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REVIEW

Health promoting properties of blueberries: a review

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ABSTRACT
With the strengthening of the link between diet and health, several foodstuffs have emerged as possessing potential health benefits such as phenolic rich fruits and vegetables. Blueberries, along with other berries, given their flavonoid and antioxidant content have long since been considered as a particularly interesting health promoting fruit. Therefore, the present work aimed to compile the existing evidences regarding the various potential benefits of blueberry and blueberry based products consumption, giving particular relevance to *in vivo* works and epidemiological studies whenever available. Overall, the results demonstrate that, while the evidences that support a beneficial role of blueberry and blueberry extracts consumption, further human based studies are still needed.

KEYWORDS
Blueberry; anthocyanins; functional foods; antitumoral; neuroprotection

Introduction

The rise in life expectancy has led to an increase of the concern with the quality of life. Fruits and vegetables have been systematically associated with a reduction of the risk of chronic diseases, actual public health concerns, namely cardiovascular and neurodegenerative diseases (Gaziano, Prabhakaran, and Gaziano 2015; Morton et al. 2000; Wang et al. 2005; Krikorian et al. 2010). The consumption of fruits and vegetables has been systematically associated with a reduction of the risk of these pathologies (namely through the improvement of blood flow, protection against oxidative stress and exacerbated inflammatory responses) and, considering that phenolic compounds are present in high amounts in these food products it stands to reason that they have been associated with these benefits (Shukitt-Hale et al. 2008; Del Bo' et al. 2015; Wu, Cao, and Prior 2002). Furthermore, in later years, with the information flowing from the scientific community to the general population, the consumers' demand (and hence the industry's search) for healthier or health promoting foodstuffs has grown (Rossi et al. 2009; Gibson and Williams 2000; Lee, Durst, and Wrolstad 2002; Neto 2007; Szajdek and Borowska 2008; Wu et al. 2011).

Dubbed by the media as a "superfruit", blueberry is a prime example of a foodstuff that has gained a strong health promoting connotation, association that is supported by scientific literature where blueberries have been associated with several health benefits, namely their role in the maintenance of blood sugar levels, reduction of oxidative stress, anti-inflammatory effect, prevention of cardiovascular diseases, antimicrobial and antitumoural activity (Wood 2009; Cassileth 1999; Neto 2007). This makes the incorporation of blueberries or their extracts, into foodstuffs a relatively easy way to grant them some functionality and increase their commercial value (Rossi et al. 2009; Gibson and Williams 2000; Szajdek and Borowska 2008).

Considering the above made arguments, the present work aimed to compile the available evidences that link blueberry and blueberry based products with several health promoting properties.

Blueberry composition

From a nutritional standpoint, blueberries are rich in water and sugars, particularly glucose and fructose though other sugars such as galactose and rhamnose may be found, frequently as sugar moieties associated with phenolic compounds. These berries also possess a relatively high amount of organic acids (e.g. citric and ascorbic acids), minerals (e.g. phosphorus, potassium and magnesium) and fiber, particularly pectins (Vrhovsek et al. 2012; Prior et al. 2001; Sousa et al. 2007).

Blueberries have long since been recognized as a good source of phenolic compounds. Anthocyanins are the most prevalent family of flavonoids in blueberries with authors reporting the presence of up to fifteen different anthocyanins (monoarabinosides, monoglucosides and monogalactosides of cyanidin, peonidin, delphinidin, petunidin and malvidin) (Barnes et al. 2009; Routray and Orsat 2011; Gavrilova et al. 2011). In spite of being the most abundant family of compounds, and therefore the one most frequently associated with blueberries biological activity, several other

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phenolics have been reported. Brambilla et al. (2008), Kader et al. (1996) and Skrede, Wrolstad, and Durst (2000) reported the presence of three types of phenolic acids (gallic, syringic and vanillic) and five different cinnamic acids (chlorogenic, the major derivative present, caffeic, ferulic, *o*- and *p*-coumaric acids). Another group of phenolic compounds frequently associated with blueberries, are flavonoids. Though less studied, other phenolic compounds have been reported to be present in blueberries. Kader et al. (1996) and Taruscio, Barney, and Exon (2004) have reported the presence of other flavonoids, and their glycosylated forms (arabinosides, glucosides and galactosides), namely catechin, epicatechin, myricetin, kaempferol and quercetin. Vrhovsek et al. (2012) found an array of different flavonoid glycosides, though some appeared to be cultivar specific, such as pentosides, glucosides, galactosides of isorhamnetin, syringetin and laricitrin as well as their aglycone counterpart.

Health promoting potential of blueberries

There is a vast array of epidemiological evidences supporting the notion that a fruit and vegetable rich diet plays an important role in the prevention of several pathologies (e.g. reduction of the risk of cardiovascular disease and some forms of cancer, for example). As phenolic compounds and other antioxidants are abundantly present in fruits and vegetables, it stands to reason that they could be, at least in part, responsible for some of the potential beneficial health effects their consumption brings (Rossi et al. 2009; Graf, Milbury, and Blumberg 2005; Neto 2007; Szajdek and Borowska 2008). Blueberries, widely recognized as possessing both an elevated content and variety of phenolic compounds (particularly anthocyanins), have been the focus of several works that aim to characterize their intrinsic health promoting potential.

Antioxidant activity

Reactive oxygen and nitrogen species (ROS and RNS, respectively) are highly reactive compounds, both radical and non-radical, that can interact with several biologically relevant molecules (e.g. proteins and deoxyribonucleic acid (DNA)) potentially compromising their function, altering metabolic pathways and associated homeostatic balance (Borek 2001; Milbury and Richer 2008). Consequently, their presence has been associated with the development of several inflammatory conditions, degenerative diseases, cancer, etc. However, cells possess mechanisms that allow them to overcome the oxidative challenge posed by human metabolism (Sies 2007). In some instances, due either to an excessive production, a deficient elimination of reactive species, imbalances between the amount of ROS/RNS present and the body's natural capacity to cope with therefore allowing oxidative stress to occur. An increase in the consumption of antioxidants, exogenous compounds that are able to interact with the radicals originating stable compounds and prevent the oxidation of other molecules, may be a way to cope with oxidative stress (Yao and Vieira 2007; Cooper et al. 2002; Mathew, Abraham, and Zakaria 2015).

Blueberries are perceived as fruits with a strong antioxidant capacity (a property that has been ascribed to be a direct consequence of this fruit's richness in phenolic compounds) (Prior et al. 1998; Kalt et al. 1999; Burdulis et al. 2009; Szajdek and Borowska 2008; Piljac-Žegarac, Belščak, and Piljac 2009). This is supported by the results of Wu, Cao, and Prior (2002) and Mazza et al. (2002), who reported a significant increase in human plasmatic hydrophilic and lipophilic antioxidant capacity after blueberry ingestion. On their own, anthocyanins (one of the major groups of blueberry phenolics) have been described as being not only inhibitors of lipid peroxidation but also as capable of protecting liver and red blood cells against *in vitro* and *in vivo* oxidative damage (Ramirez-Tortosa et al. 2001; Kong et al. 2003; Narayan et al. 1999; Youdim, Martin, and Joseph 2000; Youdim et al. 2000; Heinonen, Meyer, and Frankel 1998). In fact, anthocyanidins' (the aglycone form of anthocyanins) capacity to inhibit lipid oxidation has been linked with its capacity to chelate metal ions, namely through its *o*-dyhydroxy structure of the B-ring. Moreover they can also donate electrons, in conjunction with a proton, from the hydroxyl groups attached to the phenol rings and therefore stabilizing the radicals (Pekkarinen, Heinonen, and Hopia 1999; Castañeda-Ovando et al. 2009; Nijveldt et al. 2001; Van Acker et al. 1996).

Anti-mutagenic effect

Alterations in DNA, either the result of errors in DNA replication or of environmental stimuli, can lead to mutated proteins with a compromised/nullified activity which, in turn, may lead to an array of different diseases. As blueberries are known for their antioxidant capacity it stands to reason that they may possess some protective effect against DNA oxidation. Pepe et al. (2013) reported that blueberries were capable of reducing the frequency of micronuclei appearance in mice exposed to 7,12-dimethylbenz[a]anthracene (DMBA) or N-methyl-N′-nitro-N-nitrosoguanidine (MNNG), two known mutagenic agents. In vitro, these authors reported that pre-treating cells with blueberry extract led to a reduction of MNNG's induction of micronuclei although the simultaneous and post-exposure treatment had no preventive effects. These authors hypothesize that blueberry antioxidants are capable of interacting with the reactive degradation products of MNNG and therefore curb it's cytotoxicity. This could explain the results observed for the pre- and post-treatment. However, no explanation is given for the lack of effect for the simultaneous exposure to MNNG and blueberry extract other than that MNNG decomposition could have occurred before the action of blueberry. Moreover, it is interesting to denote that while the frequency of micronuclei also decreased after exposure to DMBA it was accompanied by a significant reduction of the cell numbers which hints at some cytotoxicity (although the amounts of extract used were significantly higher than those recommended by the manufacturer). Overall the in vivo antimutagenic effect of blueberries appears to depend on several factors (e.g. duration and timing of mutagen ingestion). The duration of blueberry consumption was also demonstrated to play an important role in the prevention of mutagenesis. In fact, Del Bo' et al. (2015) reported that, while the consumption of blueberry led to a reduction of H_2O_2 induced DNA damage in mice, the protective effect was observed after 8 weeks of blueberry consumption but not after 4 weeks, i.e. longer continuous ingestion of blueberries was required in order to prevent DNA damage. Most authors associate blueberries' antimutagenic effect with a direct quenching of radical species by blueberry antioxidants. However, this does not fit with the need for a prolonged ingestion observed by (Del Bo' et al. 2015). These authors hypothesized that an indirect effect could be responsible for the antimutagenic effect observed, namely the upregulation of genes associated with peroxide removal. This could not only explain the need for longer ingestion periods observed (metabolic modulation would take longer than a direct chemical reaction) but also why the reduction of oxidative DNA damage was observed without significant differences in plasma antioxidant activity being registered. Moreover, this possibility is further supported by the fact that anthocyanins have been associated not only with the upregulation of phase II antioxidant and detoxifying enzymes (such as glutathione-related enzymes and NAD(P)H:quinone oxidoredutase) in Clone 9 rat liver cells but also with the restauration of p53 gene expression (Shih, Yeh, and Yen 2007; Giudice and Montella 2006; Liu, Wang, et al. 2013). Regardless, of the fact that these results that disregard a direct plasmatic antioxidant effect, some evidences can be found that support this hypothesis. In fact, anthocyanin rich blueberry extracts have been reported as reducing ultraviolet (UV) induced DNA damage in HepG2 cells, effect that has been associated with a reduction of intracellular ROS production/accumulation (Liu, Lu, et al. 2013). Overall, it is likely that a combination of both direct and indirect effects are associated with the potential antimutagenic effect associated with blueberries, for while anthocyanins have been reported to disappear from the blood stream 4 h after the last ingestion (which could strengthen the indirect effect theory) they have also been reported to accumulate in the organism and are therefore able to exert a direct antioxidant effect (Felgines et al. 2002; Del Bo' et al. 2015; Kalt et al. 2008).

Antitumoural effect

Blueberry, and its extracts, have been described as possessing interesting antitumoural/anticancer properties. Dried blueberry powder has been shown to reduce some of the toxicity of acrylamide (a known genotoxic and carcinogenic agent) by reversing acrylamide induced alterations in the liver's enzymatic levels and by reducing lymphocytes, liver and bone marrow cells' DNA damage an effect that the authors associated with blueberry antioxidants compounds and their mitigation of acrylamide induced oxidative stress (i.e. reduction of ROS accumulation and prevention of DNA oxidation) (Zhao et al. 2015). Blueberry extracts have also been reported as possessing some antitumoural activity. Seeram et al. (2006) and Diaconeasa et al. (2015) showed that blueberry extracts were capable of effectively inhibiting, *in vitro*, the proliferation of several tumor cell lines from the colon (HT-29 and HCT116), prostate (LNCaP), breast (breast), mouth (KB and CAL-27), cervix (HeLa), ovaries (A2780) and skin (B16F10). Moreover, Seeram et al. (2006) demonstrated that a blueberry extract was capable of inducing apoptosis in HT-29 colon cancer cells, as this mechanism is considered to play an important role in cancer suppression (namely through the removal of damaged and neoplastic cells) it stands to reason that this effect could translate into a potential antimoural effect (although *in vivo* human studies must be considered before any potential applications are considered).

Kou et al. (2016) and Vuong et al. (2016) reported that blueberry extracts were capable of reducing cellular viability, mobility and migration of MDA-MB-231, MCF-7 and 4T1 breast cancer cells *in vitro* as well as *ex vivo* mammosphere formation, while oral administration of the extracts to mice led to lower tumor growth. Parallel results were observed by Aqil et al. (2016), who reported that a dietary supplement comprised of berry powder led to smaller lung tumors in mice, and by Sun et al. (2015) who reported that the consumption of a polysaccharide isolated from blueberries led to ca. 73% inhibition of tumor growth in Kun-Ming mice. Liu et al. (2016) stated that acylated blueberry anthocyanins not only exhibited a strong antitumoural effect on H22 murine tumors, but they were also able to function synergistically with cyclophosphamide (a known chemotropic agent) attenuating its toxic effect upon the liver while stimulating tumor necrosis, while Jeyabalan et al. (2014) reported that a dietary supplement of blueberry was effective in inhibiting estrogen mediated mammary tumorigenesis in female ACI rats, both as a preventive factor as a therapeutic component.

Natural compounds have been associated with the control of aberrant inflammatory signals and signaling pathways associated with cancer stem cells. Vuong et al. (2016) hypothesized that a polyphenol rich blueberry extract was capable of modulating regulators associated with cell transformation and inflammation, namely a reduction of the STAT3 (essential in cancer stem cells) pathway, the activation of AMPK and the consequent inhibition of the mitogen-activated protein kinase (MAPK) pathway as well as a inactivation of the PI3K/AKT (Vuong et al. 2016; Li et al. 2015). Moreover, Hou, Tong, et al. (2005) and Feng et al. (2007) found that anthocyanins (delphininidin-3-sambubioside and cyanidin-3-rutinoside) were capable of inducing apoptosis through a ROS-mediated mitochondrial pathway while Zhang et al. (2005) reported that proanthocyanindins have been associated with an enhancement of doxorubicin-induced antitumoral effects. As both types of compounds can be found in blueberries it stands to reason that these mechanisms may also play a role in the potential antitumoural effect of blueberries. Although, to the best of our knowledge, no reasons as to why have been proposed, blueberry extracts have also been associated with a reduction of cell motility that, in vivo, translated into a reduction of lung metastasis in a murine breast cancer model. Overall, the regulatory and the immunomodulatory properties of phenolic compounds have been marked as an important factor in the establishment of the boundary between inflammation and neoplasia development (Vuong et al. 2016).

Anti-inflammatory potential

Inflammatory processes, while important for the immunologic response, can also be an important factor in the development of several chronic diseases namely diabetes, cardiovascular diseases, arthritis and osteoporosis (Libby 2007). Torri et al. (2007) reported that the consumption of a crude blueberry extract (ca. $300\,mg\,kg^{-1}\,d^{-1}$) by rats resulted in a positive anti-inflammatory effect, as it led to a reduction in paw edema, myeloperoxidase activity (a maker for neutrophil infiltration) and formation of granulomatous tissue. Figueira et al. (2016) reported that a blueberry extract caused a reduction in joint degradation in a mice model for rheumatoid arthritis in mice, results that support the observations of Zhong et al. (2015) who found that blueberry juice consumption by adolescents suffering from Juvenile idiopathic arthritis (thought to be inflammatory in nature) led not only to a considerable improvement of the activity of etanercept (a known remedy) but also an amelioration of the drugs secondary effects. Ebenezer et al. (2016) described that the supplementation of the diet with 2% of freeze-dried blueberry powders, led to a decrease in inflammation in a post-traumatic stress disorder rat model. Furthermore, through a study containing 2375 participants, Cassidy et al. (2015) found that anthocyanin consumption was inversely associated with 12 different inflammatory biomarkers, while Giongo et al. (2011) reported that consumption of blueberries (either fresh or puréed) had a similar effect upon 24 obese children.

Anthocyanins's (one of the main classes of phenolic compounds present in blueberries) antioxidant activity has been associated not only with a direct quenching of reactive species but also with an upregulation of antioxidant and detoxifying enzymes (phase II enzymes that contribute to the reduction of oxidative stress such as gluthatione-S-transferase or quinone reductase) (Srivastava et al. 2007; Shih, Yeh, and Yen 2007). In fact, while the activation mechanism remains somewhat unclear, anthocyanins (and their metabolites), have been described to stimulate the redox nuclear factor erythroid 2 (NF-E2) related factor 2 (nrf2)/Antioxidant Response Element (ARE) pathway, stimulating the expression of ARE, which will in turn modulate the expression of antioxidant and phase II detoxifying enzymes that will then contribute to the modulation of the inflammatory response. For instance, the action of antioxidant enzymes may reduce ROS-mediated pro-inflammatory stimuli (e.g. inhibition of protein kinase pathways and monocyte chemoattractant protein-1 (MCP-1)) (Chen and Kunsch 2004; Shih, Yeh, and Yen 2007; Srivastava et al. 2007). On a different note, anthocyanins have also been reported to exert some anti-inflammatory effect through non-antioxidant mediated pathways namely through the modulation of Tumour Necrosis Factor α (TNFα) and lipopolysaccharide (LPS) stimulated inflammatory responses. In fact Hou, Yanagita, et al. (2005) reported that anthocyanidins (delphinidin, cyanidin, peonidin and malvidin but not pelargonidin) were capable of inhibiting the expression of pro-inflammatory enzyme cyclooxygenase-2 (COX-2) enzyme in LPS stimulated RAW macrophages. On the other hand, Wang and Mazza (2002) reported that, in a LPS/interferon γ (IFNγ) stimulated RAW macrophages system, anthocyanidins and anthocyanins stimulated the production of TNFα, therefore enhancing the inflammatory response. This demonstrates that the effect induced by anthocyanidins and anthocyanins may be dependent on the cells as well as the pro-inflammatory stimulus, particularly as one of the largest differences between these contradictory works is that Hou, Yanagita, et al. (2005) used LPS as a stimulus and Wang and Mazza (2002) used LPS/IFNγ, a combination that has been reported to function synergistically to induce higher levels of TNFα production (Orlicek, Meals, and English 1996).

Other blueberry compounds have been characterized in regards to their anti-inflammatory potential. Quercetin has been described to suppress LPS induced TNFα production not only through the direct inhibition of TNFα gene transcription as well as through post-transcription regulation mechanism, namely through the inhibition of MAPK and signal-related kinase (ERK1 and ERK2) (Park et al. 2000; Min et al. 2007). Gallic and chlorogenic acids were reported to have little to no impact upon TNFα production in RAW macrophages stimulated with LPS/IFNγ but, in a LPS stimulated RAW model, chlorogenic acid was able to reduce the expression of COX-2, TNFα and other pro-inflammatory markers (interleukin-1β (IL-1β) and interleukin-6 (IL-6)) as well as the nuclear translocation of nuclear-factor κB (NF-κB) (Wang and Mazza 2002; Hwang et al. 2014). These differences in behavior are similar to those previously observed when considering the potential role of anthocyanins and anthocyanidins and accentuate the need for further studies considering an array of factors (such as synergistic interactions between compounds, different cell lines and inflammatory stimuli) before considering the use of blueberries as a source of anti-inflammatory compounds.

