vanhees, L. (2014). Exercise-based cardiac rehabilitation improves endothelial function assessed by flow-mediated dilation but not by pulse amplitude tonometry. *European Journal of Preventive Cardiology.* **21**(1): 39-48.

Covic, L., Gresser, A. L., and Kuliopulos, A. (2000). Biphasic kinetics of activation and signaling for PAR1 and PAR4 thrombin receptors in platelets. *Biochemistry.* **39**(18): 5458-5467.

Cuccioloni, M., Mozzicafreddo, M., Sparapani, L., Spina, M., Eleuteri, A. M., Fioretti, E., and Angeletti, M. (2009). Pomegranate fruit components modulate human thrombin. *Fitoterapia.* **80**(5): 301-305.

Dalgard, C., Nielsen FMorrow, J. D., Enghusen-Poulsen, H., Jonung, T., Horder, M., and de Maat, M. P. (2009). Supplementation with orange and blackcurrant juice, but not vitamin E, improves inflammatory markers in patients with peripheral arterial disease. *British Journal of Nutrition.* **101**(2): 263-269.

Davidson, M. H., Kurlandsky, S. B., Kleinpell, R. M., and Maki, K. C. (2010). Lipid management and the elderly. *Prev Cardiol.* **6**(3): 128-135.

Davinelli, S., Bertoglio, J. C., Zarrelli, A., Pina, R., and Scapagnini, G. (2015). A Randomized Clinical Trial Evaluating the Efficacy of an Anthocyanin-Maqui Berry Extract (Delphinol®) on Oxidative Stress Biomarkers. *Journal of the American College of Nutrition.* **34**(sup1): 28-33.

De, P. S., Moreno, D. A., and Garcíaviguera, C. (2010). Flavanols and anthocyanins in cardiovascular health: a review of current evidence. *International Journal of Molecular Sciences.* **11**(4): 1679.

El-Baz, F. K., Khalil, W. K. B., Aly, H. F., and Booles, H. F. (2016). Berry extracts improved inflammatory cytokines, antioxidant enzyme and suppressed the gene expression alterations in diabetic rats.

Erlund, I., Koli, R., Alfthan, G., Marniemi, J., Puukka, P., Mustonen, P., Mattila, P., and Jula, A. (2008). Favorable effects of berry consumption on platelet function, blood pressure, and HDL cholesterol. *The American journal of clinical nutrition.* **87**(2): 323-331.

Fan, J., Johnson, M. H., Lila, M. A., Yousef, G., and Mejia, E. G. D. (2013). Berry and Citrus Phenolic Compounds Inhibit Dipeptidyl Peptidase IV: Implications in Diabetes Management. *Evidence-based complementary and alternative medicine : eCAM.* **2013**(3): 479505.

ACCEPTED MANUSCRIPT

Ferlay, J., Shin, H. R., Bray, F., Forman, D., Mathers, C., and Parkin, D. M. (2010). Cancer incidence and mortality worldwide: IARC CancerBase No. *International Journal of Cancer Journal International Du Cancer.* **136**(5): E359–E386.

Fernandes, I., Marques, F., De, F. V., and Mateus, N. (2013). Antioxidant and antiproliferative properties of methylated metabolites of anthocyanins. *Food Chemistry.* **141**(3): 2923-2933.

Fernandez, M. L., and Barona, J. (2016). *Grapes and Atherosclerosis*: Springer International Publishing.

Freese, R., Vaarala, O., Turpeinen, A. M., and Mutanen, M. (2004). No difference in platelet activation or inflammation markers after diets rich or poor in vegetables, berries and apple in healthy subjects. *European Journal of Nutrition.* **43**(3): 175-182.

Giampieri, F., Forbes-Hernandez, T. Y., Gasparrini, M., Alvarez-Suarez, J. M., Afrin, S., Bompadre, S., Quiles, J. L., Mezzetti, B., and Battino, M. (2015). Strawberry as a health promoter: an evidence based review. *Food & Function.* **6**(5): 1386-1398.

