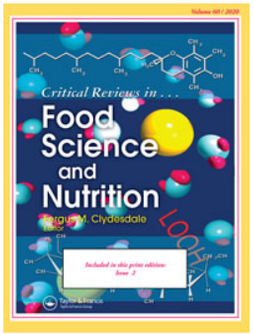

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REVIEW

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 cereus*, *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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