Immunomodulatory effect

One of the means through which anthocyanins are thought to inhibit tumor formation is linked with their potential immunomodulatory effects, possibly through the stimulation of natural killer cells (NKC; a group of lymphocytes responsible for the immune response to abnormal cells) (Seeram 2008; Vivier et al. 2008; McAnulty et al. 2011; Sun et al. 2015). This possibility is supported by the work of McAnulty et al. (2011), who reported that chronic consumption of blueberries, by humans, led to higher basal levels not only of NKC but also interleukin-10 (IL-10; which downregulates the inflammatory response) (Sanjabi et al. 2009; McAnulty et al. 2011). This increase in the production of anti-inflammatory cytokines was also observed by Huang, Liu, et al. (2014), when exposing VECs to malvidin-3-glucoside and malvidin-3-galactoside (two of the major anthocyanins of blueberries), and by Sun et al. (2015), when feeding mice with a blueberry polysaccharide. Another example of the possible role of blueberry in immunomodulation is given by Shukitt-Hale et al. (2008). These authors reported that a blueberry supplemented diet allowed for an attenuation of kainic acid (a potential neurotoxic acid) induced production of inflammatory cytokines in rat hippocampus, which in turn resulted in a reduction of neurotoxicity (Shukitt-Hale et al. 2008, Zhang and Zhu 2011). Blueberry anthocyanins have been widely reported to play an important role in the immunomodulatory potential of blueberries, although the overall mechanisms behind their interaction with the innate immune system are still relatively obscured, a consensus exists that they are likely to act through both antioxidant dependent and independent pathways.

Neuroprotection

Several authors have hinted that the consumption of blueberries may aid in the reversal of some age-related and oxidative stress induced decline in brain function (Wang et al. 2005; Krikorian et al. 2010). In fact, the neurotoxic effects of kainic acid, in rats, have been reported to be reduced after consumption of blueberry, which ameliorated the exacerbated kainic acid induced inflammatory response in the hippocampus (Shukitt-Hale et al. 2008). In fact, blueberry consumption (either directly or through anthocyanin rich extracts) has been demonstrated to have an *in vitro* neuroprotective effect against damage induced by an array of neurotoxic agents (such as trimethyltin and ketamine), while also exhibiting some *in vivo* effects in protecting and, in some cases, even enhancing the learning and memory capabilities of mice (Jo et al. 2015; Andres-Lacueva et al. 2005; Debom et al. 2016). An effect that Krikorian et al. (2010) showed to be expanded to humans, as the consumption of blueberries by older adults improved memory capabilities, which may be explained by an increase in synaptic plasticity resulting from a modulation of the microglia phenotype towards a more favorable M2 phenotype and an improvement of the microglia-neuron crosstalk through the increase of the expression of CX3CR1 receptor (an element of the CXCR1/CX3CL1 axis that connects microglia and neuron cells) (Meireles et al. 2016). On a different note, blueberry consumption by aged rats has also been linked with a reduction of reduction of ischemia induced apoptosis of brain cells as a possible result of their capacity to interact with ROS and RNS, which accumulate during the ischemic phase, particularly as anthocyanins are known to accumulate in the central nervous system (Wang et al. 2005; Andres-Lacueva et al. 2005).

Anthocyanins (blueberry pigments) have been described as exerting some neuroprotective effect through four different means by functioning as antioxidant, promoting Ca^{2+} homeostasis, by acting as anti-inflammatory agents and by inhibiting apoptosis. Normal mitochondrial activity represents one of the major sources of intracellular ROS with neurons, given their high demand for mitochondrial derived energy, being particularly susceptible to damages resulting from an abnormal ROS production (Lin and Beal 2006; Krantic et al. 2005; Murata, Ohtsuka, and Terayama 2008). In turn, anthocyanins have been reported not only as being capable of traversing the blood brain barrier (therefore possibly acting as quenching direct ROS quenching agents) but also as inducing the production of phase II detoxifying and antioxidant enzymes (Shih, Yeh, and Yen 2007; Ramirez-Tortosa et al. 2001; Andres-Lacueva et al. 2005; Kalt et al. 2008). The overstimulation of neurons by excitatory neurotransmitters (e.g. glutamate) results in a Ca^{2+} overload (excitotoxicity) that, in turn, triggers a series of signaling cascades that result in increased nitric oxide and ROS production, the depolarization of the mitochondrial membrane, the degradation of proteins, DNA and membranes, events that culminate with neuron death (Dong, Wang, and Qin 2009; Jung et al. 2009; Ward et al. 2000). Therefore, the maintenance of Ca^{2+} homeostasis represents an important factor in the suppression of excitotoxicity mediated neurodegenerative diseases and neuron apoptosis. Anthocyanins have been reported as playing an important role in the maintenance of calcium levels in the presence of different stimuli but, to the best of our knowledge no information is available regarding the underlying mechanisms observed for this effect (Shih et al. 2011; Martin, Giannone, Andriantsitohaina, and Martinez 2003; Wiart 2013). Prolonged inflammation of some areas of the central nervous system may result in neuron death (Wyss-Coray and Mucke 2002; Lucin and Wyss-Coray 2009). As such, the previously described blueberry (and blueberry compounds) potential to function as anti-inflammatory agents (e.g. inhibition of MAPK, ERK, COX-2 and c-Jun N-terminal kinase (JNK) enzymes, pro-inflammatory cytokines production and NKκB transcription) may prove to be an important contributor to their neuroprotective potential (Zafra-Stone et al. 2007; Rasheed et al. 2009; Mulabagal et al. 2009; Park et al. 2000; Shih, Yeh, and Yen 2007; Shah, Yoon, and Kim 2015; Hou, Yanagita, et al. 2005; South et al. 2016). Anthocyanins have been reported to play a role in the modulation of neuronal anti-apoptotic pathways (both through caspase dependent and independent pathways) (Reddivari et al. 2007). For instance Shin, Park, and Kim (2006) reported that anthocyanins inhibited the JNK and p53 pathways in a ischemia mice model while Min et al. (2011) reported that anthocyanins prevented the mitochondrial release of Apoptosis Inducing Factor (AIF). Anthocyanins have also been reported to stimulate the production of Bcl-2 proteins (pro-survival), suppress cytochrome c release and inhibit Bax protein (pro-apoptotic) expression (Lu et al. 2010; Ye et al. 2010; Shin, Park, and Kim 2006; Min et al. 2011; Kang et al. 2006; Kim et al. 2010).

Cardiovascular disease prevention

Cardiovascular diseases have emerged as one of the leading causes of death in developed countries with the diet having been identified as one of the possible means to reduce the risk of developing these pathologies (Gaziano, Prabhakaran, and Gaziano 2015; Morton et al. 2000). Relatively recent data has suggested that the intake of specific fruits, among which are blueberries, may be more effective in managing cardiovascular diseases, as flavonoids have been associated with improved blood flow and endothelial function, and blueberry consumption, in particular, has been related to a reduction of the risk of myocardial infarction in women. (Cassidy et al. 2016; Cassidy et al. 2013). Additionally, considering that low grade chronic inflammation has been associated with higher risks of developing cardiovascular disease the anti-inflammatory potential associated with blueberry (namely the inhibition of the inducible nitric oxide synthase (iNOS), of COX-2 expression which is frequently upregulated in CVD and inhibition of the NF-κB pathway) may also play an important role in reducing the risk of developing these pathologies (Danesh et al. 2000; Riso et al. 2013; Basu, Rhone, and Lyons 2010; Zhang et al. 2008). Moreover, vascular endothelial cells (VEC), whose damage has also been linked with the development of vascular diseases, have been described as being capable of integrating anthocyanins into their membrane and cytosol. In turn, anthocyanins are thought to aid in the preservation of VEC function, either by aiding in the stabilization of the cellular membrane or by helping maintain oxidative balance (Ramirez-Tortosa et al. 2001; Youdim, Martin, and Joseph 2000). Huang et al. (2016) reported that malvidins (a major class of blueberry anthocyanins) were capable of decreasing the concentration of ROS (intracellular) and xanthine oxidase-1 (intra- and extracellular) while leading to higher levels of superoxide dismutase (SOD) in umbilical cord VECs (Cisowska, Wojnicz, and Hendrich 2011). This may contribute to explain the observations of Stull et al. (2015) who found that blueberry consumption by adults with metabolic syndrome led to an improvement of endothelial function, though it did not translate into an improvement of blood pressure levels. However, a reduction of blood pressure, as well as a reduction of arterial stiffness, was observed by Johnson et al. (2015) when evaluating the impact of daily blueberry consumption in postmenopausal woman (with either pre- r stage 1-hypertension). When considering the overall effect of blueberry consumption in human blood pressure, the presence of a positive effect varies from study to study. Zhu et al. (2016) performed a meta-analysis on several randomized clinical trials and found no significant impact of blueberry consumption on either systolic or diastolic blood pressures, though they marked the overall lack of studies considering large populations and the need for some separation between the groups of individuals (e.g. healthy, obese or insulin resistant) may be an important trait. Regardless, anthocyanins have been reported as exhibiting some vasodilatory action induced through endothelium-dependent and nitric oxide-dependent vasorelaxation. Cyanidin-3-glucoside resulted in an increase of nitric oxide production by endothelial cells (whose accumulation results in vasodilation) through the activation of endothelial nitric oxide synthase (eNOS) and protein kinase B (AKT/PKB) has been reported to induce the vasodilation of aortic rings through a process that is critically mediated by bilitranslocase. These authors hypothesized that the overall vasodilatory potential of flavonoids could be a byproduct of the endothelium intrinsic defense mechanism that responds to the increase in oxidative stress by increasing the nitric oxide levels (Ziberna et al. 2013).

Platelet aggregation may also contribute to the development of CVD because they can aid plaque formation during early atherogenesis (Assmann et al. 1999). For this to happen collagen and con Willebrand factor (vWF), produced by damaged endothelial cells, must bind to a glycoprotein receptor complex present in the surface of platelets. In turn, this will trigger the secretion of several adhesion molecules and the binding of plasmatic fibrinogen while also secreting molecules that will upregulate the platelet response (e.g. thromboxane A_2 (TxA_2)) (Ruggeri 2002; Ruggeri 2003; Davì and Patrono 2007). Flavonoids have been reported to inhibit platelet aggregation by functioning as antagonists for TxA_2 (i.e. competing for the receptor) (Guerrero et al. 2005; Guerrero et al. 2007). Anthocyanins (one of the main flavonoids found in blueberries) have been demonstrated to exhibit some effect *in vitro* however, when considering *in vivo* applications the body of work available focuses more on demonstrating the effect of anthocyanin rich fruits than on describing the potential underlying mechanisms. Regardless, some mechanisms may be hypothesized. For instance, as platelet function may be inhibited by the reduction of hydrogen peroxide levels, anthocyanin's intrinsic antioxidant capacity may play an important role in this aspect (Kroon et al. 2004; Scalbert et al. 2005; Scalbert and Williamson 2000; Pignatelli et al. 2000). Similarly, as platelet aggregation is dependent on phosphatidylserine (PS) exposure, phenolics' capacity to inhibit its exposure through the inhibition of phosphatidylinositol 4,5-bisphosphate (PIP_2) (Bucki et al. 2003).

Anti-obesity

Obesity is widely recognized as one of today's major health threats, as it is both a major risk factor in an array of health problems such as diabetes and cardiovascular diseases and considerably hard to treat (Caballero 2007; Hill et al. 1998). As treating obesity with drugs is frequently associated with negative side effects and little to none long term efficacy, some authors have defended that using natural plant extracts could pose an interesting alternative for long term weight management and blueberries were proposed as one of the possible sources to be exploited (Song, Park, et al. 2013). Blueberries, when lyophilized or processed unto a juice, had no significant impact in either weight gain or body fat accumulation in mice fed with a high-fat diet (Prior et al. 2008; Prior et al. 2010, DeFuria et al. 2009). However, when considering an anthocyanin extract, the same authors described a significant reduction in body weight and fat accumulation. Seymour et al. (2011), Vendrame et al. (2013) and Vendrame, Daugherty, et al. (2014) reported that the supplementation of a high-fat diet with blueberry powder led to

Table 1. Summary of the bioactive activities associated with some of their constituents.

	Properties	Reference
Phenolic compounds		
Anthocyanins		
Cyanidin-3-glucoside	Antioxidant capacity	(Shih, Yeh, and Yen 2007, Acquaviva et al. 2003, Song, Zhao, et al. 2013, Elisia and Kitts 2008, Kähkönen and Heinonen 2003)
	Apoptosis modulation	(Chen et al. 2005, Lee, Kim, Song, et al. 2015, Cimino et al. 2006, Lee, Kim, Park, et al. 2015, Pratheeshkumar et al. 2014, Elisia and Kitts 2008)
	Antimutagenic activity	(Shih, Yeh, and Yen 2007, Song, Zhao, et al. 2013)
	Antitumoural	(Aqil et al. 2016, Shih, Yeh, and Yen 2007, Chen et al. 2006, Ding et al. 2006, Cooke et al. 2006, Chen et al. 2005, Zhang, Vareed, and Nair 2005)
	Immunomodulation	(Serra et al. 2013, Pratheeshkumar et al. 2014, Zhang et al. 2010)
	Anti-diabetic	(Sasaki et al. 2007, Guo et al. 2012, Guo et al. 2008)
	Anti-obesity	(Guo et al. 2012, Sun et al. 2012, Tsuda et al. 2003, Kaume et al. 2012)
	CVD prevention	(Xu, Ikeda, and Yamori 2004b, a, Nasri et al. 2011)
	Neuroprotection	(Chen et al. 2009, Ke et al. 2011, Bhuiyan et al. 2011, Nasri et al. 2012)
Cyanidin-3-galactoside	Antitumoural	(Zhang, Vareed, and Nair 2005, Kähkönen and Heinonen 2003)
	Anti-diabetic	(Adisakwattana et al. 2004)
Malvidin-3-glucoside	Antioxidant capacity	(Shih, Yeh, and Yen 2007, Sasaki et al. 2007, Rossetto et al. 2002, Fukumoto and Mazza 2000, Kulisic-Bilusic et al. 2009, Paixao, Dinis, and Almeida 2012)
	Anti-diabetic	(Rossetto et al. 2002)
	Anti-obesity	(Prior et al. 2009)
	Apoptosis modulation	(Paixao, Dinis, and Almeida 2012)
	Immunomodulation	(Huang, Liu, et al. 2014, Lee et al. 2014, Kulisic-Bilusic et al. 2009)
	CVD prevention	(Huang, Liu, et al. 2014, Paixao, Dinis, and Almeida 2012)
	Neuroprotection	(Schroeter et al. 2000)
	Antimutagenic activity	(Shih, Yeh, and Yen 2007)
Malvidin-3-galactoside	Immunomodulation	(Huang, Liu, et al. 2014)
	CVD prevention	(Huang, Liu, et al. 2014)
Peonidin-3-glucoside	Antioxidant capacity	(Shih, Yeh, and Yen 2007)
	Apoptosis modulation	(Chen et al. 2005)
	Antimutagenic activity	(Shih, Yeh, and Yen 2007)
	Antitumoural	(Chen et al. 2005, Ho et al. 2010)
Delphinidin-3-glucoside	Antioxidant capacity	(Jin et al. 2014, Miller and Rice-Evans 1997)
	CVD prevention	(Yang, Shi, et al. 2012, Jin et al. 2013, Xie, Zhao, and Shen 2012)
	Apoptosis modulation	(Xie, Zhao, and Shen 2012)
Delphinidin-3-galactoside	Antitumoural	(Zhang, Vareed, and Nair 2005)
Anthocyanidins		
Cyanidin	Antioxidant capacity	(Shih, Yeh, and Yen 2007, Acquaviva et al. 2003, Fukumoto and Mazza 2000, Kähkönen and Heinonen 2003, Porter, Hrstich, and Chan 1985, Tsuda et al. 1994, Meyer, Heinonen, and Frankel 1998, Noda et al. 2002)
	Antimutagenic activity	(Shih, Yeh, and Yen 2007)
	Antitumoural	(Aqil et al. 2016)
	Anti-diabetic	(Gharib, Faezizadeh, and Godarzee 2013)
	Immunomodulation	(Porter, Hrstich, and Chan 1985)
	Neuroprotection	(Schroeter et al. 2000, Thummayot et al. 2016, Lopez-Cid et al. 2014)
Delphinidin	Antioxidant capacity	(Shih, Yeh, and Yen 2007, Fukumoto and Mazza 2000, Kähkönen and Heinonen 2003, Noda et al. 2002)
	CVD prevention	(Martin, Giannone, Andriantsitohaina, and Carmen Martinez 2003)
	Anti-obesity	(Rahman, Jeon, and Kim 2016, Parra-Vargas et al. 2018)
	Apoptosis modulation	(Hafeez et al. 2008, Krauss and Fischer 2013)
	Immunomodulation	(Chamcheu et al. 2015, Seong et al. 2011, Bae et al. 2014)
	Neuroprotection	(Kim et al. 2009, Lin, Tsai, and Wu 2014)
	Anti-diabetic	(Gharib, Faezizadeh, and Godarzee 2013)
	Antimutagenic activity	(Shih, Yeh, and Yen 2007)
Malvidin	Antioxidant capacity	(Shih, Yeh, and Yen 2007, Kähkönen and Heinonen 2003)
	Apoptosis regulation	(Hyun and Chung 2004, Shih, Yeh, and Yen 2005, Krauss and Fischer 2013)
	Antimutagenic activity	(Shih, Yeh, and Yen 2007)
	Immunomodulation	(Huang, Wang, et al. 2014, Dai et al. 2017)
	Neuroprotection	(Schroeter et al. 2000, Lopez-Cid et al. 2014, Baba et al. 2017, Lin, Tsai, and Wu 2014)
Peonidin	Antioxidant capacity	(Shih, Yeh, and Yen 2007, Kähkönen and Heinonen 2003)
	Antimutagenic activity	(Shih, Yeh, and Yen 2007)
Petunidin	Antioxidant capacity	(Shih, Yeh, and Yen 2007, Kähkönen and Heinonen 2003)
	Antimutagenic activity	(Shih, Yeh, and Yen 2007)
Other compounds		
Quercetin	Antioxidant capacity	(Meyer, Heinonen, and Frankel 1998, Pinelo et al. 2004, Manach et al. 1998, Morand et al. 1998, da Silva et al. 1998, Chopra et al. 2000)
	Antitumoural	(Zhang et al. 2012, Tan, Wang, and Zhu 2009, Choi et al. 2001, Chou et al. 2010)
	Apoptosis modulation	(Wei et al. 1994, Choi et al. 2001, Chou et al. 2010, Nguyen et al. 2003, Yang et al. 2005, Granado-Serrano et al. 2006, Priyadarsini et al. 2010, Lee et al. 2002)
	Immunomodulation	(Guardia et al. 2001, Hämäläinen et al. 2007, Comalada et al. 2005, García-Mediavilla et al. 2007, Kleemann et al. 2011, Boots et al. 2008, Rogerio et al. 2010, Egert et al. 2009)
	CVD prevention	(Kleemann et al. 2011, Egert et al. 2009, Hayek et al. 1997, Juźwiak et al. 2005, Kamada et al. 2005, Shen et al. 2013)

(*continued*)

Table 1. Continued.