Hafeez, B. B., Siddiqui, I. A., Asim, M., Malik, A., Afaq, F., Adhami, V. M., Saleem, M., Din, M., and Mukhtar, H. (2008). A Dietary Anthocyanidin Delphinidin Induces Apoptosis of Human Prostate Cancer PC3 Cells In vitro and In vivo: Involvement of Nuclear Factor-κB Signaling. *Cancer Research.* **68**(20): 8564-8572.

Hamburg, N. M., and Benjamin, E. J. (2009). Assessment of endothelial function using digital

ACCEPTED MANUSCRIPT

pulse amplitude tonometry. *Trends Cardiovasc Med.* **19**(1): 6.

Hardie, D. G. (2007). AMP-Activated Protein Kinase as a Drug Target. *Annual Review of Pharmacology & Toxicology.* **47**(1): 185-210.

Harris, G. K., Gupta, A., Nines, R. G., Kresty, L. A., Habib, S. G., Frankel, W. L., Laperle, K., Gallaher, D. D., Schwartz, S. J., and Stoner, G. D. (2001). Effects of lyophilized black raspberries on azoxymethane-induced colon cancer and 8-hydroxy-2'-deoxyguanosine levels in the Fischer 344 rat. *Nutrition & Cancer.* **40**(2): 125-133.

Hjartåker, A., Knudsen, M. D., Tretli, S., and Weiderpass, E. (2015). Consumption of berries, fruits and vegetables and mortality among 10,000 Norwegian men followed for four decades. *European Journal of Nutrition.* **54**(4): 599-608.

Ho, M. L., Chen, P. N., Chu, S. C., Kuo, D. Y., Kuo, W. H., Chen, J. Y., and Hsieh, Y. S. (2010). Peonidin 3-glucoside inhibits lung cancer metastasis by downregulation of proteinases activities and MAPK pathway. *Nutrition & Cancer.* **62**(4): 505-516.

Hooper, L., Kroon, P. A., Rimm, E. B., Cohn, J. S., Harvey, I., Le, C. K., Ryder, J. J., Hall, W. L., and Cassidy, A. (2008). Flavonoids, flavonoid-rich foods, and cardiovascular risk: a meta-analysis of randomized controlled trials. *American Journal of Clinical Nutrition.* **88**(1): 38-50.

Huang, H. P., Chang, Y. C., Wu, C. H., Hung, C. N., and Wang, C. J. (2011). Anthocyanin-rich Mulberry extract inhibit the gastric cancer cell growth in vitro and xenograft mice by inducing signals of p38/p53 and c-jun. *Food Chemistry.* **129**(4): 1703-1709.

Huang, M., Wang, F., Zhou, X., Yang, H., and Wang, Y. (2015). Hypoglycemic and hypolipidemic properties of polysaccharides from Enterobacter cloacae Z0206 in KKAy mice. *Carbohydrate polymers.* **117**: 91-98.

Hui, C., Xie, Y., and Chen, X. (2015). Type 2 diabetes diminishes the benefits of dietary antioxidants: Evidence from the different free radical scavenging potential. *Food Chemistry.* **186**: 106-112.

Hurst, R. D., Wells, R. W., Hurst, S. M., Mcghie, T. K., Cooney, J. M., and Jensen, D. J. (2010). Blueberry fruit polyphenolics suppress oxidative stress‐induced skeletal muscle cell damage in vitro. *Molecular Nutrition & Food Research.* **54**(3): 353-363.

Iff, B., and Wachtel-Galor, S. (2011). Bilberry (Vaccinium myrtillus L.) -- Herbal Medicine: Biomolecular and Clinical Aspects. *Crc Press.* 172–210.

Jackson, L. S. (2014). Polyphenol-rich fruits attenuate impaired endothelial function induced by glucose and free fatty acids in vitro in human endothelial cells. *International Journal of Food Science Nutrition & Dietetics.* **3**: 99-108.

Jiang, S., Du, P., An, L., Yuan, G., and Sun, Z. (2013). Anti-diabetic effect of Coptis Chinensis polysaccharide in high-fat diet with STZ-induced diabetic mice. *International Journal of Biological Macromolecules.* **55**(3): 118-122.

