INTERNATIONAL JOURNAL OF FOOD SCIENCES and NUTRITION

http://informahealthcare.com/ijf
ISSN: 0963-7486 (print), 1465-3478 (electronic)

Int J Food Sci Nutr, Early Online: 1–8
 DOI: 10.3109/09637486.2014.880672

informa healthcare

RESEARCH ARTICLE

Potential cardiovascular implications of Sea Buckthorn berry consumption in humans

Marietta Sayegh, Cristiana Miglio, and Sumantra Ray

Nutrition and Vascular Studies and the Need for Nutrition and Education Programme (NNEdPro), c/o the Medical Research Council (MRC) Human Nutrition Research (HNR) Unit, Elsie Widdowson Laboratory, Cambridge, UK

Abstract

Diets rich in fruits and vegetables have been correlated with decreased risks of cardiovascular disease. Particularly, berry consumption has been associated with reductions in cardiovascular risk. Despite the range of potentially beneficial phytochemical components (vitamins, polyphenols, carotenoids, and fatty acids), there is little evidence underpinning the cardiovascular effects of sea buckthorn (SB) berries. The purpose of this review is to evaluate the benefits of SB consumption on cardiovascular health in human trials. Only six human studies were found, which examine the effect of SB berries on cardiovascular outcomes (i.e. lipid metabolism, platelet aggregation, and inflammation). Although there appears to be an inverse association between SB consumption and cardiovascular risk factors, the evidence is still scarce and the results are inconsistent. In addition, limitations in study design made it difficult to form firm conclusions. More "high-quality" human clinical trials are needed in order to establish the cardio-protective benefits of SB berries.

Keywords

Blood lipids, inflammation, phytonutrients, platelet aggregation, sea buckthorn berries

History

Received 14 November 2013
Revised 23 December 2013
Accepted 31 December 2013
Published online 4 February 2014

Introduction

Cardiovascular disease (CVD) remains the main cause of death in England and Wales, costing billions per year to the UK economy. A number of studies and reviews have shown the benefit of dietary approaches to CVD prevention. Diets, such as the Mediterranean diet, which is mainly based on foods of plant origin, alongside a low intake of saturated fatty acids and a high intake of essential fatty acids, and in general, diets rich in fruits and vegetables have been associated with protection against CVD (Dauchet et al., 2006; Mente et al., 2009). Fruits and vegetables contain vitamins, fibre, and a large number of phytochemicals such as carotenoids and polyphenols. However, it is not entirely clear which of these components contribute significantly to cardiovascular protection. The emerging hypothesis is that the cumulative effect of food components in a diet, including phytonutrients, fiber, and fatty acids, is of major importance in CVD prevention (Mente et al., 2009).

Berries are known to contain high amounts of vitamins (particularly vitamin C and E), phenolic compounds (mainly flavonols), trace elements and fibres, as well as having a beneficial fatty acid composition (essential fatty acids). This combination of potentially active compounds in berries has attracted significant research interest both for their antioxidant and anti-inflammatory roles, which have potential implications upon several oxidative stress-related pathologies, including CVD and cancer (Beattie et al., 2005). In recent years, several berries such as blueberry, cranberry, and strawberry have been studied for their beneficial effects on cardiovascular health (Basu et al., 2010; Chong et al., 2010). In addition, in a systematic review, it was highlighted that pomegranate and purple grapes appeared to be the most frequently investigated fruits and were found to be effective in reducing CVD risk factors (Chong et al., 2010).

Comparatively little work has been done to date on sea buckthorn (SB) berry, which due to their near-unique phytochemical composition, combining a cocktail of components usually found separately (Sabir et al., 2005; Tiitinen et al., 2005), may in fact be a more suitable fruit to study in the cardiovascular context. The SB berry has been considered to be among the most nutritious and vitamin-rich fruit and has been used for centuries in Eastern traditional medicine (Zeb, 2004). The aim of this review is to explore the potential benefits of SB consumption on cardiovascular health.