	Properties	Reference
	Anti-obesity	(Juźwiak et al. 2005, Ahn et al. 2008, Dong et al. 2014, Rivera et al. 2008, Stewart et al. 2009, Kim et al. 2015)
	Anti-diabetic	(Rivera et al. 2008, Stewart et al. 2009, Dias et al. 2005, Kim et al. 2011, Chuang et al. 2010, Shisheva and Shechter 1992, Bhattacharya et al. 2014)
	Neuroprotection	(Dok-Go et al. 2003, Pu et al. 2007, Arredondo et al. 2010, Zhang et al. 2011, Haleagrahara et al. 2011, Tongjaroenbuangam et al. 2011, Schültke et al. 2005)
Caffeic acid	Antioxidant capacity	(Meyer, Heinonen, and Frankel 1998, Jung et al. 2006, Sato et al. 2011, Nardini et al. 1997, Kono et al. 1997)
	Apoptosis modulation	(Chen, Shiao, and Wang 2001, Lee et al. 2003, Khanduja et al. 2006)
	Immunomodulation	(Norata et al. 2007, Chao, Hsu, and Yin 2009, Da Cunha et al. 2004)
	Antitumoural	(Huang et al. 1988)
	CVD prevention	(Meyer, Heinonen, and Frankel 1998, Norata et al. 2007, Chao, Hsu, and Yin 2009)
	Anti-diabetic	(Jung et al. 2006, Oboh et al. 2015, Bhattacharya et al. 2014)
	Neuroprotection	(Zhang et al. 2007, Vauzour, Corona, and Spencer 2010, Zhou et al. 2006)
Chlorogenic acid	Antioxidant capacity	(Sato et al. 2011, Kono et al. 1997)
	Antitumoural	(Huang et al. 1988, Xu et al. 2013)
	Apoptosis modulation	(Granado-Serrano et al. 2007, Bandyopadhyay et al. 2004, Rakshit et al. 2010, Jiang et al. 2000, Yang, Liu, et al. 2012)
	Anti-diabetic	(Oboh et al. 2015, Ma, Gao, and Liu 2015, Ong, Hsu, and Tan 2013, Meng et al. 2013, Tsuda et al. 2012)
	Anti-obesity	(Cho et al. 2010, Meng et al. 2013, Karthikesan, Pari, and Menon 2010)
	CVD prevention	(de Sotillo et al. 2002, Wan et al. 2013, Wu et al. 2014)
	Neuroprotection	(Li et al. 2008, Kwon et al. 2010, Huang et al. 2008, Shen et al. 2012, Ito et al. 2008, Lee et al. 2011)
	Immunomodulation	(Shi et al. 2013, Dos Santos et al. 2006, Hwang et al. 2014, Yun, Kang, and Lee 2012, Shin et al. 2015, Krakauer 2002, Shan et al. 2009)
Polysaccharides		
BBP3-1 (2:3:4 rhamnose:galactose:glucose; 18.6 Da average molecular weight)	Antitumoural	(Sun et al. 2015)
	Immunomodulation	(Sun et al. 2015)

less intraperitoneal accumulation of fat, an increase of adiponectin levels, a decrease of inflammatory markers and an amelioration of dyslipidaemia. Both anthocyanins and anthocyanin rich extracts have been described to stimulate transcription of peroxisome proliferator-activated receptor (PPAR; involved in energy homeostasis regulation) whose stimulation has been associated with an improvement of insulin resistance and with promotion of fat metabolism coupled with the inhibition of fat storage. In fact Seymour et al. (2011) reported that blueberry consumption resulted in an increase of PPAR (in mice fed with both a high and a low fat diet) in both skeletal muscle and abdominal fat. Adipocyte dysfunction has also been associated with the development of both obesity and insulin resistance therefore it stands to reason that the control of adipokine secretion and adipocyte gene expression present two interesting targets for diabetes amelioration and obesity prevention. In fact, the treatment of adipocytes with cyanidin or cyanidin-3-glucoside has been reported to result in an increase in the expression and secretion of adiponectin and leptin as well as an upregulation of specific adipocyte genes without any activation of PPARγ, with the authors of this study hypothesizing that AMP-activated protein kinase (AMPK) activation could be responsible for the modulation observed, particularly as the AMP/ATP ratio decreased in the presence of anthocyanins (Tsuda et al. 2004). However, while the association between AMPK, leptin and adiponectin and its potential anti-obesity potential has been documented, weather anthocyanins stimulate AMPK than then results in an increased adipokine production or vice versa remains unclear (Tsuda et al. 2004; Minokoshi et al. 2002; Hardie et al. 2003).

Anti-diabetes

Diabetes is a group of diseases characterized by high blood glucose levels. Given its rising prevalence and potential harmful effects diabetes are one of the major concerns of modern medicine (Carvalho, Carvalho, and Ferreira 2003; Wild et al. 2004). Anthocyanin rich extracts have been demonstrated to attenuate insulin sensitivity and hyperglycemia, while a diet supplemented with blueberry powder has been shown to enhance glucose tolerance in post-menopausal mice, normalize glucose metabolism markers in obese rats and enhance the insulin sensitivity in humans (Elks et al. 2015; Stull et al. 2010; Takikawa et al. 2010; Vendrame, Zhao, et al. 2014). Moreover, anthocyanins have been demonstrated to induce the production of glucagon-like pepetide-1 (GLP-1), which interacts with pancreatic cells responsible for the induction of insulin secretion. The molecules that block GLP-1 degradation have been used for therapeutic purposes and thus this food mediated increase of GLP-1 production could pose an interesting new strategy for the treatment of diabetes (Herman et al. 2006; Vilsbøll et al. 2008; Tsuda 2015).

Antimicrobial potential

Phenolic compounds have long since been associated with antimicrobial activity. Therefore blueberries, as a good source of these compounds, have been regarded as a potential source for antimicrobial agents for medicinal, pharmaceutical, cosmetic and food industries (Burdulis et al. 2009; Hohtola et al. 2004; Cisowska, Wojnicz, and Hendrich 2011). Several authors have reported on the *in vitro* antimicrobial activity of blueberry extracts, having found them to be capable of inhibiting the growth of known potential pathogens such as *Escherichia coli, Vibrio cholerae, Vibrio parahaemolyticus, Acinetobacter baumannii, Salmonella thypimurium, Salmonella enteritidis, Pseudomonas aeruginosa, Shigella flexneri, Shigella sonnei, Listeria monocytogenes, Bacillus cereu*s, *Staphylococcus epidermidis,* methicillin sensitive and methicillin resistant *Staphylococcus aureus*, (Pertuzatti et al. 2016; Khalifa et al. 2015; Shen et al. 2014; Lacombe et al. 2012; Zimmer et al. 2014). Furthermore, Khalifa et al. (2015) described blueberry extracts as being effective inhibitor of *V. cholerae* virulence factors. These results, which stand in line with those published in an earlier work regarding the effect of a blueberry extract upon *S. aureus* virulence factors, indicate that these blueberry extracts, even when present at concentrations bellow in which they are unable to inhibit bacterial growth they may still affect their metabolism in an advantageous way (Silva et al. 2015). Moreover, some authors have reported that blueberry extracts may be effective in reducing biofilm formation, bacterial resistance structures notorious for their imperviousness to traditional antimicrobial agents (Zimmer et al. 2014; Bjarnsholt 2013; Bridier et al. 2015; Fux et al. 2005; Silva et al. 2016). However, it is important to note that the use of blueberry extracts to aid in the treatment of infections is, so far, an unlikely possibility, even if phenolic compounds have been hypothesized as interesting antibiotic coadjuvants (Alves et al. 2014). As, to the best of our knowledge, none of the antimicrobial assays consider the implications of oral consumption (i.e. the impact of the digestive process) or the actual levels at which the compounds may be absorbed.

Prebiotic potential

In the last decade, the importance of the gut microbiota in human metabolism and health has become almost impossible to dispute. Given that a large fraction of anthocyanins are not absorbed in the upper gastrointestinal tract, most of ingested anthocyanins end up exposed to the intestinal microbiota which, in turn, ends up metabolizing them and can, therefore affect not only anthocyanin bioavailability and bioactivity, but also originate different metabolites which, in turn, may have different health promoting effects (Kay 2006; Bingham 2006). Lee et al. (2016) described that a blueberry consumption by obese Winstar rats caused a decrease in *Firmicutes* and *Bacteroidetes* as well as increases in *Proteobacteria* and *Fusobacteria*. Hidalgo et al. (2012), reported that the incubation of malvidin-3-glucoside (typically the most abundant anthocyanin in blueberries) with fecal slurry has caused an increase of beneficial bacteria (e.g. *Lactobacillus* spp. and *Bifidobacterium* spp.) with (Vendrame et al. (2011)) reporting similar observations, for humans, after a six-week consumption of a blueberry powder drink. Phenolic compounds modification throughout the gastrointestinal tract and subsequent metabolization has been the target of several reviews (Selma, Espín, and Tomás-Barberán 2009; Pasinetti et al. 2018). However, in order to understand the potential modulatory potential of blueberry compounds it important to determine which strains are responsible for their (and their metabolites) metabolization. While some information is available regarding the fate of some phenolic compounds (e.g. ferulic and hydroxycinnamic acid is metabolized by *Lactobacillus*) there is a lack of information regarding the full complex interaction of all compounds, metabolites and the members of the microbiota while contextualizing with their actual proliferation therefore there is little to no insight into the mechanisms behind the modulations observed (Pasinetti et al. 2018).

Conclusions

Overall, several evidences can be found that link the consumption of blueberry and blueberry products with several different potential health benefits, with human based studies granting some strength to the potential health claims. However, to the best of our knowledge, only three health claims pertaining blueberry have been submitted to the European Food Safety Authority (EFSA), with both being denied on the grounds of lack of compliance with European legislation due to the either a lack of substantial scientific evidence or an insufficient characterization of the food product (Efsa Panel on Dietetic Products, Nutrition, and Allergies 2011a, 2011b, 2010). The immunomodulatory and antioxidant activities of blueberries and blueberry extracts, appear to be at the root of most of its potential to reduce the risk of disease. Nevertheless, the establishment of cause effect relationships is a complex matter, particularly in humans, where several extrinsic and intrinsic factors may introduce unforeseen bias into any given studies. Considering these arguments, while blueberry and its constituents exhibit an interesting potential, further studies are required in order to gather a better understanding of the real impact that their ingestion might bring. Moreover a better understanding of the underlying action mechanisms, potential synergies between ingredients is still needed as well as a perception of the concrete doses of phytochemicals required to exert the desired effects, information that is relatively scarce in literature.

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References

Acquaviva, R., A. Russo, F. Galvano, G. Galvano, M. L. Barcellona, G. Li Volti, and A. Vanella. 2003. Cyanidin and cyanidin 3-O-beta-D

-glucoside as DNA cleavage protectors and antioxidants. *Cell Biology and Toxicology* 19 (4):243–52.
Adisakwattana, S., N. Ngamrojanavanich, K. Kalampakorn, W. Tiravanit, S. Roengsumran, and S. Yibchok-Anun. 2004. Inhibitory activity of cyanidin-3-rutinoside on α-glucosidase. *Journal of Enzyme Inhibition and Medicinal Chemistry* 19 (4):313–6.
Ahn, J., H. Lee, S. Kim, J. Park, and T. Ha. 2008. The anti-obesity effect of quercetin is mediated by the AMPK and MAPK signaling pathways. *Biochemical and Biophysical Research Communications* 373 (4):545–9.
Alves, M., H. Froufe, A. Costa, A. Santos, L. Oliveira, S. Osório, R. Abreu, M. Pintado, and I. Ferreira. 2014. Docking studies in target proteins involved in antibacterial action mechanisms: Extending the knowledge on standard antibiotics to antimicrobial mushroom compounds. *Molecules* 19 (2):1672.
Andres-Lacueva, C., B. Shukitt-Hale, R. L. Galli, O. Jauregui, R. M. Lamuela-Raventos, and J. A. Joseph. 2005. Anthocyanins in aged blueberry-fed rats are found centrally and may enhance memory. *Nutritional Neuroscience* 8 (2):111–20. doi: 10.1080/10284150500078117.
Aqil, F., J. Jeyabalan, H. Kausar, R. Munagala, I. P. Singh, and R. Gupta. 2016. Lung cancer inhibitory activity of dietary berries and berry polyphenolics. *Journal of Berry Research* 6 (2):105–14. doi: 10.3233/JBR-160120.
Arredondo, F., C. Echeverry, J. A. Abin-Carriquiry, F. Blasina, K. Antúnez, D. P. Jones, Y.-M. Go, Y.-L. Liang, and F. Dajas. 2010. After cellular internalization, quercetin causes Nrf2 nuclear translocation, increases glutathione levels, and prevents neuronal death against an oxidative insult. *Free Radical Biology &Amp; Medicine* 49 (5):738–47.
Assmann, G., P. Cullen, F. Jossa, B. Lewis, and M. Mancini. 1999. Coronary heart disease: Reducing the risk: the scientific background to primary and secondary prevention of coronary heart disease a worldwide view. *Arteriosclerosis, Thrombosis, and Vascular Biology* 19 (8):1819–24.
Baba, A. B., R. Nivetha, I. Chattopadhyay, and S. Nagini. 2017. Blueberry and malvidin inhibit cell cycle progression and induce mitochondrial-mediated apoptosis by abrogating the JAK/STAT-3 signalling pathway. *Food and Chemical Toxicology : an International Journal Published for the British Industrial Biological Research Association* 109(Pt 1):534–43.
Bae, C. H., B. S. Jeon, Y. S. Choi, S.-Y. Song, and Y.-D. Kim. 2014. Delphinidin inhibits LPS-induced MUC8 and MUC5B expression through toll-like receptor 4-mediated ERK1/2 and p38 MAPK in human airway epithelial cells. *Clinical and Experimental Otorhinolaryngology* 7 (3):198
Bandyopadhyay, G., T. Biswas, K. C. Roy, S. Mandal, C. Mandal, B. C. Pal, S. Bhattacharya, S. Rakshit, D. K. Bhattacharya, U. Chaudhuri., et al. 2004. Chlorogenic acid inhibits Bcr-Abl tyrosine kinase and triggers p38 mitogen-activated protein kinase-dependent apoptosis in chronic myelogenous leukemic cells. *Blood* 104 (8):2514–22.
Barnes, J. S., H. P. Nguyen, S. Shen, and K. A. Schug. 2009. General method for extraction of blueberry anthocyanins and identification using high performance liquid chromatography–electrospray ionization-ion trap-time of flight-mass spectrometry. *Journal of Chromatography A* 1216 (23):4728–35. doi: http://dx.doi.org/10.1016/j.chroma.2009.04.032.
Basu, A., M. Rhone, and T. J. Lyons. 2010. Berries: emerging impact on cardiovascular health. *Nutrition Reviews* 68 (3):168–77. doi: 10.1111/j.1753-4887.2010.00273.x.
Bhattacharya, S., N. Oksbjerg, J. F. Young, and P. B. Jeppesen. 2014. Caffeic acid, naringenin and quercetin enhance glucose-stimulated insulin secretion and glucose sensitivity in INS-1E cells. *Diabetes, Obesity and Metabolism* 16 (7):602–12.
Bhuiyan, M. I. H., H.-B. Kim, S. Y. Kim, and K.-O. Cho. 2011. The neuroprotective potential of cyanidin-3-glucoside fraction extracted from mulberry following oxygen-glucose deprivation." *The. The Korean Journal of Physiology &Amp; Pharmacology : Official Journal of the Korean Physiological Society and the Korean Society of Pharmacology* 15(6):353–61.
Bingham, M. 2006. "The metabolism of polyphenols by the huma gut microbiota." In *Gatsrointestinal microbiology*. edited by Arthur C. Ouwehand and Elaine E. Vaughan, 155–168. New York, USA: Taylor & Francis Group.
Bjarnsholt, T. 2013. The role of bacterial biofilms in chronic infections. *APMIS Suppl* (136):1–51. doi: 10.1111/apm.12099.
Boots, A. W., L. C. Wilms, E. L. R. Swennen, J. C. S. Kleinjans, A. Bast, and G. R. M. M. Haenen. 2008. In vitro and ex vivo anti-inflammatory activity of quercetin in healthy volunteers. *Nutrition* 24 (7-8):703–10.
Borek, C. 2001. Antioxidant health effects of aged garlic extract. *The Journal of Nutrition* 131 (3s):1010S–5s.
Brambilla, A., R. Lo Scalzo, G. Bertolo, and D. Torreggiani. 2008. Steam-Blanched highbush blueberry (vaccinium corymbosum L.) juice: Phenolic profile and antioxidant capacity in relation to cultivar selection. *Journal of Agricultural and Food Chemistry* 56 (8):2643–8. doi: 10.1021/jf0731191.
Bridier, A., P. Sanchez-Vizuete, M. Guilbaud, J. C. Piard, M. Naïtali, and R. Briandet. 2015. Biofilm-associated persistence of food-borne pathogens. *Food Microbiology* 45 (0):167–78. doi: http://dx.doi.org/10.1016/j.fm.2014.04.015.
Bucki, R., J. J. Pastore, F. Giraud, J.-C. Sulpice, and P. A. Janmey. 2003. Flavonoid inhibition of platelet procoagulant activity and phosphoinositide synthesis. *Journal of Thrombosis and Haemostasis* 1 (8):1820–8. doi: doi:10.1046/j.1538-7836.2003.00294.x.
Burdulis, D., A. Sarkinas, I. Jasutiené, E. Stackevicené, L. Nikolajevas, and V. Janulis. 2009. Comparative study of anthocyanin composition, antimicrobial and antioxidant activity in bilberry (vaccinium myrtillus L.) and blueberry (vaccinium corymbosum L.) fruits. *Acta Poloniae Pharmaceutica* 66 (4):399–408.
Caballero, B. 2007. The global epidemic of obesity: An overview. *Epidemiologic Reviews* 29 (1):1–5. doi: 10.1093/epirev/mxm012.
Carvalho, E. N. D., N. A. Schmidt de Carvalho, and L. M. Ferreira. 2003. Experimental model of induction of diabetes mellitus in rats. *Acta Cirurgica Brasileira* 18(spe):60–4.
Cassidy, A., K. J. Mukamal, L. Liu, M. Franz, A. H. Eliassen, and E. B. Rimm. 2013. High anthocyanin intake is associated with a reduced risk of myocardial infarction in young and Middle-aged women. *Circulation* 127 (2):188–96. doi: 10.1161/circulationaha.112.122408.
Cassidy, A., M. Bertoia, S. Chiuve, A. Flint, J. Forman, and E. B. Rimm. 2016. Habitual intake of anthocyanins and flavanones and risk of cardiovascular disease in men. *The American Journal of Clinical Nutrition* 104 (3):587–94. doi: 10.3945/ajcn.116.133132.
Cassidy, A., G. Rogers, J. J. Peterson, J. T. Dwyer, H. Lin, and P. F. Jacques. 2015. Higher dietary anthocyanin and flavonol intakes are associated with anti-inflammatory effects in a population of US adults. *The American Journal of Clinical Nutrition* 102 (1):172–81. doi: 10.3945/ajcn.115.108555.
Cassileth, B. R. 1999. Complementary and alternative cancer medicine. *Journal of Clinical Oncology* 17 (suppl (1):44–52.
Castañeda-Ovando, A., M. D L. Pacheco-Hernández, M. E. Páez-Hernández, J. A. Rodríguez, and C. A. Galán-Vidal. 2009. Chemical studies of anthocyanins: a review. *Food Chemistry* 113 (4):859–71. doi: http://dx.doi.org/10.1016/j.foodchem.2008.09.001.
Chamcheu, J. C., H. C. Pal, I. A. Siddiqui, V. M. Adhami, S. Ayehunie, B. T. Boylan, F. K. Noubissi, N. Khan, D. N. Syed, C. A. Elmets., et al. 2015. Prodifferentiation, anti-inflammatory and antiproliferative effects of delphinidin, a dietary anthocyanidin, in a full-thickness three-dimensional reconstituted human skin model of psoriasis. *Skin Pharmacology and Physiology* 28 (4):177–88.
Chao, P-C, C-C Hsu, and M-C Yin. 2009. Anti-inflammatory and anticoagulatory activities of caffeic acid and ellagic acid in cardiac tissue of diabetic mice. *Nutrition &Amp; Metabolism* 6 (1):33
Chen, G., K. A. Bower, M. Xu, M. Ding, X. Shi, Z.-J. Ke, and J. Luo. 2009. Cyanidin-3-glucoside reverses ethanol-induced inhibition of neurite outgrowth: role of glycogen synthase kinase 3 beta. *Neurotoxicity Research* 15 (4):321–31.
Chen, P.-N., S.-C. Chu, H.-L. Chiou, C.-L. Chiang, S.-F. Yang, and Y.-S. Hsieh. 2005. Cyanidin 3-glucoside and peonidin 3-glucoside

inhibit tumor cell growth and induce apoptosis in vitro and suppress tumor growth in vivo. *Nutrition and Cancer* 53 (2):232–43.