Jin, L. I., Wei-Jing, Q. U., Liu, C., and Shi, D. H. (2007). Effect of Lycium ruthenicum Pigment

ACCEPTED MANUSCRIPT

on Blood Lipids Level and Lipid Peroxidation in Mice with Hyperlipemia. *Food Science.*

Johansson, A. K., Korte, H., Yang, B., Stanley, J. C., and Kallio, H. P. (2000). Sea buckthorn berry oil inhibits platelet aggregation. *Journal of Nutritional Biochemistry.* **11**(10): 491-495.

Joseph, J. A., Shukitthale, B., Denisova, N. A., Bielinski, D., Martin, A., Mcewen, J. J., and Bickford, P. C. (1999). *Reversals of age-related declines in neuronal signal transduction, cognitive, and motor behavioral deficits with blueberry, spinach, or strawberry dietary supplementation*: Brookings Institution.

Kähkönen, M. P., and Heinonen, M. (2003). Antioxidant activity of anthocyanins and their aglycons. *Journal of Agricultural & Food Chemistry.* **51**(3): 628-633.

Kausar, H., Jeyabalan, J., Aqil, F., Chabba, D., Sidana, J., Singh, I. P., and Gupta, R. C. (2012). Berry anthocyanidins synergistically suppress growth and invasive potential of human non-small-cell lung cancer cells. *Cancer Letters.* **325**(1): 54-62.

Kedzierska, M., Olas, B., Wachowicz, B., Stochmal, A., Oleszek, W., Jeziorski, A., Piekarski, J., and Glowacki, R. (2009). An extract from berries of Aronia melanocarpa modulates the generation of superoxide anion radicals in blood platelets from breast cancer patients. *Planta Medica.* **75**(13): 1405-1409.

Kellogg, J., Wang, J., Flint, C., Ribnicky, D., Kuhn, P., De Mejia, E. G., Raskin, I., and Lila, M. A. (2010). Alaskan wild berry resources and human health under the cloud of climate change. *Journal of Agricultural & Food Chemistry.* **58**(7): 3884-3900.

Kim, B., Ku, C. S., Pham, T. X., Park, Y., Martin, D. A., Xie, L., Taheri, R., Lee, J., and Bolling, B. W. (2013). Aronia melanocarpa (chokeberry) polyphenol-rich extract improves antioxidant function and reduces total plasma cholesterol in apolipoprotein E knockout mice. *Nutrition Research.* **33**(5): 406-413.

Kim, J. Y., Hong, J. H., Jung, H. K., Jeong, Y. S., and Cho, K. H. (2012). Grape skin and loquat leaf extracts and acai puree have potent anti-atherosclerotic and anti-diabetic activity in vitro and in vivo in hypercholesterolemic zebrafish. *International Journal of Molecular Medicine.* **30**(3): 606-614.

Kleihues, P., and Stewart, B. W. (2003). World Cancer Report.

Knekt, P., Kumpulainen, J., Järvinen, R., Rissanen, H., Heliövaara, M., Reunanen, A., Hakulinen, T., and Aromaa, A. (2002). Folate intake and risk of Parkinson's disease.

Kresty, L. A., Morse, M. A., Morgan, C., Carlton, P. S., Lu, J., Gupta, A., Blackwood, M., and Stoner, G. D. (2001). Chemoprevention of esophageal tumorigenesis by dietary administration of lyophilized black raspberries. *Cancer Research.* **61**(16): 6112-6119.

Krijnen, P. A. J., Suat, S., and Niessen, H. W. M. (2009). Apoptosis in diabetes. *Apoptosis.* **14**(12): 1387-1388.

Kujawska, M., Ignatowicz, E., Ewertowska, M., Oszmiański, J., and Jodynisliebert, J. (2011). Protective effect of chokeberry on chemical-induced oxidative stress in rat. *Human &*

Experimental Toxicology. **30**(3): 199-208.

Landberg, R., Sun, Q., Rimm, E. B., Cassidy, A., Scalbert, A., Mantzoros, C. S., Hu, F. B., and van Dam, R. M. (2011). Selected dietary flavonoids are associated with markers of inflammation and endothelial dysfunction in U.S. women. *Journal of Nutrition.* **141**(4): 618-625.

Larmo, P. S., Kangas, A. J., Soininen, P., Lehtonen, H. M., Suomela, J. P., Yang, B., Viikari, J., Alakorpela, M., and Kallio, H. P. (2013). Effects of sea buckthorn and bilberry on serum metabolites differ according to baseline metabolic profiles in overweight women: a randomized crossover trial. *American Journal of Clinical Nutrition.* **98**(4): 941-951.