Only the effects of SB berry consumption in human studies published to date, in English, are discussed in this review, whereas any available literature concerning animal or *in vitro* studies are outside the scope of this review.

Sea Buckthorn berry details

Geographic distribution and global consumption

Sea buckthorn (*Hippophae rhamnoides* L.) is a deciduous spiny shrub or small tree widely distributed in China, Mongolia, Russia, and most parts of Northern Europe. Figure 1 shows the natural distribution of SB (Yang & Kallio, 2002). SB berry is traditionally known for its medicinal properties. However, due to its high nutritional value, SB berry is also commonly consumed as food. In many European countries, SB can be found in the market in different forms including juice, candy, jelly, jam, alcoholic or non-alcoholic beverages, or as flavoring of dairy products (Christaki, 2012). Furthermore, SB components, including oil

Correspondence: Dr Sumantra Ray, MRC HNR, Elsie Widdowson Laboratory, Cambridge CB1 9NL, UK. E-mail: Sumantra.Ray@mrc-hnr.cam.ac.uk

Figure 1. The natural distribution of sea buckthorn in Europe and Asia (Yang & Kallio, 2002).

Figure 2. Sea Buckthorn berries.

extracted from seeds and flavonoids have been widely used in cosmetic preparations (Beveridge et al., 1999).

Bioactive compounds

The SB fruit is a yellow-orange berry (Figure 2), which consists of seed (23%), pulp (68%), and peel (7.75%) (Bal et al., 2011). Published literature reports that all these components are sources of proteins and essential amino acids, sugars (mainly glucose and fructose), mineral elements (especially K), fatty acids, vitamins (A, C, E, and K), and flavonoids (mainly flavonols) (Yang & Kallio, 2002; Zeb, 2004). They also have a good content of organic acids, such as malic, quinic, oxalic, citric, and tartaric acids (Bal et al., 2011).

SB berry and its derivatives have been shown to possess antioxidant activity both *in vitro* and *in vivo* (Allmann et al., 2006; Rosch et al., 2003). The antioxidant composition of SB juice is reported in Table 1.

The vitamin C concentration in SB berry is among the highest content in fruits and vegetables, and it has been reported to be higher than in strawberries, kiwis, oranges, tomatoes, or carrots (Bal et al., 2011). Due to its high concentration, vitamin C contributes approximately 75% of total antioxidant activity of the

Table 1. Antioxidants in Sea Buckthorn berry juice.

Compound	Concentration (mg/l)
Vitamin C	1540
Flavonoids	1182
Vitamin E	13.5
Carotenoids	7.3

Source: Christaki (2012).

juice, while flavonoids contribute only a 5% (Rosch et al., 2003). However, as compared with other wild berries, SB berry rates second for total flavonol content and therefore represent an excellent source of these bioactive compounds (Riihinen, 2005; Figure 3). The structural composition of common flavonols found in the SB berry is reported in Figure 4. Isorhamnetin and its glycosides are typically found in the largest quantities, together with quercetin and small amounts of kaempferol (Rosch et al., 2003; Suomela et al., 2006).

SB berry is also a good source of essential fatty acids, which are present in the oily fractions of the seeds and the pulp. The seed oil is characterized by its high oleic acid content (17%) and its one to one ratio of omega-3 (alpha linolenic) and omega-6 (linoleic) at approximately 34% and 31%, respectively (Bal et al., 2011). According to Yang & Kallio (2001), linoleic and α-linolenic acids constitute approximately 70% of the seed oil fatty acid, whereas palmitoleic acid is the predominant fatty acid in soft tissue oil.