Chen, P.-N., S.-C. Chu, H.-L. Chiou, W.-H. Kuo, C.-L. Chiang, and Y.-S. Hsieh. 2006. Mulberry anthocyanins, cyanidin 3-rutinoside and cyanidin 3-glucoside, exhibited an inhibitory effect on the migration and invasion of a human lung cancer cell line. *Cancer Letters* 235 (2):248–59. doi: http://dx.doi.org/10.1016/j.canlet.2005.04.033.

Chen, X.-L., and C. Kunsch. 2004. Induction of cytoprotective genes through Nrf2/antioxidant response element pathway: a new therapeutic approach for the treatment of inflammatory diseases. *Current Pharmaceutical Design* 10 (8):879–91. doi: 10.2174/1381612043452901.

Chen, Y.-J., M.-S. Shiao, and S.-Y. Wang. 2001. The antioxidant caffeic acid phenethyl ester induces apoptosis associated with selective scavenging of hydrogen peroxide in human leukemic HL-60 cells. *Anti-Cancer Drugs* 12 (2):143–9.

Cho, A.-S., S.-M. Jeon, M.-J. Kim, J. Yeo, K.-I. Seo, M.-S. Choi, and M.-K. Lee. 2010. Chlorogenic acid exhibits anti-obesity property and improves lipid metabolism in high-fat diet-induced-obese mice. *Food and Chemical Toxicology : an International Journal Published for the British Industrial Biological Research Association* 48 (3):937–43.

Choi, J.-A., J.-Y. Kim, J.-Y. Lee, C.-M. Kang, H.-J. Kwon, Y.-D. Yoo, T.-W. Kim, Y.-S. Lee, and S.-J. Lee. 2001. Induction of cell cycle arrest and apoptosis in human breast cancer cells by quercetin. *International Journal of Oncology* 19 (4):837–44.

Chopra, M., P. E. E. Fitzsimons, J. S. John, I. T. David, and N. H. Alan. 2000. Nonalcoholic red wine extract and quercetin inhibit LDL oxidation without affecting plasma antioxidant vitamin and carotenoid concentrations. *Clinical Chemistry* 46 (8):1162–70.

Chou, C.-C., J.-S. Yang, H.-F. Lu, S.-W. Ip, C. Lo, C.-C. Wu, J.-P. Lin, N.-Y. Tang, J.-G. Chung, M.-J. Chou., et al. 2010. Quercetin-mediated cell cycle arrest and apoptosis involving activation of a caspase Cascade through the mitochondrial pathway in human breast cancer MCF-7 cells. *Archives of Pharmacal Research* 33 (8):1181–91.

Chuang, C.-C., K. Martinez, G. Xie, A. Kennedy, A. Bumrungpert, A. Overman, W. Jia, and M. K. McIntosh. 2010. Quercetin is equally or more effective than resveratrol in attenuating tumor necrosis factor-{alpha}-mediated inflammation and insulin resistance in primary human adipocytes–. *The American Journal of Clinical Nutrition* 92 (6):1511–21.

Cimino, F., R. Ambra, R. Canali, A. Saija, and F. Virgili. 2006. Effect of cyanidin-3-O-glucoside on UVB-induced response in human keratinocytes. *Journal of Agricultural and Food Chemistry* 54 (11):4041–7.

Cisowska, A., D. Wojnicz, and A. B. Hendrich. 2011. Anthocyanins as antimicrobial agents of natural plant origin. *Natural Products Communication* 6 (1):149–56.

Comalada, M., D. Camuesco, S. Sierra, I. Ballester, J. Xaus, J. Gálvez, and A. Zarzuelo. 2005. In vivo quercitrin anti-inflammatory effect involves release of quercetin, which inhibits inflammation through down-regulation of the NF-kappaB pathway . *European Journal of Immunology* 35 (2):584–92.

Cooke, D., M. Schwarz, D. Boocock, P. Winterhalter, W. P. Steward, A. J. Gescher, and T. H. Marczylo. 2006. Effect of cyanidin-3-glucoside and an anthocyanin mixture from bilberry on adenoma development in the ApcMin mouse model of intestinal carcinogenesis-relationship with tissue anthocyanin levels. *International Journal of Cancer* 119 (9):2213–20.

Cooper, C. E., N. B. J. Vollaard, T. Choueiri, and M. T. Wilson. 2002. Exercise, free radicals and oxidative stress. *Biochemical Society Transactions* 30 (2):280–5. doi: 10.1042/bst0300280.

Da Cunha, F. M., D. Duma, J. Assreuy, F. C. Buzzi, R. Niero, M. M. Campos, and J. B. Calixto. 2004. Caffeic acid derivatives: in vitro and in vivo anti-inflammatory properties. *Free Radical Research* 38 (11):1241–53.

da Silva, E. L., M. K. Piskula, N. Yamamoto, J.-H. Moon, and J. Terao. 1998. Quercetin metabolites inhibit copper ion-induced lipid peroxidation in rat plasma 1. *FEBS Letters* 430 (3):405–8.

Dai, T., K. Shi, G. Chen, Y. Shen, and T. Pan. 2017. Malvidin attenuates pain and inflammation in rats with osteoarthritis by suppressing NF-κB signaling pathway. *Inflamm. Res.]* 66 (12):1075–84.

Danesh, J., P. W. M. W. L. L. A. T. P. A. Ruth, J. G. Mark, and B. Pepys. 2000. Low grade inflammation and coronary heart disease: prospective study and updated Meta-analyses. *Bmj* 321 (7255):199–204. doi: 10.1136/bmj.321.7255.199.

Davì, G., and C. Patrono. 2007. Platelet activation and atherothrombosis. *The New England Journal of Medicine* 357 (24):2482–94.

de Sotillo, D., V. Rodriguez, and M. Hadley. 2002. Chlorogenic acid modifies plasma and liver concentrations of: cholesterol, triacylglycerol, and minerals in (fa/fa) zucker rats. *The Journal of Nutritional Biochemistry* 13 (12):717–26.

Debom, G., Gazal, M. M. S. P. Soares, C. A. T. do Couto, B. Mattos, C. Lencina, M. P. Kaster, G. C. Ghisleni, R. Tavares, E. Braganhol, V. C., et al. 2016. Preventive effects of blueberry extract on behavioral and biochemical dysfunctions in rats submitted to a model of manic behavior induced by ketamine. *Brain Research Bulletin* 127 :260–9. doi: http://dx.doi.org/10.1016/j.brainresbull.2016.10.008.

DeFuria, J., G. Bennett, K. J. Strissel, J. W. Perfield, P. E. Milbury, A. S. Greenberg, and M. S. Obin. 2009. Dietary blueberry attenuates Whole-Body insulin resistance in high Fat-Fed mice by reducing adipocyte death and its inflammatory sequelae. *The Journal of Nutrition* 139 (8):1510–6. doi: 10.3945/jn.109.105155.

Del Bo', C., D. Fracassetti, C. Lanti, M. Porrini, and P. Riso. 2015. Comparison of DNA damage by the comet assay in fresh versus cryopreserved peripheral blood mononuclear cells obtained following dietary intervention. *Mutagenesis* 30 (1):29–35. doi: 10.1093/mutage/geu058.

Del Bo', C., D. Martini, S. Vendrame, P. Riso, S. Ciappellano, D. Klimis-Zacas, and M. Porrini. 2010. Improvement of lymphocyte resistance against H2O2-induced DNA damage in sprague–dawley rats after eight weeks of a wild blueberry (vaccinium angustifolium)-enriched diet. *Mutation Research/Genetic Toxicology and Environmental Mutagenesis* 703 (2):158–62. doi: http://dx.doi.org/10.1016/j.mrgentox.2010.08.013.

Diaconeasa, Z., L. Leopold, D. Rugină, H. Ayvaz, and C. Socaciu. 2015. Antiproliferative and antioxidant properties of anthocyanin rich extracts from blueberry and blackcurrant juice. *International Journal of Molecular Sciences* 16 (2):2352

Dias, A. S., M. Porawski, M. Alonso, N. Marroni, P. S. Collado, and J. Gonzalez-Gallego. 2005. Quercetin decreases oxidative stress, NF-kappaB activation, and iNOS overexpression in liver of streptozotocin-induced diabetic rats. *J. Nutr* 135 (10):2299–304.

Ding, M., R. Feng, S. Y. Wang, L. Bowman, Y. Lu, Y. Qian, V. Castranova, B.-H. Jiang, and X. Shi. 2006. Cyanidin-3-glucoside, a natural product derived from blackberry, exhibits chemopreventive and chemotherapeutic activity. *The Journal of Biological Chemistry* 281 (25):17359–68.

Dok-Go, H., K. H. Lee, H. J. Kim, E. H. Lee, J. Lee, Y. S. Song, Y.-H. Lee, C. Jin, Y. S. Lee, and J. Cho. 2003. Neuroprotective effects of antioxidative flavonoids, quercetin,(+)-dihydroquercetin and quercetin 3-methyl ether, isolated from opuntia ficus-indica var. saboten. *Brain Research* 965 (1-2):130–6.

Dong, J., X. Zhang, L. Zhang, H.-X. Bian, N. Xu, B. Bao, and J. Liu. 2014. Quercetin reduces obesity-associated adipose tissue macrophage infiltration and inflammation in mice: a mechanism including AMPKα1/SIRT1. *Journal of Lipid Research:jlr* M038786

Dong, X-X, Y. Wang, and Z-h Qin. 2009. Molecular mechanisms of excitotoxicity and their relevance to pathogenesis of neurodegenerative diseases. *Acta Pharmacologica Sinica* 30 (4):379

Dos Santos, M. D., M. C. Almeida, N. P. Lopes, and G. E. P. De Souza. 2006. Evaluation of the anti-inflammatory, analgesic and antipyretic activities of the natural polyphenol chlorogenic acid." *biological and Biological &Amp; Pharmaceutical Bulletin* 29(11):2236–40.

Ebenezer, P. J., C. B. Wilson, L. D. Wilson, A. R. Nair, and F. J. 2016. The anti-Inflammatory Effects of blueberries in an animal model of Post-Traumatic stress disorder (PTSD). *Plos One* 11 (9):e0160923. doi: 10.1371/journal.pone.0160923.

Efsa Panel on Dietetic Products, Nutrition, and Allergies. 2010. Scientific opinion on the substantiation of health claims related to various food(s)/food constituent(s) and protection of cells from premature ageing (ID 1668, 1917, 2515, 2527, 2530, 2575, 2580, 2591, 2620, 3178, 3179, 3180, 3181, 4329, 4415), antioxidant activity, antioxidant content and antioxidant properties (ID 857, 1306, 2515, 2527, 2530, 2575, 2580, 2591, 2629, 2728, 4327, 4365, 4380, 4390, 4394, 4455, 4464, 4507, 4694, 4705), protection of DNA, proteins and lipids from oxidative damage (ID 1196, 1211, 1216, 1306, 1312, 1440, 1441, 1666, 1668, 1692, 1900, 1914, 1948, 2023, 2158, 2517, 2522, 2527, 2575, 2591, 2620, 2637, 2639, 2663, 2860, 3079, 3276, 3564, 3818, 4324, 4329, 4351, 4397, 4416, 4424, 4507, 4527, 4528, 4542, 4611, 4629, 4659) and bioavailability of anthocyanins in black currants (ID 4220) pursuant to article 13(1) of regulation (EC) no 1924/2006. *EFSA Journal* 8 (10):1752. n/a. doi: 10.2903/j.efsa.2010.1752.

Efsa Panel on Dietetic Products, Nutrition, and Allergies. 2011a. Scientific opinion on the substantiation of health claims related to: a combination of millet seed extract, L-cystine and pantothenic acid (ID 1514), amino acids (ID 1711), carbohydrate and protein combination (ID 461), ribes nigrum L. (ID 2191), Vitis vinifera L. (ID 2157), grifola frondosa (ID 2556), juice concentrate from berries of vaccinium macrocarpon aiton and vaccinium vitis-idaea L. (ID 1125, 1288), blueberry juice drink and blueberry extracts (ID 1370, 2638), a combination of anthocyanins from bilberry and blackcurrant (ID 2796), inulin-type fructans (ID 766, 767, 768, 769, 770, 771, 772, 804, 848, 849, 2922, 3092), green clay (ID 347, 1952), foods and beverages "low in energy", "energy-free" and "energy-reduced" (ID 1146, 1147), and carbohydrate foods and beverages (ID 458, 459, 470, 471, 654, 1277, 1278, 1279) pursuant to article 13(1) of regulation (EC) No 1924/2006. *EFSA Journal* 9(6):2244. n/a. doi: 10.2903/j.efsa.2011.2244.

Efsa Panel on Dietetic Products, Nutrition, and Allergies. 2011b. Scientific opinion part I on the substantiation of health claims related to various food(s)/food constituent(s) not supported by pertinent human data (ID 411, 559, 1174, 1184, 1197, 1380, 1409, 1656, 1667, 1670, 1763, 1767, 1806, 1884, 1908, 1997, 2141, 2159, 2243, 2244, 2325, 2331, 2333, 2336, 2652, 2717, 2727, 2752, 2788, 2861, 2870, 2885, 2894, 3077, 3101, 3516, 3595, 3726, 4252, 4288, 4290, 4406, 4509, 4709) pursuant to article 13(1) of regulation (EC) no 1924/2006. *EFSA Journal* 9 (6):2246. n/a. doi: 10.2903/j.efsa.2011.2246.

Egert, S., A. Bosy-Westphal, J. Seiberl, C. Kürbitz, U. Settler, S. Plachta-Danielzik, A. E. Wagner, J. Frank, J. Schrezenmeir, G. Rimbach., et al. 2009. Quercetin reduces systolic blood pressure and plasma oxidised low-density lipoprotein concentrations in overweight subjects with a high-cardiovascular disease risk phenotype: a double-blinded, placebo-controlled cross-over study. *The British Journal of Nutrition* 102 (7):1065–74.

Elisia, I., and D. D. Kitts. 2008. Anthocyanins inhibit peroxyl radical-induced apoptosis in caco-2 cells. *Molecular and Cellular Biochemistry* 312 (1-2):139–45.

Elks, C. M., J. D. Terrebonne, D. K. Ingram, and J. M. Stephens. 2015. Blueberries improve glucose tolerance without altering body composition in obese postmenopausal mice. *Obesity (Silver Spring, Md.)* 23 (3):573–80.

Felgines, C., O. Texier, C. Besson, D. Fraisse, J.-L. Lamaison, and C. Rémésy. 2002. Blackberry anthocyanins are slightly bioavailable in rats. *J. Nutr* 132 (6):1249–53.

Feng, R., H.-M. Ni, S. Y. Wang, I. L. Tourkova, M. R. Shurin, H. Harada, and X.-M. Yin. 2007. Cyanidin-3-rutinoside, a natural polyphenol antioxidant, selectively kills leukemic cells by induction of oxidative stress. *The Journal of Biological Chemistry* 282 (18):13468–76.

Figueira, M.-E., O. Mónica, D. Rosa, R. João, A. Paula, A.-T. Serra, C. Duarte, R. Bronze, F. Adelaide, B. Dora., et al. 2016. Protective effects of a blueberry extract in acute inflammation and collagen-induced arthritis in the rat. *Biomedicine & Pharmacotherapy* 83 : 1191–202. doi: http://dx.doi.org/10.1016/j.biopha.2016.08.040.

Fukumoto, L. R., and G. Mazza. 2000. Assessing antioxidant and prooxidant activities of phenolic compounds. *Journal of Agricultural and Food Chemistry* 48 (8):3597–604.

Fux, C. A., J. W. Costerton, P. S. Stewart, and P. Stoodley. 2005. Survival strategies of infectious biofilms. *Trends in Microbiology* 13 (1):34–40. doi: 10.1016/j.tim.2004.11.010.

García-Mediavilla, V., I. Crespo, P. S. Collado, A. Esteller, S. Sánchez-Campos, M. J. Tuñón, and J. González-Gallego. 2007. The anti-inflammatory flavones quercetin and kaempferol cause inhibition of inducible nitric oxide synthase, cyclooxygenase-2 and reactive C-protein, and down-regulation of the nuclear factor kappaB pathway in chang liver cells. *European Journal of Pharmacology* 557 (2-3):221–9.

Gavrilova, V., M. KajdžAnoska, V. Gjamovski, and M. Stefova. 2011. Separation, characterization and quantification of phenolic compounds in blueberries and red and black currants by HPLC – DAD – ESI-MSn. *Journal of Agricultural and Food Chemistry* 59(8):4009–18. no. doi: 10.1021/jf104565y.

Gaziano, T. A., D. Prabhakaran, and J. Michael Gaziano. 2015. "Global bruden of cardiovascular disease." In *Traunwald's heart Disease - A textbook of cardiovascular medicine*, edited by Douglas L. Mann, Dougals P. Zipes, Peter Libby and Robert O Bonow. Philadelphia, USA: Elsevier Saunders.

Gharib, A., Z. Faezizadeh, and M. Godarzee. 2013. Treatment of diabetes in the mouse model by delphinidin and cyanidin hydrochloride in free and liposomal forms. *Planta Medica* 79 (17):1599–604.

Gibson, G. R., and C. M. Williams. 2000. *Functional foods: Concept to product*. Cambridge, England: Woodhead Publishing Limited.

Giongo, L., E. Bozza, C. Patrizio, E. Valente, M. T. Pasquazzo, C. Pedrolli, E. L. Iorio, and A. Costa. 2011. "Short-term blueberry intake enhances biological antioxidant potential and modulates inflammation markers in overweight and obese children. *Journal of Berry Research* 1 (3):147–158.

Giudice, A., and M. Montella. 2006. Activation of the Nrf2-ARE signaling pathway: a promising strategy in cancer prevention. *Bioessays : News and Reviews in Molecular, Cellular and Developmental Biology* 28 (2):169–81.

Graf, B. A., P. E. Milbury, and J. B. Blumberg. 2005. Flavonols, flavones, flavanones, and human health: Epidemiological evidence. *Journal of Medicinal Food* 8 (3):281–90. doi: 10.1089/jmf.2005.8.281.