Lehtonen, H. M., Suomela, J. P., Tahvonen, R., Yang, B., Venojärvi, M., Viikari, J., and Kallio, H. (2011). Different berries and berry fractions have various but slightly positive effects on the associated variables of metabolic diseases on overweight and obese women. *European Journal of Clinical Nutrition.* **65**(3): 394-401.

Liao, F. H., Shieh, M. J., Chang, N. C., and Chien, Y. W. (2007). Chitosan supplementation lowers serum lipids and maintains normal calcium, magnesium, and iron status in hyperlipidemic patients. *Nutrition Research.* **27**(3): 146-151.

Libby, P., Okamoto, Y., Rocha, V. Z., and Folco, E. (2010). Inflammation in atherosclerosis: transition from theory to practice. *Circulation Journal Official Journal of the Japanese Circulation Society.* **74**(2): 213-220.

ACCEPTED MANUSCRIPT

Licari, L. G., and Kovacic, J. P. (2010). Thrombin physiology and pathophysiology. *Journal of Veterinary Emergency & Critical Care.* **19**(1): 11-22.

Lin, L., Li, J., Lv, H., Ma, Y., and Qian, Y. (2012). [Effect of Lycium ruthenicum anthocyanins on atherosclerosis in mice]. *China Journal of Chinese Materia Medica.* **37**(10): 1460.

Listed, N. (1995). Summary of the national guidelines for the diagnosis and management of lipid disorders in Taiwan. The experts panel. *Zhonghua yi xue za zhi = Chinese medical journal; Free China ed.* **55**(1): 1-14.

Liu, W., Lu, X., He, G., Gao, X., Li, M., Wu, J., Li, Z., Wu, J., Wang, J., and Luo, C. (2013). Cytosolic protection against ultraviolet induced DNA damage by blueberry anthocyanins and anthocyanidins in hepatocarcinoma HepG2 cells. *Biotechnology Letters.* **35**(4): 491-498.

Mao, F., Xiao, B., Jiang, Z., Zhao, J., Huang, X., and Guo, J. (2011). Anticancer effect of Lycium barbarum polysaccharides on colon cancer cells involves G0/G1 phase arrest. *Medical Oncology.* **28**(1): 121-126.

Martineau, L. C., Couture, A., Spoor, D., Benhaddou-Andaloussi, A., Harris, C., Meddah, B., Leduc, C., Burt, A., Vuong, T., and Le, P. M. (2006). Anti-diabetic properties of the Canadian lowbush blueberry Vaccinium angustifolium Ait. *Phytomedicine International Journal of Phytotherapy & Phytopharmacology.* **13**(9): 612-623.

Mazzoni, L., Perezlopez, P., Giampieri, F., Alvarezsuarez, J. M., Gasparrini, M., Forbeshernandez, T. Y., Quiles, J. L., Mezzetti, B., and Battino, M. (2016). The genetic aspects of berries: from field to health. *Journal of the Science of Food & Agriculture.* **96**(2): 365-371.

Mcdougall, G. J., Shpiro, F., Dobson, P., Smith, P., Blake, A., and Stewart, D. (2005). Different polyphenolic components of soft fruits inhibit alpha-amylase and alpha-glucosidase. *Journal of Agricultural & Food Chemistry.* **53**(7): 2760-2766.

Michelson, A. D. (2010). Antiplatelet therapies for the treatment of cardiovascular disease. *Nature Reviews Drug Discovery.* **9**(2): 154.

Mozzicafreddo, M., Cuccioloni, M., Eleuteri, A. M., Fioretti, E., and Angeletti, M. (2006). Flavonoids inhibit the amidolytic activity of human thrombin. *Biochimie.* **88**(9): 1297-1306.

Natella, F., Ghiselli, A., Guidi, A., Ursini, F., and Scaccini, C. (2001). Red wine mitigates the postprandial increase of LDL susceptibility to oxidation. *Free Radical Biology and Medicine.* **30**(9): 1036-1044.