Other potentially beneficial lipophilic compounds of SB seeds and berry include phytosterols, carotenoids, and vitamin E. Sitosterol is the predominant phytosterol, constituting 57–76% and 61–83% of seed and soft-tissue sterols, respectively (Yang & Kallio, 2002). The total quantity of phytosterol in SB oils (SBos) is quite high (1.3–2%) and may exceed soybean oil by 4–20 times (Bal et al., 2011). Carotenoids in the whole fruit may vary between a range of 1.5–18.5 mg/100 g (Andersson et al., 2009). The major carotenoids found in the SB berry include lutein, zeaxanthin, β-cryptoxanthin, lycopene, γ-carotene, β-carotene, and esterified carotenoids (Gao et al., 2000; Yang & Kallio, 2002). Vitamin E concentration ranged between studies from 40.1 to 103 mg/100 g in whole seeds, from 61 to 113 mg/100 g in seed oil and from 390 to 540 mg/100 g in the residue (Bal et al., 2011; Beveridge et al., 1999).

Genetic and environmental factors affecting phytochemical content

It is known that phytonutrient content of fruits and vegetables is strongly influenced by both genetic and environmental factors, including geographical origin. Vitamin C content in SB fruit has been reported to vary from 2 to 500 mg/100 g depending on genetic background and ripeness of the fruit (Gao et al., 2000; Sabir et al., 2005; Tiitinen et al., 2005). Total phenolic content and antioxidant capacity have also been reported to have statistical significant variations among different genotypes (Yildiz et al., 2012). Carotenoids content ranges 1.5–18.5 mg/100 g of fresh weight depending on cultivar, harvest time, and year (Andersson et al., 2009). A study by Gao et al. (2000) investigated the change in antioxidant capacity and phytonutrient content during maturation in different fractions of SB fruits. The capacity to scavenge radicals decreased with increased maturity of SB fruits, whereas the antioxidant capacity of the lipophilic extract increased significantly and corresponded to the increase in total carotenoids. Method of extraction has also been shown to influence the concentration of bioactive molecules in the oils from SB seeds and pulp (Cenkowski et al., 2006). Finally, berries from different geographic areas have been

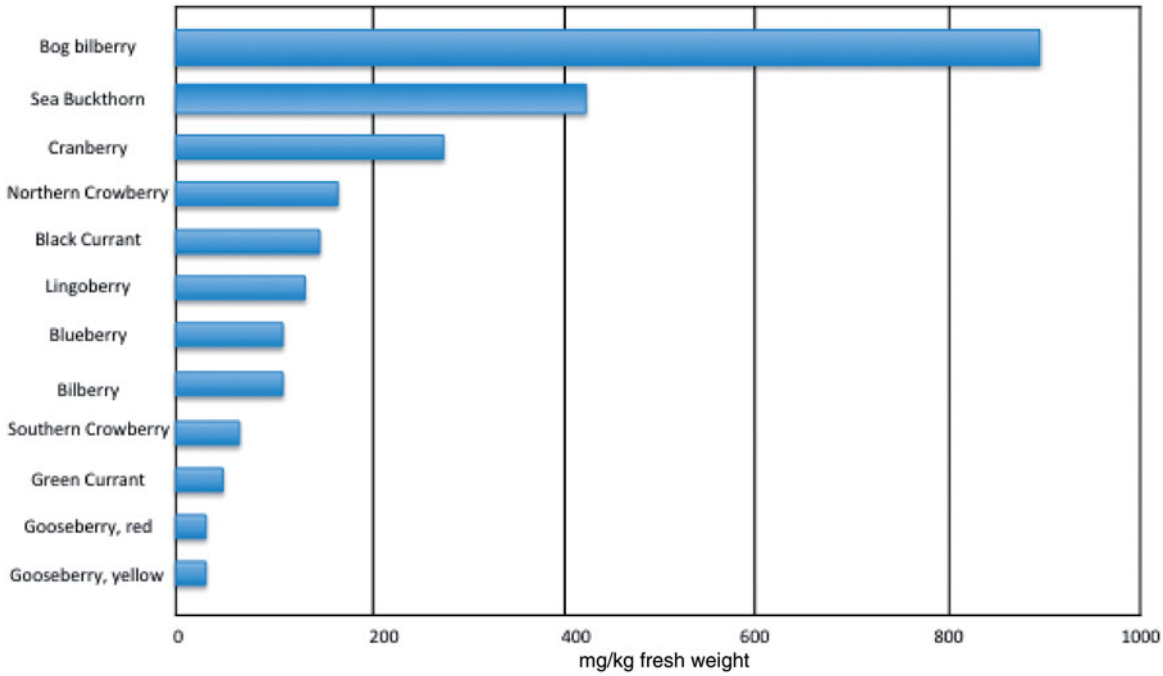
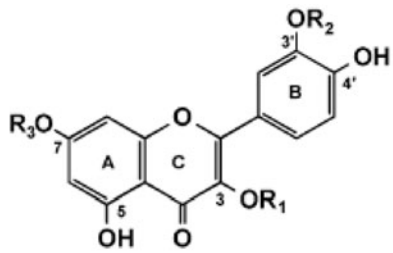