Granado-Serrano, A. B., M. Angeles Martín, M. Izquierdo-Pulido, L. Goya, L. Bravo, and S. Ramos. 2007. Molecular mechanisms of (−)-epicatechin and chlorogenic acid on the regulation of the apoptotic and survival/proliferation pathways in a human hepatoma cell line. *Journal of Agricultural and Food Chemistry* 55 (5):2020–7.

Granado-Serrano, A. B., M. A. Martín, L. Bravo, L. Goya, and S. Ramos. 2006. Quercetin induces apoptosis via caspase activation, regulation of bcl-2, and inhibition of PI-3-kinase/akt and ERK pathways in a human hepatoma cell line (HepG2). *The Journal of Nutrition* 136(11):2715–21. no.

Guardia, T., A. E. Rotelli, A. O. Juarez, and L. E. Pelzer. 2001. Anti-inflammatory properties of plant flavonoids. Effects of rutin, quercetin and hesperidin on adjuvant arthritis in rat. *Il Farmaco* 56 (9):683–7.

Guerrero, J. A., M. L. Lozano, J. Castillo, O. Benavente-García, V. Vicente, and J. Rivera. 2005. Flavonoids inhibit platelet function through binding to the thromboxane A2 receptor. *Journal of Thrombosis and Haemostasis* 3 (2):369–76. doi: doi:10.1111/j.1538-7836.2004.01099.x.

Guerrero, J. A., L. Navarro-Nuñez, M. L. Lozano, C. Martínez, V. Vicente, J. M. Gibbins, and J. Rivera. 2007. Flavonoids inhibit the platelet TxA2 signalling pathway and antagonize TxA2 receptors (TP) in platelets and smooth muscle cells. *British Journal of Clinical Pharmacology* 64 (2):133–44. doi: 10.1111/j.1365-2125.2007.02881.x.

Guo, H., W. Ling, Q. Wang, C. Liu, Y. Hu, and M. Xia. 2008. Cyanidin 3-glucoside protects 3T3-L1 adipocytes against H2O2-or TNF-α-induced insulin resistance by inhibiting c-Jun NH2-terminal kinase activation. *Biochemical Pharmacology* 75 (6):1393–401.

Guo, H., M. Xia, T. Zou, W. Ling, R. Zhong, and W. Zhang. 2012. Cyanidin 3-glucoside attenuates obesity-associated insulin resistance and hepatic steatosis in high-fat diet-fed and db/db mice via the transcription factor FoxO1. *The Journal of Nutritional Biochemistry* 23 (4):349–60.

Hafeez, B. B., I. A. Siddiqui, M. Asim, A. Malik, F. Afaq, V. M. Adhami, M. Saleem, M. Din, and H. Mukhtar. 2008. A dietary anthocyanidin delphinidin induces apoptosis of human prostate cancer PC3 cells in vitro and in vivo: involvement of nuclear factor-kappaB signaling. *Cancer Research* 68 (20):8564–72.

Haleagrahara, N., C. J. Siew, N. K. Mitra, and M. Kumari. 2011. Neuroprotective effect of bioflavonoid quercetin in 6-hydroxydopamine-induced oxidative stress biomarkers in the rat striatum. *Neuroscience Letters* 500 (2):139–43. doi: https://doi.org/10.1016/j.neulet.2011.06.021.

Hämäläinen, M., R. Nieminen, P. Vuorela, M. Heinonen, and E. Moilanen. 2007. Anti-inflammatory effects of flavonoids: genistein, kaempferol, quercetin, and daidzein inhibit STAT-1 and NF-κB activations, whereas flavone, isorhamnetin, naringenin, and pelargonidin inhibit only NF-κB activation along with their inhibitory effect on iNOS expression and NO production in activated macrophages. *Mediators of Inflammation* 2007 :1.

Hardie, D. G., J. W. Scott, D. A. Pan, and E. R. Hudson. 2003. Management of cellular energy by the AMP-activated protein kinase system. *FEBS Letters* 546 (1):113–20.

Hayek, T., B. Fuhrman, J. Vaya, M. Rosenblat, P. Belinky, R. Coleman, A. Elis, and M. Aviram. 1997. Reduced progression of atherosclerosis in apolipoprotein E–deficient mice following consumption of red wine, or its polyphenols quercetin or catechin, is associated with reduced susceptibility of LDL to oxidation and aggregation. *Arteriosclerosis, Thrombosis, and Vascular Biology* 17 (11):2744–52.

Heinonen, I. M., A. S. Meyer, and E. N. Frankel. 1998. Antioxidant activity of berry phenolics on human Low-Density lipoprotein and liposome oxidation. *Journal of Agricultural and Food Chemistry* 46 (10):4107–12. doi: 10.1021/jf980181c.

Herman, G. A., A. Bergman, C. Stevens, P. Kotey, B. Yi, P. Zhao, B. Dietrich, G. Golor, A. Schrodter, B. Keymeulen., et al. 2006. Effect of single oral doses of sitagliptin, a dipeptidyl peptidase-4 inhibitor, on incretin and plasma glucose levels after an oral glucose tolerance test in patients with type 2 diabetes. *The Journal of Clinical Endocrinology and Metabolism* 91 (11):4612–9.

Hidalgo, M., M. J. Oruna-Concha, S. Kolida, G. E. Walton, S. Kallithraka, J. P. E. Spencer, G. R. Gibson, and S. de Pascual-Teresa. 2012. Metabolism of anthocyanins by human gut microflora and their influence on gut bacterial growth. *Journal of Agricultural and Food Chemistry* 60 (15):3882–90. doi: 10.1021/jf3002153.

Hill, J. O., John, and C. Peters. 1998. Environmental contributions to the obesity epidemic. *Science* 280 (5368):1371–4. doi: 10.1126/science.280.5368.1371.

Ho, M.-L., P.-N. Chen, S.-C. Chu, D.-Y. Kuo, W.-H. Kuo, J.-Y. Chen, and Y.-S. Hsieh. 2010. Peonidin 3-glucoside inhibits lung cancer metastasis by downregulation of proteinases activities and MAPK pathway. *Nutrition and Cancer* 62 (4):505–16.

Hou, D.-X., X. Tong, N. Terahara, D. Luo, and M. Fujii. 2005. Delphinidin 3-sambubioside, a hibiscus anthocyanin, induces apoptosis in human leukemia cells through reactive oxygen species-mediated mitochondrial pathway. *Archives of Biochemistry and Biophysics* 440 (1):101–9.

Hou, D.-X., T. Yanagita, T. Uto, S. Masuzaki, and M. Fujii. 2005. Anthocyanidins inhibit cyclooxygenase-2 expression in LPS-evoked macrophages: Structure–activity relationship and molecular mechanisms involved. *Biochemical Pharmacology* 70 (3):417–25. doi: https://doi.org/10.1016/j.bcp.2005.05.003.

Huang, M.-T., R. C. Smart, C.-Q. Wong, and A. H. Conney. 1988. Inhibitory effect of curcumin, chlorogenic acid, caffeic acid, and ferulic acid on tumor promotion in mouse skin by 12-O-tetradecanoylphorbol-13-acetate. *Cancer Research* 9 (12):2221–5946.

Huang, S.-M., H.-C. Chuang, C.-H. Wu, and G.-C. Yen. 2008. Cytoprotective effects of phenolic acids on methylglyoxal-induced apoptosis in Neuro-2A cells. *Molecular Nutrition &Amp; Food Research* 52 (8):940–9.

Huang, W.-Y., Y.-M. Liu, J. Wang, X.-N. Wang, and C.-Y. Li. 2014. Anti-inflammatory effect of the blueberry anthocyanins malvidin-3-glucoside and malvidin-3-galactoside in endothelial cells. *Molecules* 19 (8):12827–41.

Huang, W.-Y., J. Wang, Y.-M. Liu, Q.-S. Zheng, and C.-Y. Li. 2014. Inhibitory effect of malvidin on TNF-α-induced inflammatory response in endothelial cells. *European Journal of Pharmacology* 723 :67–72.

Huang, W., Y. Zhu, C. Li, Z. Sui, and W. Min. 2016. Effect of blueberry anthocyanins malvidin and glycosides on the antioxidant properties in endothelial cells. *Oxidative Medicine and Cellular Longevity* 2016 :1. 10. doi: 10.1155/2016/1591803.

Hwang, S. J., Y.-W. Kim, Y. Park, H.-J. Lee, and K.-W. Kim. 2014. Anti-inflammatory effects of chlorogenic acid in lipopolysaccharide-stimulated RAW 264.7 cells. *Inflammation Research* 63 (1):81–90.

Hyun, J. W., and H. S. Chung. 2004. Cyanidin and malvidin from Oryza sativa cv. Heugjinjubyeo mediate cytotoxicity against human monocytic leukemia cells by arrest of G2/M phase and induction of apoptosis. *Journal of Agricultural and Food Chemistry* 52(8):2213–7.

Ito, H., X.-L. Sun, M. Watanabe, M. Okamoto, and T. Hatano. 2008. Chlorogenic acid and its metabolite m-coumaric acid evoke neurite outgrowth in hippocampal neuronal cells. *Bioscience, Biotechnology, and Biochemistry* 72 (3):885–8.

Hohtola, A., L. Jaakola, K. Määttä-Riihinen, and S. Kärenlampi. 2004. Activation of flavonoid biosynthesis by solar radiation in bilberry (vaccinium myrtillus L.) leaves. *Planta* 218 (5):721–8. doi: 10.1007/s00425-003-1161-x.

Jeyabalan, J., F. Aqil, R. Munagala, L. Annamalai, M. V. Vadhanam, and R. C. Gupta. 2014. Chemopreventive and therapeutic activity of dietary blueberry against estrogen-mediated breast cancer. *Journal of Agricultural and Food Chemistry* 62 (18):3963–71. doi: 10.1021/jf403734j.

Jiang, Y., K. Kusama, K. Satoh, F. Takayama, S. Watanabe, and H. Sakagami. 2000. Induction of cytotoxicity by chlorogenic acid in human oral tumor cell lines. *Phytomedicine : International Journal of Phytotherapy and Phytopharmacology* 7 (6):483–91.

Jin, X., M. Chen, L. Yi, H. Chang, T. Zhang, L. Wang, W. Ma, X. Peng, Y. Zhou, and M. Mi. 2014. Delphinidin-3-glucoside protects human umbilical vein endothelial cells against oxidized low-density lipoprotein-induced injury by autophagy upregulation via the AMPK/SIRT1 signaling pathway. *Molecular Nutrition & Food Research* 58 (10):1941–51.

Jin, X., L. Yi, M-L Chen, C-y Chen, H. Chang, T. Zhang, L. Wang, J-D Zhu, Q-y Zhang, and M-T Mi. 2013. Delphinidin-3-glucoside protects against oxidized low-density lipoprotein-induced mitochondrial dysfunction in vascular endothelial cells via the sodium-dependent glucose transporter SGLT1. *PloS One* 8 (7):e68617

Jo, Y. N., D. E. Jin, J. H. Jeong, H. J. Kim, D.-O. Kim, and H. J. Heo. 2015. Effect of anthocyanins from rabbit-eye blueberry (*Vaccinium virgatum*) on cognitive function in mice under trimethyltin-induced neurotoxicity. *Food Science and Biotechnology* 24 (3):1077–85. doi:10.1007/s10068-015-0138-4.

Johnson, S. A., A. Figueroa, N. Navaei, A. Wong, R. Kalfon, L. T. Ormsbee, R. G. Feresin, M. L. Elam, S. Hooshmand, M. E. Payton, and B. H. Arjmandi. 2015. Daily blueberry consumption improves blood pressure and arterial stiffness in postmenopausal women with pre- and stage 1-Hypertension: a randomized, Double-Blind, Placebo-Controlled clinical trial. *Journal of the Academy of Nutrition and Dietetics* 115 (3):369–77. doi: http://dx.doi.org/10.1016/j.jand.2014.11.001.

Jung, K.-H., K. Chu, S.-T. Lee, H.-K. Park, J.-H. Kim, K.-M. Kang, M. Kim, S. K. Lee, and J.-K. Roh. 2009. Augmentation of nitrite therapy in cerebral ischemia by NMDA receptor inhibition. *Biochemical and Biophysical Research Communications* 378 (3):507–12.

Jung, U. J., M.-K. Lee, Y. B. Park, S.-M. Jeon, and M.-S. Choi. 2006. Antihyperglycemic and antioxidant properties of caffeic acid in db/db mice. *The Journal of Pharmacology and Experimental Therapeutics* 318 (2):476–83.

Juźwiak, S., J. Wójcicki, K. Mokrzycki, M. Marchlewicz, M. Białecka, L. Wenda-Rózewicka, B. Gawrońska-Szklarz, and M. Droździk. 2005.

Effect of quercetin on experimental hyperlipidemia and atherosclerosis in rabbits. *Pharmacological Reports: Pr* 57(5):604–9.):

Kader, F., B. Rovel, M. Girardin, and M. Metche. 1996. Fractionation and identification of the phenolic compounds of highbush blueberries (*Vaccinium corymbosum*, L.). *Food Chemistry* 55 (1):35–40. doi: http://dx.doi.org/10.1016/0308-8146(95)00068-2.

Kähkönen, M. P., and M. Heinonen. 2003. Antioxidant activity of anthocyanins and their aglycons. *Journal of Agricultural and Food Chemistry* 51 (3):628–33.

Kalt, W., J. B. Blumberg, J. E. McDonald, M. R. Vinqvist-Tymchuk, S. A. E. Fillmore, B. A. Graf, J. M. O'Leary, and P. E. Milbury. 2008. Identification of anthocyanins in the liver, eye, and brain of blueberry-fed pigs. *Journal of Agricultural and Food Chemistry* 56 (3): 705–12. doi: 10.1021/jf071998l.

Kalt, W., C. F. Forney, A. Martin, and R. L. Prior. 1999. Antioxidant capacity, vitamin C, phenolics, and anthocyanins after fresh storage of small fruits. *Journal of Agricultural and Food Chemistry* 47 (11): 4638–44. doi: 10.1021/jf990266t.

Kamada, C., E. L. da Silva, M. Ohnishi-Kameyama, J.-H. Moon, and J. Terao. 2005. Attenuation of lipid peroxidation and hyperlipidemia by quercetin glucoside in the aorta of high cholesterol-fed rabbit. *Free Radical Research* 39 (2):185–94.

Kang, T. H., J. Y. Hur, H. B. Kim, J. H. Ryu, and S. Y. Kim. 2006. Neuroprotective effects of the cyanidin-3-O-β-d-glucopyranoside isolated from mulberry fruit against cerebral ischemia. *Neuroscience Letters* 391 (3):122–6.

Karthikesan, K.,. L. Pari, and V. P. Menon. 2010. Antihyperlipidemic effect of chlorogenic acid and tetrahydrocurcumin in rats subjected to diabetogenic agents. *Chemico-Biological Interactions* 188 (3): 643–50.

Kaume, L., W. C. Gilbert, C. Brownmiller, L. R. Howard, and L. Devareddy. 2012. Cyanidin 3-O-β-D-glucoside-rich blackberries modulate hepatic gene expression, and anti-obesity effects in ovariectomized rats. *Journal of Functional Foods* 4 (2):480–8.

Kay, C. D. 2006. Aspects of anthocyanin absorption, metabolism and pharmacokinetics in humans. *Nutrition Research Reviews* 19(01): 137–46. doi: 10.1079/nrr2005116.

Ke, Z., Y. Liu, X. Wang, Z. Fan, G. Chen, M. Xu, K. A. Bower, J. A. Frank, X. Ou, X. Shi, and J. Luo. 2011. Cyanidin-3-glucoside ameliorates ethanol neurotoxicity in the developing brain. *Journal of Neuroscience Research* 89 (10):1676–84.

Khalifa, H. O., M. Kamimoto, T. Shimamoto, and T. Shimamoto. 2015. Antimicrobial effects of blueberry, raspberry, and strawberry aqueous extracts and their effects on virulence gene expression in Vibrio cholerae. *Phytotherapy Research* 29(11):1791–7. doi: 10.1002/ptr.5436.

Khanduja, K. L., P. K. Avti, S. Kumar, N. Mittal, K. K. Sohi, and C. M. Pathak. 2006. Anti-apoptotic activity of caffeic acid, ellagic acid and ferulic acid in normal human peripheral blood mononuclear cells: a bcl-2 independent mechanism. *Biochimica et Biophysica Acta (BBA)-General Subjects* 1760 (2):283–9.

Kim, C.-S., Y. Kwon, S.-Y. Choe, S.-M. Hong, H. Yoo, T. Goto, T. Kawada, H.-S. Choi, Y. Joe, H. T. Chung, and R. Yu. 2015. Quercetin reduces obesity-induced hepatosteatosis by enhancing mitochondrial oxidative metabolism via heme oxygenase-1. *Nutrition & Metabolism* 12 (1):33

Kim, H.-S., D. Sul, J.-Y. Lim, D. Lee, S. S. Joo, K. W. Hwang, and S.-Y. Park. 2009. Delphinidin ameliorates beta-amyloid-induced neurotoxicity by inhibiting calcium influx and tau hyperphosphorylation. *Bioscience, Biotechnology, and Biochemistry* 73 (7):1685–9.

Kim, H. G., M. S. Ju, J. S. Shim, M. C. Kim, S.-H. Lee, Y. Huh, S. Y. Kim, and M. S. Oh. 2010. Mulberry fruit protects dopaminergic neurons in toxin-induced Parkinson's disease models. *The British Journal of Nutrition* 104 (1):8–16.

Kim, J.-H., M.-J. Kang, H.-N. Choi, S.-M. Jeong, Y.-M. Lee, and J.-I. Kim. 2011. Quercetin attenuates fasting and postprandial hyperglycemia in animal models of diabetes mellitus. *Nutrition Research and Practice* 5 (2):107–11.

Kleemann, R., L. Verschuren, M. Morrison, S. Zadelaar, M. J. van Erk, P. Y. Wielinga, and T. Kooistra. 2011. Anti-inflammatory, anti-proliferative and anti-atherosclerotic effects of quercetin in human in vitro and in vivo models. *Atherosclerosis* 218 (1):44–52.

Kong, J.-M., L.-S. Chia, N.-K. Goh, T.-F. Chia, and R. Brouillard. 2003. Analysis and biological activities of anthocyanins. *Phytochemistry* 64 (5):923–33. doi: http://dx.doi.org/10.1016/S0031-9422(03)00438-2.

Kono, Y., K. Kobayashi, S. Tagawa, K. Adachi, A. Ueda, Y. Sawa, and H. Shibata. 1997. Antioxidant activity of polyphenolics in diets: rate constants of reactions of chlorogenic acid and caffeic acid with reactive species of oxygen and nitrogen. *Biochimica et Biophysica Acta (BBA)-General Subjects* 1335 (3):335–42.

Kou, X., L. Han, X. Li, Z. Xue, and F. Zhou. 2016. Antioxidant and antitumor effects and immunomodulatory activities of crude and purified polyphenol extract from blueberries. *Frontiers of Chemical Science and Engineering* 10 (1):108–19. doi: 10.1007/s11705-016-1553-7.

Krakauer, T. 2002. The polyphenol chlorogenic acid inhibits staphylococcal exotoxin-induced inflammatory cytokines and chemokines. *Immunopharmacology and Immunotoxicology* 24 (1):113–9.

Krantic, S., N. Mechawar, S. Reix, and R. Quirion. 2005. Molecular basis of programmed cell death involved in neurodegeneration. *Trends in Neurosciences* 28 (12):670–6.