Nguyen, V., Tang, J., Oroudjev, E., Lee, C. J., Marasigan, C., Wilson, L., and Ayoub, G. (2010). Cytotoxic effects of bilberry extract on MCF7-GFP-tubulin breast cancer cells. *Journal of Medicinal Food.* **13**(2): 278-285.

Nile, S. H., and Park, S. W. (2014). Edible berries: Bioactive components and their effect on human health. *Nutrition.* **30**(2): 134-144.

ACCEPTED MANUSCRIPT

Noda, Y., Kneyuki, T., Igarashi, K., Mori, A., and Packer, L. (2005). Antioxidant activity of nasunin, an anthocyanin in eggplant peels. *Research Communications in Molecular Pathology & Pharmacology.* **53**(16): 6272-6275.

Nurden, A. T. (2011). Platelets, inflammation and tissue regeneration. *Thrombosis & Haemostasis.* **1**(Suppl. 1): 13-33.

Paredeslópez, O., Cervantesceja, M. L., Vignapérez, M., and Hernándezpérez, T. (2010). Berries: improving human health and healthy aging, and promoting quality life - a review. *Plant Foods for Human Nutrition.* **65**(3): 299-308.

Pucel, N. W. (2013). Improvement of Functional Bioactivity in Pear:Blackberry Synergies with Lactic Acid Fermentation for Type 2 Diabetes and Hypertension Management.

Ramalingam, M., and Kim, S. J. (2012). Reactive oxygen/nitrogen species and their functional correlations in neurodegenerative diseases. *Journal of Neural Transmission.* **119**(8): 891-910.

Ramana, K. V., Srivastava, S., and Singhal, S. S. (2017). Lipid peroxidation products in human health and disease. *Oxidative Medicine & Cellular Longevity.* **2014**(4): 583438.

Ravoori, S., Kausar, H., Aqil, F., and Gupta, R. C. (2011). Abstract 1887: Distinct molecular targets of blueberry and black raspberry in breast cancer prevention. *Clinical Toxicology.* **70**(8 Supplement): 1887-1887.

Rodrigues, N. R., Rowan, A., Smith, M. E., Kerr, I. B., Bodmer, W. F., Gannon, J. V., and Lane,

D. P. (1990). p53 mutations in colorectal cancer. *Proceedings of the National Academy of Sciences of the United States of America*. **87**(19): 7555-7559.

Roglic, G. (2016). WHO Global report on diabetes: A summary. *International Journal of Noncommunicable Diseases*. **1**(1): 3.

Sano, A., Uchida, R., M, Shioya, N., Komori, Y., Tho, Y., and Hashizume, N. (2007). Beneficial effects of grape seed extract on malondialdehyde-modified LDL. *Journal of Nutritional Science & Vitaminology*. **53**(2): 174-182.

Scalbert, A., Johnson, I. T., and Saltmarsh, M. (2005). Polyphenols: antioxidants and beyond. *American Journal of Clinical Nutrition*. **81**(1 Suppl): 215S.

Seeram, N. P., Adams, L. S., Zhang, Y., Lee, R., Sand, D., Scheuller, H. S., and Heber, D. (2006). Blackberry, black raspberry, blueberry, cranberry, red raspberry, and strawberry extracts inhibit growth and stimulate apoptosis of human cancer cells in vitro. *Journal of Agricultural & Food Chemistry*. **54**(25): 9329.

Shan, T. Z., Wang, Y. Z., and Min, L. I. (2006). Cloning of Lipoprotein Lipase(LPL)Gene of Swine and the Difference of LPL Gene Expression at Different Avoirdupois Stages. *Journal of Agricultural Biotechnology*. **14**(2): 151-155.

Sorelle, R. (1999). Global epidemic of cardiovascular disease expected by the year 2050. *Circulation*. **100**(20): e101.

Ştefãnuţ, M. N., Căta, A., Pop, R., Tănasie, C., Boc, D., Ienaşcu, I., and Ordodi, V. (2013).

Anti-hyperglycemic Effect of Bilberry, Blackberry and Mulberry Ultrasonic Extracts on Diabetic Rats. *Plant Foods for Human Nutrition.* **68**(4): 378-384.