Figure 3. Total flavonol content of different berries. Source: Riihinen (2005).

Figure 4. Molecular structure of principal flavonols found in SB berries. Source: Rosch (2003).



R1 = rutinose, R2 = CH3 and R3 = H: isorhamnetin 3-o-rutinosidae
R1 = glucose, R2 = CH3 and R3 = H: isorhamnetin 3-o-glucoside
R1 = glucose, R2 = CH3 and R3 = rhamnose: isorhamnetin 3-o-glucoside-7-o-rhamnoside
R1 = rutinose, R2 = H and R3 = H: quercetin 3-o-rutinosidae

reported to have different compositions. Ranjith et al. (2006) compared the chemical composition of pulp oil of three major SB species from different locations in the Himalayas. The results showed that the pulp oil of two Indian SB berries (*H. rhamnoides* and *Hippophae tibetana*) were richer sources of bioactive lipophilic compounds, i.e. carotenoids and tocopherols, and had a distinct fatty acid profile, with palmitoleic acid as the major compound.

Flavonols bioavailability

Mounting evidence exists for a specific role of polyphenols and polyphenol-rich foods in CVD prevention (Habauzit & Morand, 2012). However, the poor bioavailability of phenolic compounds leads to relatively low plasma concentrations as compared with other vitamin and carotenoid antioxidants, complicating the study of their *in vivo* effects (Halliwell, 2008). To date, scarce information exists about bioavailability of flavonols from SB berry consumption.

In a randomised crossover study with six healthy volunteers, the subjects were given a single oral dose of either 150 ml of a commercially available SB juice or 150 ml of tap water (control), with a seven-day wash-out phase between interventions (Allmann et al., 2006). Following ingestion, significant increases in urinary excretion of total polyphenols (113%) and ascorbic acid (478%) were recorded as well as an increase in total antioxidant capacity. Within 24 h, the urinary excretion of total polyphenols and ascorbic acid was 28.0% and 49.9% of the administered doses, respectively. This indicates that the polyphenolic compounds and ascorbic acid from SB juice are bioavailable to humans and are active as antioxidants *in vivo* (Allmann et al., 2006). Increased circulating levels of isorhamnetin and quercetin and their conjugated forms have been reported in both postprandial intervention, 8-h postingestion of an SB breakfast (Lehtonen et al., 2010a) and after 3 months of supplementation with an SB frozen puree, delivering 9 mg a day of flavonols (Larmo et al., 2009). Suomela et al. (2006) reported higher plasma levels of isorhamnetin 1 h following consumption of an SB extract added to a oatmeal porridge, but this increase reached statistical significance only at higher concentrations of flavonols in the extract (78 mg of total flavonols) and in presence of a small amount of SB seed oil (Suomela et al., 2006). However, these results should be interpreted with caution, as the porridge meal may have contained milk proteins that are reported to affect flavonoids absorption (Serafini & Crozier, 2003).