Krauss, A., and J. Fischer. 2013. *Malvidin and delphinidin exhibit a dose-dependent effect on cell viability and apoptosis in HT-29 cells*. Georgia, USA: University of Georgia.

Krikorian, R., M. D. Shidler, T. A. Nash, W. Kalt, M. R. Vinqvist-Tymchuk, B. Shukitt-Hale, and J. A. Joseph. 2010. Blueberry supplementation improves memory in older adults. *Journal of Agricultural and Food Chemistry* 58 (7):3996–4000. doi: 10.1021/jf9029332.

Kroon, P. A., M. N. Clifford, A. Crozier, A. J. Day, J. L. Donovan, C. Manach, and G. Williamson. 2004. How should we assess the effects of exposure to dietary polyphenols in vitro? *The American Journal of Clinical Nutrition* 80 (1):15–21.

Kulisic-Bilusic, T., K. Schnäbele, I. Schmöller, V. Dragovic-Uzelac, A. Krisko, B. Dejanovic, M. Milos, and G. Pifat. 2009. Antioxidant activity versus cytotoxic and nuclear factor kappa B regulatory activities on HT-29 cells by natural fruit juices. *European Food Research and Technology* 228 (3):417–24.

Kwon, S.-H., H.-K. Lee, J.-A. Kim, S.-I. Hong, H.-C. Kim, T.-H. Jo, Y.-I. Park, C.-K. Lee, Y.-B. Kim, S.-Y. Lee, and C.-G. Jang. 2010. Neuroprotective effects of chlorogenic acid on scopolamine-induced amnesia via anti-acetylcholinesterase and anti-oxidative activities in mice. *European Journal of Pharmacology* 649 (1-3):210–7.

Lacombe, A., V. C. H. Wu, J. White, S. Tadepalli, and E. E. Andre. 2012. The antimicrobial properties of the lowbush blueberry (*Vaccinium angustifolium*) fractional components against foodborne pathogens and the conservation of probiotic Lactobacillus rhamnosus. *Food Microbiology* 30(1):124–31. doi: http://dx.doi.org/10.1016/j.fm.2011.10.006.

Lee, C.-W., T.-J. Won, H.-R. Kim, D.-H. Lee, K.-W. Hwang, and S.-Y. Park. 2011. Protective effect of chlorogenic acid against Aβ-induced neurotoxicity. *Biomolecules & Therapeutics* 19 (2):181–6.

Lee, J., R. W. Durst, and R. E. Wrolstad. 2002. Impact of juice processing on blueberry anthocyanins and polyphenolics: Comparison of two pretreatments. *Journal of Food Science* 67 (5):1660–7. doi: 10.1111/j.1365-2621.2002.tb08701.x.

Lee, J. S., Y. R. Kim, J. M. Park, Y. E. Kim, N. I. Baek, and E. K. Hong. 2015. Cyanidin-3-glucoside isolated from mulberry fruits protects pancreatic β-cells against glucotoxicity-induced apoptosis. *Molecular Medicine Reports* 11(4):2723–8.

Lee, J. S., Y. R. Kim, I. G. Song, S.-J. Ha, Y. E. Kim, N.-I. Baek, and E. K. Hong. 2015. Cyanidin-3-glucoside isolated from mulberry fruit protects pancreatic β-cells against oxidative stress-induced apoptosis. *International Journal of Molecular Medicine* 35 (2):405–12.

Lee, L.-T., Y.-T. Huang, J.-J. Hwang, P. P. Lee, F.-C. Ke, P. N. Madhavan, C. Kanadaswam, and M.-T. Lee. 2002. Blockade of the epidermal growth factor receptor tyrosine kinase activity by quercetin and luteolin leads to growth inhibition and apoptosis of pancreatic tumor cells. *Anticancer Research* 22 (3):1615–27.

Lee, S. G., B. Kim, Y. Yang, T. X. Pham, Y.-K. Park, J. Manatou, S. I. Koo, O. K. Chun, and J.-Y. Lee. 2014. Berry anthocyanins suppress the expression and secretion of proinflammatory mediators in macrophages by inhibiting nuclear translocation of NF-κB independent of NRF2-mediated mechanism. *The Journal of Nutritional Biochemistry* 25 (4):404–11.

Lee, S., R. Kirkland, G. F. Joan, and C. D L. Serre. 2016. Blueberry supplementation impacts gut microbiota, inflammatory profiles, and insulin sensitivity in high-fat fed rats. *The FASEB Journal No. 30 (1 Supplement)* 692 :25.

Lee, Y.-J., H.-C. Kuo, C.-Y. Chu, C.-J. Wang, W.-C. Lin, and T.-H. Tseng. 2003. Involvement of tumor suppressor protein p53 and p38 MAPK in caffeic acid phenethyl ester-induced apoptosis of C6 glioma cells. *Biochemical Pharmacology* 66 (12):2281–9.

Li, W., S. M. Saud, M. R. Young, G. Chen, and B. Hua. 2015. Targeting AMPK for cancer prevention and treatment. *Oncotarget* 6 (10):7365–78.

Li, Y., W. Shi, Y. Li, Y. Zhou, X. Hu, C. Song, H. Ma, C. Wang, and Y. Li. 2008. Neuroprotective effects of chlorogenic acid against apoptosis of PC12 cells induced by methylmercury. *Environmental Toxicology and Pharmacology* 26 (1):13–21.

Libby, P. 2007. Inflammatory mechanisms: the molecular basis of inflammation and disease. *Nutrition Reviews* 65 (12 Pt 2):S140–S6.

Lin, M. T., and M. F. Beal. 2006. Mitochondrial dysfunction and oxidative stress in neurodegenerative diseases. *Nature* 443 (7113):787.

Lin, Y.-C., P.-F. Tsai, and J. S.-B. Wu. 2014. Protective effect of anthocyanidins against sodium dithionite-induced hypoxia injury in C6 glial cells. *Journal of Agricultural and Food Chemistry* 62 (24):5603–8.

Liu, W., X. Lu, G. He, X. Gao, M. Li, J. Wu, Z. Li, J. Wu, J. Wang, and C. Luo. 2013. Cytosolic protection against ultraviolet induced DNA damage by blueberry anthocyanins and anthocyanidins in hepatocarcinoma HepG2 cells. *Biotechnology Letters* 35 (4):491–8. doi: 10.1007/s10529-012-1105-2.

Liu, W., J. Chen, Q. Li, and A. Sun. 2016. Inhibitory effects of acylated blueberry anthocyanin on H22 murine tumors. *Food and Agricultural Immunology* 27 (4):509–22. doi: 10.1080/09540105.2015.1129599.

Liu, Z., L. Wang, H. J. Liu, Z., and X. Wang. 2013. MicroRNA-21 (miR-21) expression promotes growth, metastasis, and chemo- or radioresistance in non-small cell lung cancer cells by targeting PTEN. *Molecular and Cellular Biochemistry* 372(1-2):35. doi: 10.1007/s11010-012-1443-3.

Lopez-Cid, A., O. Palomino, E. Carretero, and T. Ortega. 2014. Neuroprotective effects of anthocyanidins on astrocytes and apoptosis induced by oxidative damage. *Planta Medica* 80 (16):P2O59.

Lu, J., D-M Wu, Y-L Zheng, B. Hu, and Z-F Zhang. 2010. Purple sweet potato color alleviates D-galactose-induced brain aging in old mice by promoting survival of neurons via PI3K pathway and inhibiting cytochrome C-mediated apoptosis. *Brain Pathology (Zurich, Switzerland)* 20 (3):598–612.

Lucin, K. M., and T. Wyss-Coray. 2009. Immune activation in brain aging and neurodegeneration: Too much or too little? *Neuron* 64 (1):110–22.

Ma, Y., M. Gao, and D. Liu. 2015. Chlorogenic acid improves high fat diet-induced hepatic steatosis and insulin resistance in mice. *Pharmaceutical Research* 32 (4):1200–9.

Manach, C., C. Morand, V. Crespy, C. Demigné, O. Texier, F. Régérat, and C. Rémésy. 1998. Quercetin is recovered in human plasma as conjugated derivatives which retain antioxidant properties. *FEBS Letters* 426 (3):331–6.

Martin, S., G. Giannone, R. Andriantsitohaina, and M. C. Martinez. 2003. Delphinidin, an active compound of red wine, inhibits endothelial cell apoptosis via nitric oxide pathway and regulation of calcium homeostasis. *British Journal of Pharmacology* 139 (6):1095–102. doi: 10.1038/sj.bjp.0705347.

Martin, S., G. Giannone, R. Andriantsitohaina, and M. Carmen Martinez. 2003. Delphinidin, an active compound of red wine, inhibits endothelial cell apoptosis via nitric oxide pathway and regulation of calcium homeostasis. *British Journal of Pharmacology* 139 (6):1095–102.

Mathew, S., T. E. Abraham, and Z. A. Zakaria. 2015. Reactivity of phenolic compounds towards free radicals under in vitro conditions. *Journal of Food Science and Technology* 52 (9):5790–8. doi: 10.1007/s13197-014-1704-0.

Mazza, G., C. D. Kay, T. Cottrell, and B. J. Holub. 2002. Absorption of anthocyanins from blueberries and serum antioxidant status in human subjects. *Journal of Agricultural and Food Chemistry* 50 (26):7731–7. doi: 10.1021/jf020690l.

McAnulty, L. S., D. C. Nieman, C. L. Dumke, L. A. Shooter, D. A. Henson, A. C. Utter, G. Milne, and S. R. McAnulty. 2011. Effect of blueberry ingestion on natural killer cell counts, oxidative stress, and inflammation prior to and after 2.5 h of running. *Applied Physiology, Nutrition, and Metabolism* 36 (6):976–84. doi: 10.1139/h11-120.

Meireles, M.,. C. Marques, S. Norberto, P. Santos, I. Fernandes, N. Mateus, A. Faria, and C. Calhau. 2016. Anthocyanin effects on microglia M1/M2 phenotype: Consequence on neuronal fractalkine expression. *Behavioural Brain Research* 305 :223–8. doi: 10.1016/j.bbr.2016.03.010.

Meng, S., J. Cao, Q. Feng, J. Peng, and Y. Hu. 2013. Roles of chlorogenic acid on regulating glucose and lipids metabolism: a review. *Evidence-Based Complementary and Alternative Medicine* 2013 :1.

Meyer, A. S., M. Heinonen, and E. N. Frankel. 1998. Antioxidant interactions of catechin, cyanidin, caffeic acid, quercetin, and ellagic acid on human LDL oxidation. *Food Chemistry* 61 (1-2):71–5.

Milbury, P. E., and A. C. Richer. 2008. *Understanding the Antioxidant Controversy: Scrutinizing the "fountain of Youth*". Santa Barbara, CA: Praeger.

Miller, N. J., and C. A. Rice-Evans. 1997. The relative contributions of ascorbic acid and phenolic antioxidants to the total antioxidant activity of orange and apple fruit juices and blackcurrant drink. *Food Chemistry* 60 (3):331–7.

Min, J., S.-W. Yu, S.-H. Baek, K. M. Nair, O.-N. Bae, A. Bhatt, M. Kassab, M. G. Nair, and A. Majid. 2011. Neuroprotective effect of cyanidin-3-O-glucoside anthocyanin in mice with focal cerebral ischemia. *Neuroscience Letters* 500 (3):157–61.

Min, Y.-D., C.-H. Choi, H. Bark, H.-Y. Son, H.-H. Park, S. Lee, J.-W. Park, E.-K. Park, H.-I. Shin, and S.-H. Kim. 2007. Quercetin inhibits expression of inflammatory cytokines through attenuation of NF-κB and p38 MAPK in HMC-1 human mast cell line. *Inflammation Research* 56 (5):210–5. doi: 10.1007/s00011-007-6172-9.

Minokoshi, Y., Y.-B. Kim, O. D. Peroni, L. G. D. Fryer, C. Müller, D. Carling, and B. B. Kahn. 2002. Leptin stimulates fatty-acid oxidation by activating AMP-activated protein kinase. *Nature* 415 (6869):339.

Morand, C., V. Crespy, C. Manach, C. Besson, C. Demigné, and C. Rémésy. 1998. Plasma metabolites of quercetin and their antioxidant properties. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology* 275 (1):R212–9.

Morton, L. W., R. A.-A. Caccetta, I. B. Puddey, and K. D. Croft. 2000. Chemistry and biological effects of dietary phenolic compounds: Relevance to cardiovascular disease. *Clinical and Experimental Pharmacology and Physiology* 27 (3):152–9. doi: 10.1046/j.1440-1681.2000.03214.x.

Mulabagal, V., G. A. Lang, D. L. DeWitt, S. S. Dalavoy, and M. G. Nair. 2009. Anthocyanin content, lipid peroxidation and cyclooxygenase enzyme inhibitory activities of sweet and sour cherries. *Journal of Agricultural and Food Chemistry* 57 (4):1239–46.

Murata, T., C. Ohtsuka, and Y. Terayama. 2008. Increased mitochondrial oxidative damage and oxidative DNA damage contributes to the neurodegenerative process in sporadic amyotrophic lateral sclerosis. *Free Radical Research* 42 (3):221–5.

Narayan, M. S., K. Akhilender Naidu, G. A. Ravishankar, L. Srinivas, and L. V. Venkataraman. 1999. Antioxidant effect of anthocyanin on enzymatic and non-enzymatic lipid peroxidation. *Prostaglandins, Leukotrienes and Essential Fatty Acids (PLEFA)* 60 (1):1–4.

Nardini, M., F. Natella, V. Gentili, M. D. Felice, and C. Scaccini. 1997. Effect of caffeic acid dietary supplementation on the antioxidant defense system in rat: Anin VivoStudy. *Archives of Biochemistry and Biophysics* 342 (1):157–60.

Nasri, S., M. Roghani, T. Baluchnejadmojarad, M. Balvardi, and T. Rabani. 2012. Chronic cyanidin-3-glucoside administration improves short-term spatial recognition memory but not passive avoidance learning and memory in streptozotocin-diabetic rats. *Phytotherapy Research : Ptr* 26 (8):1205–10.

Nasri, S., M. Roghani, T. Baluchnejadmojarad, T. Rabani, and M. Balvardi. 2011. Vascular mechanisms of cyanidin-3-glucoside response in streptozotocin-diabetic rats. *Pathophysiology : The Official Journal of the International Society for Pathophysiology* 18 (4):273–8.

Neto, C. C. 2007. Cranberry and blueberry: Evidence for protective effects against cancer and vascular diseases. *Molecular Nutrition & Food Research* 51 (6):652–64. doi: 10.1002/mnfr.200600279.

Nguyen, T. T. T., E. Tran, T. H. Nguyen, P. T. Do, T. H. Huynh, and H. Huynh. 2003. The role of activated MEK-ERK pathway in quercetin-induced growth inhibition and apoptosis in A549 lung cancer cells. *Carcinogenesis* 25 (5):647–59.

Nijveldt, R. J., E. van Nood, D. E. van Hoorn, P. G. Boelens, K. van Norren, and P. A. van Leeuwen. 2001. Flavonoids: a review of probable mechanisms of action and potential applications. *The American Journal of Clinical Nutrition* 74 (4):418–25.

Noda, Y., T. Kaneyuki, A. Mori, and L. Packer. 2002. Antioxidant activities of pomegranate fruit extract and its anthocyanidins: delphinidin, cyanidin, and pelargonidin. *Journal of Agricultural and Food Chemistry* 50 (1):166–71.

Norata, G. D., P. Marchesi, S. Passamonti, A. Pirillo, F. Violi, and A. L. Catapano. 2007. Anti-inflammatory and anti-atherogenic effects of cathechin, caffeic acid and trans-resveratrol in apolipoprotein E deficient mice. *Atherosclerosis* 191 (2):265–71.

Oboh, G., O. M. Agunloye, S. A. Adefegha, A. J. Akinyemi, and A. O. Ademiluyi. 2015. Caffeic and chlorogenic acids inhibit key enzymes linked to type 2 diabetes (in vitro): A comparative study. *Journal of Basic and Clinical Physiology and Pharmacology* 26 (2):165–70.

Ong, K. W., A. Hsu, and B. K. H. Tan. 2013. Anti-diabetic and anti-lipidemic effects of chlorogenic acid are mediated by ampk activation. *Biochemical Pharmacology* 85 (9):1341–51.

Orlicek, S. L., E. Meals, and B. K. English. 1996. Differential effects of tyrosine kinase inhibitors on tumor necrosis factor and nitric oxide production by murine macrophages. *Journal of Infectious Diseases* 174 (3):638–42.

Paixao, J., T. C. P. Dinis, and L. M. Almeida. 2012. Protective role of malvidin-3-glucoside on peroxynitrite-induced damage in endothelial cells by counteracting reactive species formation and apoptotic mitochondrial pathway. *Oxidative Medicine and Cellular Longevity* 2012 :1.

Park, Y. C., G. Rimbach, C. Saliou, G. Valacchi, and L. Packer. 2000. Activity of monomeric, dimeric, and trimeric flavonoids on NO production, TNF-alpha secretion, and NF-kappaB-dependent gene expression in RAW 264.7 macrophages. *FEBS Letters* 465 (2-3):93–7.

Parra-Vargas, M., A. Sandoval-Rodriguez, R. Rodriguez-Echevarria, J. A. Dominguez-Rosales, A. Santos-Garcia, and J. Armendariz-Borunda. 2018. Delphinidin ameliorates hepatic triglyceride accumulation in human HepG2 cells, but not in diet-induced obese mice. *Nutrients* 10 (8):1060.

Pasinetti, G. M., R. Singh, S. Westfall, F. Herman, J. Faith, and L. Ho. 2018. The role of the gut microbiota in the metabolism of polyphenols as characterized by gnotobiotic mice. *Journal of Alzheimer's Disease* 63 (2):409–21. doi: 10.3233/jad-171151.

Pekkarinen, S. S., I. M. Heinonen, and A. I. Hopia. 1999. Flavonoids quercetin, myricetin, kaemferol and (+)-catechin as antioxidants in methyl linoleate. *Journal of the Science of Food and Agriculture* 79 (4):499–506. doi: 10.1002/(SICI)1097-0010(19990315)79:4 < 499::AID-JSFA204 > 3.0.CO;2-U.

Pepe, G., M. R. Grossi, A. Berni, S. Filippi, R. K. Shanmugakani, C. Papeschi, P. Mosesso, A. T. Natarajan, and F. Palitti. 2013. Effect of blueberries (BB) on micronuclei induced by N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) and 7,12-dimethylbenz(a)anthracene (DMBA) in mammalian cells, assessed in in vitro and in vivo assays. *Mutation Research* 758 (1-2):6–11. doi: 10.1016/j.mrgentox.2013.07.012.

Pertuzatti, P. B., M. T. Barcia, L. P. G. Rebello, S. Gómez-Alonso, R. M. T. Duarte, M. C. T. Duarte, H. T. Godoy, and I. Hermosín-Gutiérrez. 2016. Antimicrobial activity and differentiation of anthocyanin profiles of rabbiteye and highbush blueberries using HPLC–DAD–ESI-MSn and multivariate analysis. *Journal of Functional Foods* 26 :506–16. doi: http://dx.doi.org/10.1016/j.jff.2016.07.026.

Pignatelli, P.,. F. M. Pulcinelli, A. Celestini, L. Lenti, A. Ghiselli, P. P. Gazzaniga, and F. Violi. 2000. The flavonoids quercetin and catechin synergistically inhibit platelet function by antagonizing the intracellular production of hydrogen peroxide. *The American Journal of Clinical Nutrition* 72 (5):1150–5.