Stoner, G. D., Wang, L. S., and Casto, B. C. (2008). Laboratory and clinical studies of cancer chemoprevention by antioxidants in berries. *Carcinogenesis.* **29**(9): 1665-1674.

Stoner, G. D., Wang, L. S., Seguin, C., Rocha, C., Stoner, K., Chiu, S., and Kinghorn, A. D. (2010). Multiple Berry Types Prevent N-nitrosomethylbenzylamine-Induced Esophageal Cancer in Rats. *Pharmaceutical Research.* **27**(6): 1138-1145.

Sultana, R., Perluigi, M., and Allan, B. D. (2013). Lipid peroxidation triggers neurodegeneration: a redox proteomics view into the Alzheimer disease brain. *Free Radical Biology & Medicine.* **62**(1): 157-169.

Szajdek, A., and Borowska, E. J. (2008). Bioactive compounds and health-promoting properties of berry fruits: a review. *Plant Foods for Human Nutrition.* **63**(4): 147-156.

Takasawa, R., Saeki, K., Tao, A., Yoshimori, A., Uchiro, H., Fujiwara, M., and Tanuma, S. (2010). Delphinidin, a dietary anthocyanidin in berry fruits, inhibits human glyoxalase I. *Bioorganic & Medicinal Chemistry.* **18**(19): 7029-7033.

Tangney, C. C., and Rasmussen, H. E. (2013). Polyphenols, Inflammation, and Cardiovascular Disease. *Current Atherosclerosis Reports.* **15**(5): 324.

Thomas, T., and Pfeiffer, A. F. (2012). Foods for the prevention of diabetes: how do they work? *Diabetes/metabolism Research & Reviews.* **28**(1): 25-49.

ACCEPTED MANUSCRIPT

Traynelis, S. F., and Trejo, J. (2007). Protease-activated receptor signaling: new roles and regulatory mechanisms. *Current Opinion in Hematology.* **14**(3): 230-235.

Tsuda, T., Horio, F., Uchida, K., Aoki, H., and Osawa, T. (2003). Dietary cyanidin 3-O-beta-D-glucoside-rich purple corn color prevents obesity and ameliorates hyperglycemia in mice. *Journal of Nutrition.* **133**(7): 2125-2130.

Tsuda, T., Ueno, Y., Aoki, H., Koda, T., Horio, F., Takahashi, N., Kawada, T., and Osawa, T. (2004). Anthocyanin enhances adipocytokine secretion and adipocyte-specific gene expression in isolated rat adipocytes. *Biochemical & Biophysical Research Communications.* **316**(1): 149-157.

Tsuda, T., Ueno, Y., Kojo, H., Yoshikawa, T., and Osawa, T. (2005). Gene expression profile of isolated rat adipocytes treated with anthocyanins. *Biochimica Et Biophysica Acta.* **1733**(2): 137-147.

Tsutsumi, K. (2003). Lipoprotein lipase and atherosclerosis. *Current vascular pharmacology.* **1**(1): 11-17.

Tulipani, S., Armeni, T., Giampieri, F., Alvarezsuarez, J. M., Gonzalezparamás, A. M., Santosbuelga, C., Busco, F., Principato, G., Bompadre, S., and Quiles, J. L. (2014). Strawberry intake increases blood fluid, erythrocyte and mononuclear cell defenses against oxidative challenge. *Food Chemistry.* **156**(2): 87.

Veberic, R., Slatnar, A., Bizjak, J., Stampar, F., and Mikulic-Petkovsek, M. (2015). Anthocyanin

ACCEPTED MANUSCRIPT

composition of different wild and cultivated berry species. *LWT - Food Science and Technology.* **60**(1): 509-517.

Ventura, P., Bini, A., Panini, R., Marri, L., Tomasi, A., and Salvioli, G. (2004). Red wine consumption prevents vascular oxidative stress induced by a high-fat meal in healthy volunteers. *International Journal for Vitamin & Nutrition Research.* **74**(2): 137-143.

Vuong, T., Martineau, L. C., Ramassamy, C., Matar, C., and Haddad, P. S. (2007). Fermented Canadian lowbush blueberry juice stimulates glucose uptake and AMP-activated protein kinase in insulin-sensitive cultured muscle cells and adipocytes. *Canadian Journal of Physiology & Pharmacology.* **85**(9): 956-965.