Potential health benefits of SB berry

A number of human studies have focused on the potential health benefits of SB on various chronic diseases and infections. Olsson et al. (2004) reported that SB extracts decreased proliferation of colon cancer and breast cancer cells *in vitro*. Similar results

were also found by Boivin et al. (2007). Intake of SBo was found to positively affect xeropthalmia symptoms when it was administered in 86 participants experiencing ''dry eye'' (Larmo et al., 2010). Studies have also shown that SB is effective against atopic dermatitis (Yang et al., 1999) by increasing the level of α-linolenic, linoleic, and eicosapentaenoic acids as well as wound healing (Upadhyay et al., 2011).

A SB extract taken orally also had positive effects on cirrhotic patients, showing that it may inhibit the synthesis of collagen and other components of extracellular matrix (Gao et al., 2003). Larmo et al. (2008) found that SB berries consumption reduced the C-reactive protein (CRP), an inflammation marker. Lehtonen et al. (2010b) concluded that SB juice along with other berry juices decreased the levels of alanine aminotransferase (ALAT), which is a liver disease marker. Studies have also shown that SB berry have anti-ulcer effects (Wang, 1992) and improve the symptoms of dry mouth (Erkkola & Yang, 2003).

In addition to these beneficial effects of SB to various chronic diseases, few human clinical studies have been found that study the potential effects of the berries on reducing the cardiovascular risk. The focus of this study is on the potential beneficial effect on SB on human clinical studies and animal as well as *in vitro* studies will not be discussed in this review.

Cardiovascular disease

Only six human studies were found relating to CVD and SB consumption, which are listed in Table 2. The participants of these studies were all healthy, normolipidemic men and/or women. In two studies, subjects were overweight or obese (Larmo et al., 2013; Lehtonen et al., 2011) and in only one study (Larmo et al., 2013), the subjects were separated into two groups based on their high or low risk for CVD.

The number of participants in each study ranged from a few to more than 200 volunteers. Twelve and 14 healthy men were recruited in the studies by Johansson et al. (2000) and Suomela et al. (2006) respectively, whereas Eccleston et al. (2002) recruited 30 healthy volunteers, but only 20 completed the intervention. Larmo et al. (2009) analyzed 77 overweight and obese women in the study conducted in 2013 and 229 healthy men and women. Lehtonen et al. (2011) recruited 110 overweight and obese women and 80 subjects completed the study.

The type of intervention, doses, and study periods also varied significantly from one study to another. As shown in Table 2, each of the six studies used a different intervention, from SB juice to frozen puree, dried berries, and oil extracts or capsules. Different forms of SBs can contain different amount of vitamins, minerals as well as steroids, terpenoids, phenolics, fatty acids and other compounds making the comparison between these studies more difficult. Similarly, the exposure time varied from 30 days (Larmo et al., 2013) to 90 days (Larmo et al., 2009), which was the longest studied period. The control products used were also different in each of these studies. As a control, Eccleston et al. (2002) used a placebo juice that was developed to emulate the intervention (SB juice) in appearance and taste only. Similarly, Larmo et al. (2009) used a placebo product which was similar in appearance, taste, and smell to the active product but not in bioactive compounds. In the study by Suomela et al. (2006) where oatmeal porridge supplemented with an SB flavonol extract was the active product, the control porridge did not contain the flavonols. Johansson et al. (2000) used fractionated coconut oil as a control. Finally, Lehtonen et al. (2011) did not have any control since he compared the effects of different berries and berry fractions; i.e. SB berries, extract and berry oil, and bilberry.

The outcomes from these six studies can be classified as effects on blood lipids, platelet aggregation, and inflammation.