Piljac-Žegarac, J., A. Belščak, and A. Piljac. 2009. Antioxidant capacity and polyphenolic content of blueberry (vaccinium corymbosum L.) leaf infusions. *Journal of Medicinal Food* 12 (3):608–14. doi: 10.1089/jmf.2008.0081.

Pinelo, M., L. Manzocco, M. José Nuñez, and M. Cristina Nicoli. 2004. Solvent effect on quercetin antioxidant capacity. *Food Chemistry* 88 (2):201–7.

Porter, L. J., L. N. Hrstich, and B. G. Chan. 1985. The conversion of procyanidins and prodelphinidins to cyanidin and delphinidin. *Phytochemistry* 25 (1):223–30.

Pratheeshkumar, P.,. Y.-O. Son, X. Wang, S. P. Divya, B. Joseph, J. A. Hitron, L. Wang, D. Kim, Y. Yin, R. V. Roy., et al. 2014. Cyanidin-3-glucoside inhibits UVB-induced oxidative damage and inflammation by regulating MAP kinase and NF-κB signaling pathways in SKH-1 hairless mice skin. *Toxicology and Applied Pharmacology* 280 (1):127–37.

Prior, R. L., X. Wu, L. Gu, T. Hager, A. Hager, S. Wilkes, and L. Howard. 2009. Purified berry anthocyanins but not whole berries normalize lipid parameters in mice fed an obesogenic high fat diet. *Molecular Nutrition & Food Research* 53 (11):1406–18.

Prior, R. L., G. Cao, A. Martin, E. Sofic, J. McEwen, C. O'Brien, N. Lischner, M. Ehlenfeldt, W. Kalt, G. Krewer, and C. M. Mainland. 1998. Antioxidant capacity as influenced by total phenolic and anthocyanin content, maturity, and variety of vaccinium species. *Journal of Agricultural and Food Chemistry* 46 (7):2686–93. doi: 10.1021/jf980145d.

Prior, R. L., S. E. Wilkes, T. R. Rogers, R. C. Khanal, X. Wu, and L. R. Howard. 2010. Purified blueberry anthocyanins and blueberry juice alter development of obesity in mice fed an obesogenic High-Fat diet. *Journal of Agricultural and Food Chemistry* 58 (7):3970–6. doi: 10.1021/jf902852d.

Prior, R. L., S. A. Lazarus, G. Cao, H. Muccitelli, and J. F. Hammerstone. 2001. Identification of procyanidins and anthocyanins in blueberries and cranberries (vaccinium spp.) using High-Performance liquid chromatography/mass spectrometry. *Journal of Agricultural and Food Chemistry* 49 (3):1270–6. doi: 10.1021/jf001211q.

Prior, R. L., X. Wu, L. Gu, T. J. Hager, A. Hager, and L. R. Howard. 2008. Whole berries versus berry anthocyanins: Interactions with dietary fat levels in the C57BL/6J mouse model of obesity. *Journal of Agricultural and Food Chemistry* 56 (3):647–53. doi: 10.1021/jf071993o.

Priyadarsini, R., Vidya, R. Senthil Murugan, S. Maitreyi, K. Ramalingam, D. Karunagaran, and S. Nagini. 2010. The flavonoid quercetin induces cell cycle arrest and mitochondria-mediated apoptosis in human cervical cancer (HeLa) cells through p53 induction and NF-κB inhibition. *European Journal of Pharmacology* 649 (1-3):84–91.

Pu, F., K. Mishima, K. Irie, K. Motohashi, Y. Tanaka, K. Orito, T. Egawa, Y. Kitamura, N. Egashira, K. Iwasaki, and M. Fujiwara. 2007. Neuroprotective effects of quercetin and rutin on spatial memory impairment in an 8-arm radial maze task and neuronal death induced by repeated cerebral ischemia in rats. *Journal of Pharmacological Sciences* 104 (4):329–34.

Rahman, N., M. Jeon, and Y. -S. Kim. 2016. Delphinidin, a major anthocyanin, inhibits 3T3-L1 pre-adipocyte differentiation through activation of wnt/β-catenin signaling. *Biofactors* 42 (1):49–59.

Rakshit, S., L. Mandal, B. C. Pal, J. Bagchi, N. Biswas, J. Chaudhuri, A. A. Chowdhury, A. Manna, U. Chaudhuri, A. Konar., et al. 2010. Involvement of ROS in chlorogenic acid-induced apoptosis of Bcr-Abl + CML cells. *Biochemical Pharmacology* 80 (11):1662–75.

Ramirez-Tortosa, C., O. M. Andersen, L. Cabrita, P. T. Gardner, P. C. Morrice, S. G. Wood, S. J. Duthie, A. R. Collins, and G. G. Duthie. 2001. Anthocyanin-rich extract decreases indices of lipid peroxidation and DNA damage in vitamin E-depleted rats. *Free Radical Biology & Medicine* 31 (9):1033–7.

Rasheed, Z., N. Akhtar, A. N. Anbazhagan, S. Ramamurthy, M. Shukla, and T. M. Haqqi. 2009. Polyphenol-rich pomegranate fruit extract (POMx) suppresses PMACI-induced expression of pro-inflammatory cytokines by inhibiting the activation of MAP kinases and NF-kappaB in human KU812 cells. *Journal of Inflammation (London, England)* 6 (:1

Reddivari, L., J. Vanamala, S. Chintharlapalli, S. H. Safe, and J. Creighton Miller. Jr. 2007. Anthocyanin fraction from potato extracts is cytotoxic to prostate cancer cells through activation of caspase-dependent and caspase-independent pathways. *Carcinogenesis* 28(10):2227–2235.

Riso, P., D. Klimis-Zacas, C. Del Bo', D. Martini, J. Campolo, S. Vendrame, P. Møller, S. Loft, R. De Maria, and M. Porrini. 2013. Effect of a wild blueberry (*Vaccinium angustifolium*) drink intervention on markers of oxidative stress, inflammation and endothelial function in humans with cardiovascular risk factors. *European Journal of Nutrition* 52 (3):949–961. doi: 10.1007/s00394-012-0402-9.

Rivera, L., R. Morón, M. Sánchez, A. Zarzuelo, and M. Galisteo. 2008. Quercetin ameliorates metabolic syndrome and improves the inflammatory status in obese zucker rats. *Obesity (Silver Spring, Md.)* 16 (9):2081–2087.

Rogerio, A. P., C. L. Dora, E. L. Andrade, J. S. Chaves, L. F. C. Silva, E. Lemos-Senna, and J. B. Calixto. 2010. Anti-inflammatory effect of quercetin-loaded microemulsion in the airways allergic inflammatory model in mice. *Pharmacological Research* 61 (4):288–297.

Rossetto, M., P. Vanzani, F. Mattivi, M. Lunelli, M. Scarpa, and A. Rigo. 2002. Synergistic antioxidant effect of catechin and malvidin 3-glucoside on free radical-initiated peroxidation of linoleic acid in micelles. *Archives of Biochemistry and Biophysics* 408 (2):239–245.

Rossi, M., E. Negri, C. Bosetti, C. Pelucchi, and C. L. Vecchia. 2009. "Epidemiology behind fruit and vegetable consumption and cancer risk with focus on flavonoids." In *Plant phenolics and human health: Biochemistry, nutrition and pharmacology*, edited by C. G. Fraga, 1–51. New Jersey, USA: John Wiley & Sons Inc.

Routray, W., and V. Orsat. 2011. Blueberries and their anthocyanins: Factors affecting biosynthesis and properties. *Comprehensive Reviews in Food Science and Food Safety* 10 (6):303–320. doi: 10.1111/j.1541-4337.2011.00164.x.

Ruggeri, Z. M. 2002. Platelets in atherothrombosis. *Nature Medicine* 8 (11):1227

Ruggeri, Z. M. 2003. Von willebrand factor, platelets and endothelial cell interactions. *Journal of Thrombosis and Haemostasis: Jth* 1 (7): 1335–1342.

Sanjabi, S.,. L. A. Zenewicz, M. Kamanaka, and R. A. Flavell. 2009. Anti- and pro-inflammatory roles of TGF-β, IL-10, and IL-22 in immunity and autoimmunity. *Current Opinion in Pharmacology* 9 (4):447–453. doi: 10.1016/j.coph.2009.04.008.

Sasaki, R., N. Nishimura, H. Hoshino, Y. Isa, M. Kadowaki, T. Ichi, A. Tanaka, S. Nishiumi, I. Fukuda, H. Ashida., et al. 2007. Cyanidin 3-glucoside ameliorates hyperglycemia and insulin sensitivity due to downregulation of retinol binding protein 4 expression in diabetic mice. *Biochemical Pharmacology* 74 (11):1619–27.

Sato, Y., S. Itagaki, T. Kurokawa, J. Ogura, M. Kobayashi, T. Hirano, M. Sugawara, and K. Iseki. 2011. In vitro and in vivo antioxidant properties of chlorogenic acid and caffeic acid. *International Journal of Pharmaceutics* 403 (1-2):136–8.

Scalbert, A., C. Manach, C. Morand, C. Rémésy, and L. Jiménez. 2005. Dietary polyphenols and the prevention of diseases. *Critical Reviews in Food Science and Nutrition* 45 (4):287–306. doi: 10.1080/1040869059096.

Scalbert, A., and G. Williamson. 2000. Dietary intake and bioavailability of polyphenols. *The Journal of Nutrition* 130 (8S Suppl): 2073S–85S.

Schroeter, H., R. J. Williams, R. Matin, L. Iversen, and C. A. Rice-Evans. 2000. Phenolic antioxidants attenuate neuronal cell death following uptake of oxidized low-density lipoprotein. *Free Radical Biology and Medicine* 29 (12):1222–33.

Schültke, E., H. Kamencic, M. Zhao, G.-F. Tian, A. J. Baker, R. W. Griebel, and B. H. J. Juurlink. 2005. Neuroprotection following fluid percussion brain trauma: A pilot study using quercetin. *Journal of Neurotrauma* 22 (12):1475–84. doi: 10.1089/neu.2005.22.1475.

Seeram, N. P. 2008. Berry fruits for cancer prevention: Current status and future prospects. *Journal of Agricultural and Food Chemistry* 56 (3):630–5. doi: 10.1021/jf072504n.

Seeram, N. P., L. S. Adams, Y. Zhang, R. Lee, D. Sand, H. S. Scheuller, and D. Heber. 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 and Food Chemistry* 54 (25):9329–39. doi: 10.1021/jf061750g.

Selma, M. V., J. C. Espín, and F. A. Tomás-Barberán. 2009. Interaction between phenolics and gut microbiota: Role in human health. *Journal of Agricultural and Food Chemistry* 57(15):6485–501. no. doi: 10.1021/jf902107d.

Seong, A.-R., J.-Y. Yoo, KChul Choi, M.-H. Lee, Y.-H. Lee, J. Lee, W. Jun, S. Kim, and H.-G. Yoon. 2011. Delphinidin, a specific inhibitor of histone acetyltransferase, suppresses inflammatory signaling via prevention of NF-κB acetylation in fibroblast-like synoviocyte MH7A cells. *Biochemical and Biophysical Research Communications* 410 (3):581–6.

Serra, D., J. Paixão, C. Nunes, T. C. P. Dinis, and L. M. Almeida. 2013. Cyanidin-3-glucoside suppresses cytokine-induced inflammatory response in human intestinal cells: Comparison with 5-aminosalicylic acid. *PloS One* 8 (9):e73001.

Seymour, E. M., I. I. Tanone, D. E. Urcuyo-Llanes, S. K. Lewis, A. Kirakosyan, M. G. Kondoleon, P. B. Kaufman, and S. F. Bolling. 2011. Blueberry intake alters skeletal muscle and adipose tissue peroxisome Proliferator-Activated receptor activity and reduces insulin resistance in obese rats. *Journal of Medicinal Food* 14 (12):1511–8. doi: 10.1089/jmf.2010.0292.

Shah, S. A., G. H. Yoon, and M. O. Kim. 2015. Protection of the developing brain with anthocyanins against Ethanol-Induced oxidative stress and neurodegeneration. *Molecular Neurobiology* 51 (3): 1278–91. doi: 10.1007/s12035-014-8805-7.

Shan, J., J. Fu, Z. Zhao, X. Kong, H. Huang, L. Luo, and Z. Yin. 2009. Chlorogenic acid inhibits lipopolysaccharide-induced cyclooxygenase-2 expression in RAW264.7 cells through suppressing NF-kappaB and JNK/AP-1 activation. *International Immunopharmacology* 9 (9):1042–8.

Shen, W., R. Qi, J. Zhang, Z. Wang, H. Wang, C. Hu, Y. Zhao, M. Bie, Y. Wang, Y. Fu., et al. 2012. Chlorogenic acid inhibits LPS-induced microglial activation and improves survival of dopaminergic neurons. *Brain Research Bulletin* 88 (5):487–94.

Shen, X., X. Sun, Q. Xie, H. Liu, Y. Zhao, Y. Pan, C.-A. Hwang, and V. C. H. Wu. 2014. Antimicrobial effect of blueberry (*Vaccinium corymbosum* L.) extracts against the growth of Listeria monocytogenes and Salmonella Enteritidis. *Food Control* 35(1):159–65. doi: http://dx.doi.org/10.1016/j.foodcont.2013.06.040.

Shen, Y., N. C. Ward, J. M. Hodgson, I. B. Puddey, Y. Wang, D. Zhang, G. J. Maghzal, R. Stocker, and K. D. Croft. 2013. Dietary quercetin attenuates oxidant-induced endothelial dysfunction and atherosclerosis in apolipoprotein E knockout mice fed a high-fat diet: A critical role for heme oxygenase-1. *Free Radical Biology & Medicine* 65 :908–15.

Shi, H., L. Dong, J. Jiang, J. Zhao, G. Zhao, X. Dang, X. Lu, and M. Jia. 2013. Chlorogenic acid reduces liver inflammation and fibrosis through inhibition of toll-like receptor 4 signaling pathway. *Toxicology* 303 :107–14.

Shih, P.-H., C.-H. Wu, C.-T. Yeh, and G.-C. Yen. 2011. Protective effects of anthocyanins against amyloid β-Peptide-Induced damage in neuro-2A cells. *Journal of Agricultural and Food Chemistry* 59 (5):1683–9. doi: 10.1021/jf103822h.

Shih, P.-H., C.-T. Yeh, and G.-C. Yen. 2005. Effects of anthocyanidin on the inhibition of proliferation and induction of apoptosis in human gastric adenocarcinoma cells. *Food and Chemical Toxicology: An International Journal Published for the British Industrial Biological Research Association* 43 (10):1557–66.

Shih, P.-H., C.-T. Yeh, and G.-C. Yen. 2007. Anthocyanins induce the activation of phase II enzymes through the antioxidant response element pathway against oxidative stress-induced apoptosis. *Journal of Agricultural and Food Chemistry* 55 (23):9427–35. doi: 10.1021/jf071933i.

Shin, H. S., H. Satsu, M.-J. Bae, Z. Zhao, H. Ogiwara, M. Totsuka, and M. Shimizu. 2015. Anti-inflammatory effect of chlorogenic acid on the IL-8 production in caco-2 cells and the dextran sulphate sodium-induced colitis symptoms in C57BL/6 mice. *Food Chemistry* 168 :167–75.

Shin, W.-H., S.-J. Park, and E.-J. Kim. 2006. Protective effect of anthocyanins in Middle cerebral artery occlusion and reperfusion model of cerebral ischemia in rats. *Life Sciences* 79 (2):130–7.

Shisheva, A., and Y. Shechter. 1992. Quercetin selectively inhibits insulin receptor function in vitro and the bioresponses of insulin and insulinomimetic agents in rat adipocytes. *Biochemistry* 31 (34): 8059–63.

Shukitt-Hale, B., F. C. Lau, A. N. Carey, R. L. Galli, E. L. Spangler, D. K. Ingram, and J. A. Joseph. 2008. Blueberry polyphenols attenuate kainic acid-induced decrements in cognition and alter inflammatory gene expression in rat hippocampus. *Nutritional Neuroscience* 11 (4):172–82. doi: 10.1179/147683008X301487.

Sies, H. 2007. Total antioxidant capacity: appraisal of a concept. *The Journal of Nutrition* 137 (6):1493–5.

Silva, S., E. M. Costa, M. Mendes, R. M. Morais, C. Calhau, and M. M. Pintado. 2016. Antimicrobial, antiadhesive and antibiofilm activity of an ethanolic anthocyanin rich blueberry extract purified by solid phase extraction. *Journal of Applied Microbiology* 121 (3):693–703. doi: 10.1111/jam.13215.

Silva, S.,. E. M. Costa, M. R. Costa, M. F. Pereira, J. O. Pereira, J. C. Soares, and M. M. Pintado. 2015. Aqueous extracts of *Vaccinium corymbosum* as inhibitors of *Staphylococcus aureus*. *Food Control* 51(Supplement C):314–20. doi: https://doi.org/10.1016/j.foodcont.2014.11.040.

Skrede, G., R. E. Wrolstad, and R. W. Durst. 2000. Changes in anthocyanins and polyphenolics during juice processing of highbush blueberries (*Vaccinium corymbosum* L.). *Journal of Food Science* 65 (2): 357–64. doi: 10.1111/j.1365-2621.2000.tb16007.x.

Song, J., M. Zhao, X. Liu, Y. Zhu, X. Hu, and F. Chen. 2013. Protection of cyanidin-3-glucoside against oxidative stress induced by acrylamide in human MDA-MB-231 cells. *Food and Chemical Toxicology: An International Journal Published for the British Industrial Biological Research Association* 58 :306–10.

Song, Y., H. J. Park, S. N. Kang, S.-H. Jang, S.-J. Lee, Y.-G. Ko, G.-S. Kim, and J.-H. Cho. 2013. Blueberry peel extracts inhibit adipogenesis in 3T3-L1 cells and reduce high-fat diet-induced obesity. *PLoS ONE* 8 (7):e69925. doi: 10.1371/journal.pone.0069925.

Sousa, M. B., T. Curado, F. Negrão e Vasconcelos, and M. João Trigo. 2007. Mirtilo - Qualidade pós-colheita. *Divulgação AGRO* 8 :556. (

South, S., J. Lucero, V. Imrhan, C. Prasad, P. Vijayagopal, and S. Juma. 2016. Anti-proliferative and anti-inflammatory action of blueberry polyphenols in HIG-82 rabbit synoviocytes. *The FASEB Journal* 30(1 Supplement):1174.20.

Srivastava, A., C. C. Akoh, J. Fischer, and G. Krewer. 2007. Effect of anthocyanin fractions from selected cultivars of Georgia-Grown Blueberries on apoptosis and phase II enzymes. *Journal of Agricultural and Food Chemistry* 55 (8):3180–5. doi: 10.1021/jf062915o.

Stewart, L. K., Z. Wang, D. Ribnicky, J. L. Soileau, W. T. Cefalu, and T. W. Gettys. 2009. Failure of dietary quercetin to alter the temporal progression of insulin resistance among tissues of C57BL/6J mice during the development of diet-induced obesity. *Diabetologia* 52 (3): 514–23.

Stull, A. J., K. C. Cash, C. M. Champagne, A. K. Gupta, R. Boston, R. A. Beyl, W. D. Johnson, and W. T. Cefalu. 2015. Blueberries improve endothelial function, but not blood pressure, in adults with metabolic syndrome: A randomized, double-blind, placebo-controlled clinical trial. *Nutrients* 7 (6):4107.