Wang, L. S., Hecht, S. S., Carmella, S. G., Yu, N., Larue, B., Henry, C., Mcintyre, C., Rocha, C., Lechner, J. F., and Stoner, G. D. (2009). Anthocyanins in Black Raspberries Prevent Esophageal Tumors in Rats. *Cancer Prevention Research.* **2**(1): 84.

Wang, Y., Li, B., Zhu, J., Zhang, Q., Zhang, X., Li, L., Ma, Y., and Meng, X. (2016). Lonicera caerulea berry extract suppresses lipopolysaccharide-induced inflammation via Toll-like receptor and oxidative stress-associated mitogen-activated protein kinase signaling. *Food & Function.*

Wawruszak, A., Czerwonka, A., Okła, K., and Rzeski, W. (2015). Anticancer effect of ethanol Lycium barbarum (Goji berry) extract on human breast cancer T47D cell line. *Natural Product Research.* **30**(17): 1.

Weber, A. E. (2004). Dipeptidyl peptidase IV inhibitors for the treatment of diabetes. *Journal of Medicinal Chemistry.* **47**(17): 4135-4141.

White, B. L., Howard, L. R., and Prior, R. L. (2010). Polyphenolic composition and antioxidant capacity of extruded cranberry pomace. *Journal of Agricultural & Food Chemistry.* **58**(7): 4037-4042.

Wightman, J. D., and Heuberger, R. A. (2015). Effect of grape and other berries on cardiovascular health. *Journal of the Science of Food & Agriculture.* **95**(8): 1584-1597.

Wild, S., Roglic, G., Green, A., Sicree, R., and King, H. (2004). Global Prevalence of Diabetes — Diabetes Care.

Wilms, L. C., Boots, A. W., Boer, V. C. J. D., Lou, M. M., Pachen, D. M. F. A., Gottschalk, R. W. H., Ketelslegers, H. B., Godschalk, R. W. L., Haenen, G. R. M. M., and Schooten, F. J. V. (2007). Impact of multiple genetic polymorphisms on effects of a 4-week blueberry juice intervention on ex vivo induced lymphocytic DNA damage in human volunteers. *Carcinogenesis.* **28**(8): 1800-1806.

Wu, C. C., Wu, S. Y., Liao, C. Y., Teng, C. M., Wu, Y. C., and Kuo, S. C. (2010). The roles and mechanisms of PAR4 and P2Y12/phosphatidylinositol 3-kinase pathway in maintaining thrombin-induced platelet aggregation. *British Journal of Pharmacology.* **161**(3): 643-658.

Youdim, K. A., Mcdonald, J., Kalt, W., and Joseph, J. A. (2002). Potential role of dietary flavonoids in reducing microvascular endothelium vulnerability to oxidative and inflammatory insults (small star, filled). *Journal of Nutritional Biochemistry.* **13**(5): 282-288.

Zhang, D. W., Garuti, R., Tang, W. J., Cohen, J. C., and Hobbs, H. H. (2008). Structural Requirements for PCSK9-Mediated Degradation of the Low-Density Lipoprotein Receptor. *Proceedings of the National Academy of Sciences of the United States of America.* **105**(35): 13045-13050.

Zhang, H., Cao, C. M., Gallagher, R. J., and Timmermann, B. N. (2014). Antiproliferative withanolides from several solanaceous species. *Natural Product Research.* **28**(22): 1941-1951.

Zhao, M., Wang, P., Zhu, Y., Liu, X., Hu, X., and Chen, F. (2015). Blueberry anthocyanins extract inhibits acrylamide-induced diverse toxicity in mice by preventing oxidative stress and cytochrome P450 2E1 activation. *Journal of Functional Foods.* **14**: 95-101.

Zhao, Z. D., Niu, Y., Ge, Q., and Zhang, Y. (2016). Review of Anthocyanins from Lycium ruthenicum Murr. *Food Industry.*

Zhu, M., Hu, J., Perez, E., Phillips, D., Kim, W., Ghaedian, R., Napora, J. K., and Zou, S. (2011). Effects of Long-Term Cranberry Supplementation on Endocrine Pancreas in Aging Rats. *Journals of Gerontology.* **66**(11): 1139.