Stull, A. J., K. C. Cash, W. D. Johnson, C. M. Champagne, and W. T. Cefalu. 2010. Bioactives in blueberries improve insulin sensitivity in obese, insulin-resistant men and women. *Journal of Nutrition* 140 (10):1764–8.

Sun, C.-D., B. Zhang, J.-K. Zhang, C.-J. Xu, Y.-L. Wu, X. Li, and K.-S. Chen. 2012. Cyanidin-3-glucoside-rich extract from chinese bayberry fruit protects pancreatic β cells and ameliorates hyperglycemia in streptozotocin-induced diabetic mice. *Journal of Medicinal Food* 15 (3):288–98.

Sun, X., N. Liu, Z. Wu, Y. Feng, and X. Meng. 2015. Anti-Tumor Activity of a polysaccharide from blueberry. *Molecules (Basel, Switzerland)* 20 (3):3841

Szajdek, A., and E. J. Borowska. 2008. Bioactive compounds and Health-promoting properties of berry fruits: A review. *Plant Foods for Human Nutrition* 63 (4):147–56. doi: 10.1007/s11130-008-0097-5.

Takikawa, M., S. Inoue, F. Horio, and T. Tsuda. 2010. Dietary anthocyanin-rich bilberry extract ameliorates hyperglycemia and insulin sensitivity via activation of AMP-Activated protein kinase in diabetic mice. *The Journal of Nutrition* 140 (3):527–33. doi: 10.3945/jn.109.118216.

Tan, J., B. Wang, and L. Zhu. 2009. DNA binding and oxidative DNA damage induced by a quercetin copper(II) complex: Potential mechanism of its antitumor properties. *Journal of Biological Inorganic Chemistry : Jbic: A Publication of the Society of Biological Inorganic Chemistry* 14 (5):727–39.

Taruscio, T. G., D. L. Barney, and J. Exon. 2004. Content and profile of flavanoid and phenolic acid compounds in conjunction with the antioxidant capacity for a variety of northwest vaccinium berries. *Journal of Agricultural and Food Chemistry* 52 (10):3169–76. doi: 10.1021/jf0307595.

Thummayot, S., C. Tocharus, A. Suksamrarn, and J. Tocharus. 2016. Neuroprotective effects of cyanidin against Aβ-induced oxidative and ER stress in SK-N-SH cells. *Neurochemistry International* 101 : 15–21.

Tongjaroenbuangam, W., N. Ruksee, P. Chantiratikul, N. Pakdeenarong, W. Kongbuntad, and P. Govitrapong. 2011. Neuroprotective effects of quercetin, rutin and okra (*Abelmoschus esculentus* linn.) in dexamethasone-treated mice. *Neurochemistry International* 59 (5):677–85. doi: https://doi.org/10.1016/j.neuint.2011.06.014.

Torri, E., M. Lemos, V. Caliari, C. A. L. Kassuya, J. K. Bastos, and S. F. Andrade. 2007. Anti-inflammatory and antinociceptive properties of blueberry extract (*Vaccinium corymbosum*). *Journal of Pharmacy and Pharmacology* 59 (4):591–6. doi: 10.1211/jpp.59.4.0015.

Tsuda, S., T. Egawa, X. Ma, R. Oshima, E. Kurogi, and T. Hayashi. 2012. Coffee polyphenol caffeic acid but not chlorogenic acid increases 5'AMP-activated protein kinase and insulin-independent glucose transport in rat skeletal muscle. *The Journal of Nutritional Biochemistry* 23 (11):1403–9.

Tsuda, T. 2015. Possible abilities of dietary factors to prevent and treat diabetes via the stimulation of glucagon-like peptide-1 secretion. *Molecular Nutrition & Food Research* 59 (7):1264–73. doi: 10.1002/mnfr.201400871.

Tsuda, T., F. Horio, K. Uchida, H. Aoki, and T. Osawa. 2003. Dietary cyanidin 3-O-beta-D-glucoside-rich purple corn color prevents obesity and ameliorates hyperglycemia in mice . *The Journal of Nutrition* 133 (7):2125–30.

Tsuda, T., Y. Ueno, H. Aoki, T. Koda, F. Horio, N. Takahashi, T. Kawada, and T. Osawa. 2004. Anthocyanin enhances adipocytokine secretion and adipocyte-specific gene expression in isolated rat adipocytes. *Biochemical and Biophysical Research Communications* 316 (1):149–57. doi: https://doi.org/10.1016/j.bbrc.2004.02.031.

Tsuda, T., M. Watanabe, K. Ohshima, S. Norinobu, S.-W. Choi, S. Kawakishi, and T. Osawa. 1994. Antioxidative activity of the anthocyanin pigments cyanidin 3-O-. beta.-D-glucoside and cyanidin. *Journal of Agricultural and Food Chemistry* 42 (11):2407–10.

Van Acker, S. A. B. E., D-J Van Den Berg, MÈl. N. J. L. Tromp, D. H. Griffioen, W. P. Van Bennekom, W. J. F. Van Der Vijgh, and A. Bast. 1996. Structural aspects of antioxidant activity of flavonoids. *Free Radical Biology and Medicine* 20 (3):331–42. doi: https://doi.org/10.1016/0891-5849(95)02047-0.

Vauzour, D., G. Corona, and J. P. E. Spencer. 2010. Caffeic acid, tyrosol and p-coumaric acid are potent inhibitors of 5-S-cysteinyl-dopamine induced neurotoxicity. *Archives of Biochemistry and Biophysics* 501 (1):106–11.

Vendrame, S., A. Daugherty, A. S. Kristo, and D. Klimis-Zacas. 2014. Wild blueberry (*Vaccinium angustifolium*)-enriched diet improves dyslipidaemia and modulates the expression of genes related to lipid metabolism in obese zucker rats. *British Journal of Nutrition* 111 (02):194–200.

Vendrame, S., A. Daugherty, A. S. Kristo, P. Riso, and D. Klimis-Zacas. 2013. Wild blueberry (vaccinium angustifolium) consumption improves inflammatory status in the obese zucker rat model of the metabolic syndrome. *The Journal of Nutritional Biochemistry* 24 (8): 1508–12. doi: http://dx.doi.org/10.1016/j.jnutbio.2012.12.010.

Vendrame, S., S. Guglielmetti, P. Riso, S. Arioli, D. Klimis-Zacas, and M. Porrini. 2011. Six-Week consumption of a wild blueberry powder drink increases bifidobacteria in the human gut. *Journal of Agricultural and Food Chemistry* 59 (24):12815–20. doi: 10.1021/jf2028686.

Vendrame, S., A. Zhao, T. Merrow, and D. Klimis-Zacas. 2015. The effects of wild blueberry consumption on plasma markers and gene expression related to glucose metabolism in the obese Zucker rat. *Journal of Medicinal Food* 18 (6):619–24. doi: 10.1089/jmf.2014.0065.

Vilsbøll, T., B. Brock, H. Perrild, K. Levin, H.-H. Lervang, K. Kølendorf, T. Krarup, O. Schmitz, M. Zdravkovic, T. Le-Thi, and S. Madsbad. 2008. Liraglutide, a once-daily human GLP-1 analogue, improves pancreatic B-cell function and arginine-stimulated insulin secretion during hyperglycaemia in patients with type 2 diabetes mellitus. *Diabetic Medicine* 25 (2):152–6.

Vivier, E., E. Tomasello, M. Baratin, T. Walzer, and S. Ugolini. 2008. Functions of natural killer cells. *Nature Immunology* 9 (5):503–10. doi: http://www.nature.com/ni/journal/v9/n5/suppinfo/ni1582_S1.html.

Vrhovsek, U., D. Masuero, L. Palmieri, and F. Mattivi. 2012. Identification and quantification of flavonol glycosides in cultivated blueberry cultivars. *Journal of Food Composition and Analysis* 25 (1): 9–16. doi: http://dx.doi.org/10.1016/j.jfca.2011.04.015.

Vuong, T., J.-F. Mallet, M. Ouzounova, S. Rahbar, H. Hernandez-Vargas, Z. Herceg, and C. Matar. 2016. Role of a polyphenol-enriched preparation on chemoprevention of mammary carcinoma through cancer stem cells and inflammatory pathways modulation. *Journal of Translational Medicine* 14 (1):13. doi: 10.1186/s12967-016-0770-7.

Wan, C.-W., C. N.-Y. Wong, W.-K. Pin, M. H.-Y. Wong, C.-Y. Kwok, R. Y.-K. Chan, P. H.-F. Yu, and S.-W. Chan. 2013. Chlorogenic acid exhibits cholesterol lowering and fatty liver attenuating properties by up-regulating the gene expression of PPAR-α in hypercholesterolemic rats induced with a high-cholesterol diet. *Phytotherapy Research : Ptr* 27 (4):545–51.

Wang, J., and G. Mazza. 2002. Effects of anthocyanins and other phenolic compounds on the production of tumor necrosis factor α in LPS/IFN-γ-Activated RAW 264.7 macrophages. *Journal of Agricultural and Food Chemistry* 50 (15):4183–9. doi: 10.1021/jf011613d.

Wang, Y., C.-F. Chang, J. Chou, H.-L. Chen, X. Deng, B. K. Harvey, J. L. Cadet, and P. C. Bickford. 2005. Dietary supplementation with blueberries, spinach, or spirulina reduces ischemic brain damage. *Experimental Neurology* 193 (1):75–84. doi: http://dx.doi.org/10.1016/j.expneurol.2004.12.014.

Ward, M. W., A. C. Rego, B. G. Frenguelli, and D. G. Nicholls. 2000. Mitochondrial membrane potential and glutamate excitotoxicity in cultured cerebellar granule cells. *The Journal of Neuroscience* 20 (19):7208–19.

Wei, Y-Q, X. Zhao, Y. Kariya, H. Fukata, K. Teshigawara, and A. Uchida. 1994. Induction of apoptosis by quercetin: Involvement of heat shock protein. *Cancer Research* 54 (18):4952–7.

Wiart, C. 2013. Comment on protective effects of anthocyanins against amyloid β-Peptide-Induced damage in neuro-2A cells. *Journal of Agricultural and Food Chemistry* 61 (3):761

Wild, S., G. Roglic, A. Green, R. Sicree, and H. King. 2004. Global prevalence of diabetes estimates for the year 2000 and projections for 2030. *Diabetes Care* 27(5):1047–53. doi: 10.2337/diacare.27.5.1047.

Wood, M. 2009. *The earthwise herbal: A complete guide to new world medicinal plants*. California, USA: North Atlantic Books.

Wu, C., H. Luan, X. Zhang, S. Wang, X. Zhang, X. Sun, and P. Guo. 2014. Chlorogenic acid protects against atherosclerosis in ApoE−/− mice and promotes cholesterol efflux from RAW264. 7 macrophages. *PLoS One* 9 (9):e95452.

Wu, L. H., Z. L. Xu, D. Dong, S. A. He, and H. Yu. 2011. Protective effect of anthocyanins extract from blueberry on TNBS-Induced IBD model of mice. *Evidence-Based Complementary and Alternaternative Medicine: eCAM* 2011 :1. doi: 10.1093/ecam/neq040.

Wu, X., G. Cao, and R. L. Prior. 2002. Absorption and metabolism of anthocyanins in elderly women after consumption of elderberry or blueberry. *The Journal of Nutrition* 132 (7):1865–71.

Wyss-Coray, T., and L. Mucke. 2002. Inflammation in neurodegenerative disease-a double-edged sword. *Neuron* 35 (3):419–32.

Xie, X.,. R. Zhao, and G. X. Shen. 2012. Influence of delphinidin-3-glucoside on oxidized low-density lipoprotein-induced oxidative stress and apoptosis in cultured endothelial cells. *Journal of Agricultural and Food Chemistry* 60 (7):1850–6.

Xu, J.-W., K. Ikeda, and Y. Yamori. 2004. Cyanidin-3-glucoside regulates phosphorylation of endothelial nitric oxide synthase. *FEBS Letters* 574 (1-3):176–80.

Xu, J.-W., K. Ikeda, and Y. Yamori. 2004. Upregulation of endothelial nitric oxide synthase by cyanidin-3-glucoside, a typical anthocyanin pigment. *Hypertension* 44 (2):217–22.

Xu, R., Q. Kang, J. Ren, Z. Li, and X. Xu. 2013. Antitumor molecular mechanism of chlorogenic acid on inducting genes gsk-3β and apc and inhibiting gene β-catenin. *Journal of Analytical Methods in Chemistry* 2013 :1.

Yang, J.-S., C.-W. Liu, Y.-S. Ma, S.-W. Weng, N.-Y. Tang, S.-H. Wu, B.-C. Ji, C.-Y. Ma, Y.-C. Ko, S. Funayama, and C.-L. Kuo. 2012. Chlorogenic acid induces apoptotic cell death in U937 leukemia cells through caspase- and mitochondria-dependent pathways. *In Vivo (Athens, Greece)* 26 (6):971–8.

Yang, J.-H., T.-C. Hsia, H.-M. Kuo, P.-D. L. Chao, C.-C. Chou, Y.-H. Wei, and J.-G. Chung. 2005. Inhibition of lung cancer cell growth by quercetin glucuronides via G2/M arrest and induction of apoptosis. *Drug Metabolism and Disposition*

Yang, Y., Z. Shi, A. Reheman, J. W. Jin, C. Li, Y. Wang, M. C. Andrews, P. Chen, G. Zhu, W. Ling, and H. Ni. 2012. Plant food delphinidin-3-glucoside significantly inhibits platelet activation and thrombosis: novel protective roles against cardiovascular diseases. *PloS One* 7 (5):e37323

Yao, Y., and A. Vieira. 2007. Protective activities of vaccinium antioxidants with potential relevance to mitochondrial dysfunction and neurotoxicity. *NeuroToxicology* 28 (1):93–100. doi: http://dx.doi.org/10.1016/j.neuro.2006.07.015.

Ye, J., X. Meng, C. Yan, and C. Wang. 2010. Effect of purple sweet potato anthocyanins on beta-amyloid-mediated PC-12 cells death by inhibition of oxidative stress. *Neurochemical Research* 35 (3):357–65.

Youdim, K. A., A. Martin, and J. A. Joseph. 2000. Incorporation of the elderberry anthocyanins by endothelial cells increases protection against oxidative stress. *Free Radical Biology & Medicine* 29 (1): 51–60.

Youdim, K. A., B. Shukitt-Hale, S. MacKinnon, W. Kalt, and J. A. Joseph. 2000. Polyphenolics enhance red blood cell resistance to oxidative stress: In vitro and in vivo. *Biochimica et Biophysica Acta* 1523 (1):117–22.

Yun, N., J.-W. Kang, and S.-M. Lee. 2012. Protective effects of chlorogenic acid against ischemia/reperfusion injury in rat liver: molecular evidence of its antioxidant and anti-inflammatory properties. *The Journal of Nutritional Biochemistry* 23 (10):1249–55.

Zafra-Stone, S., Yasmin, T. M. Bagchi, A. Chatterjee, J. A. Vinson, and D. Bagchi. 2007. Berry anthocyanins as novel antioxidants in human health and disease prevention. *Molecular Nutrition &Amp; Food Research* 51 (6):675–83.

Zhang, H., M. Zhang, L. Yu, Y. Zhao, N. He, and X. Yang. 2012. Antitumor activities of quercetin and quercetin-5',8-disulfonate in human colon and breast cancer cell lines. *Food and Chemical Toxicology: An International Journal Published for the British Industrial Biological Research Association* 50 (5):1589–99.

Zhang, L., W.-P. Zhang, K.-D. Chen, X.-D. Qian, S.-H. Fang, and E.-Q. Wei. 2007. Caffeic acid attenuates neuronal damage, astrogliosis and glial scar formation in mouse brain with cryoinjury. *Life Sciences* 80 (6):530–7.

Zhang, X.-Y., D.-C. Bai, Y.-J. Wu, W.-G. Li, and N.-F. Liu. 2005. Proanthocyanidin from grape seeds enhances anti-tumor effect of doxorubicin both in vitro and in vivo. *Die Pharmazie-An International Journal of Pharmaceutical Sciences* 60 (7):533–8.

Zhang, X.-M., and J. Zhu. 2011. Kainic Acid-Induced neurotoxicity: Targeting glial responses and Glia-Derived cytokines. *Current Neuropharmacology* 9 (2):388–98. doi: 10.2174/157015911795596540.

Zhang, Y., N. P. Seeram, R. Lee, L. Feng, and D. Heber. 2008. Isolation and identification of strawberry phenolics with antioxidant and human cancer cell antiproliferative properties. *Journal of Agricultural and Food Chemistry* 56 (3):670–5.

Zhang, Y., S. K. Vareed, and M. G. Nair. 2005. Human tumor cell growth inhibition by nontoxic anthocyanidins, the pigments in fruits and vegetables. *Life Sciences* 76 (13):1465–72.

Zhang, Y., F. Lian, Y. Zhu, M. Xia, Q. Wang, W. Ling, and X.-D. Wang. 2010. Cyanidin-3-O-beta-glucoside inhibits LPS-induced expression of inflammatory mediators through decreasing IkappaBalpha phosphorylation in THP-1 cells. *Inflammation Research* 59 (9):723–30.

Zhang, Z. J., L. C. V. Cheang, M. W. Wang, and S. M.-Y. Lee. 2011. Quercetin exerts a neuroprotective effect through inhibition of the iNOS/NO system and pro-inflammation gene expression in PC12 cells and in zebrafish. *International Journal of Molecular Medicine* 27 (2):195–203.

Zhao, M., X. Liu, Y. Luo, H. Guo, X. Hu, and F. Chen. 2015. Evaluation of protective effect of Freeze-Dried strawberry, grape, and blueberry powder on acrylamide toxicity in mice. *Journal of Food Science* 80 (4):H869–74. doi: 10.1111/1750-3841.12815.

Zhong, Y., Y. Wang, J. Guo, H. Chu, Y. Gao, and L. Pang. 2015. Blueberry improves the therapeutic effect of etanercept on patients with juvenile idiopathic arthritis: Phase III study. *The Tohoku Journal of Experimental Medicine* 237 (3):183–91. doi: 10.1620/tjem.237.183.

Zhou, Y., S-h Fang, Y-L Ye, L-S Chu, W-P Zhang, M-L Wang, and E-Q Wei. 2006. Caffeic acid ameliorates early and delayed brain injuries after focal cerebral ischemia in rats 1. *Acta Pharmacologica Sinica* 27 (9):1103–10.

Zhu, Y., J. Sun, W. Lu, X. Wang, X. Wang, Z. Han, and C. Qiu. 2016. Effects of blueberry supplementation on blood pressure: a systematic review and Meta-analysis of randomized clinical trials. *J Hum Hypertens* doi: 10.1038/jhh.2016.70.

Ziberna, L., M. Lunder, F. Tramer, G. Drevenšek, and S. Passamonti. 2013. The endothelial plasma membrane transporter bilitranslocase mediates rat aortic vasodilation induced by anthocyanins. *Nutrition, Metabolism and Cardiovascular Diseases* 23 (1):68–74.

Zimmer, K. R., C. H. Blum-Silva, A. L. K. Souza, M. WulffSchuch, F. H. Reginatto, C. M. P. Pereira, A. J. Macedo, and C. L. Lencina. 2014. The antibiofilm effect of blueberry fruit cultivars against *Staphylococcus epidermidis* and *Pseudomonas aeruginosa*. *Journal of Medicinal Food* 17(3):324–31. doi: 10.1089/jmf.2013.0037.