Blood lipids

The effects of SB on blood lipids have been investigated in five out of six clinical studies. In the very recent investigation by Larmo et al. (2013), 77 overweight and obese women were classified for their higher or lower risk for CVD and then received either dried SB berries (SBs), SBo, SB phenolics ethanol extract mixed with maltodextrin (SBe + MD) (1:1), or frozen bilberries for 30 days in a randomised crossover study. Postintervention, SBs reduced tryglicerides and VLDL cholesterol, although the results did not reach statistical significance. Interestingly, the effect was more evident in the group at higher risk for CVD. SBo showed a trend of reduction in total and LDL cholesterol in all participants and a significant reduction of serum-free cholesterol. Intervention with SB juice for 8 weeks (300 ml/day) led to a non-significant 20% increase of HDL without affecting LDL cholesterol levels in healthy men (Eccleston et al., 2002). The same study also found a non-significant increase in resistance to LDL oxidation.

Overall, these data indicate that SB consumption has only a small effect on the lipid profile of healthy individuals, with the caveat that effect size may have been greatly impacted by the short duration or the small power of the studies. In addition, the fact that both the aforementioned studies involved healthy volunteers may also have contributed to only small measured changes. This hypothesis is supported by Larmo et al. (2013) who found a greater effect in people with higher risk of CVD and by other authors who found a significant (5.2%) HDL increase following 2-month supplementation with a mix of berry products, including whole fruits, nectars, and juices, in 72 individuals at risk of CVD (Erlund et al., 2008).

However, the results obtained by other authors do not seem to support these findings. The short intervention study by Johansson et al. did not detect any effect on plasma triacylglycerol, total cholesterol as well as on HDL and LDL cholesterol. The study by Suomela et al. (2006) concluded that the intake of flavonols did not affect total HDL and LDL cholesterol as well as the serum and plasma levels of oxidised LDL. This can be either due to the short intervention period or due to the fact that they used oatmeal porridge as the main product where they added SB flavonol extract. As already above reported, porridge oatmeal may have contained milk proteins that are known to reduce flavonoid bioavailability (Serafini & Crozier, 2003) and this may therefore have led to an underestimation of the *in vivo* effects of the flavonol extract in this study.

In a larger intervention, Larmo et al. (2009) examined as a primary outcome the effect of SB berry on circulating lipid markers in 229 healthy individuals. The authors concluded that the consumption of SB berry did not affect the serum total, HDL, LDL cholesterol, and triacylglycerol concentrations. This effect can be attributed to the fact that the participants were having a healthy diet where there was regular fruit and vegetables consumption as well as vitamin and nutrient supplementation during the study. Finally, consumption of SB berries, SB phenolic alcohol extract or SBo for 33–35 days showed no effects on plasma cholesterol and triacylglycerol levels in 80 overweight and obese women in the recent study by Lehtonen et al. (2011). However, in a power calculation previous to the study, the authors estimated that a minimum of 85 subjects were necessary in order to be able to detect significant changes in the measured parameters, rising doubts about the power of detection of these results (Lehtonen et al., 2011).

DOI: 10.3109/09637486.2014.880672

Table 2. Effects of sea buckthorn berry/berry fractions on CVD risk factors.

Reference	Study description	Participants	Studied dose of SB	Outcomes	Effects
Eccleston et al., 2002	Effects of SB on CVD risk factors	20 Healthy normolipidemic, non-smoking men (age 18–55 years)	300 ml/day of SB Juice (delivering 462 mg vitamin C; 355 mg flavoids/day) or placebo for 8 weeks	HDL-C, TAG, total-C, LDL-C, sICAM-1, oxidized LDL, platelet aggregation	↑ Not significant No change
Johansson, 2000	Effects of the combined SB pulp and seed oil (SBo) on plasma lipid levels and on platelet aggregation	12 Healthy normolipidemic men (age 20–59 years)	10 Capsules/day of SB berry oil (seed and berry pulp oil, delivering about 4 g of fatty acids/day) or placebo (fractionated coconut oil) for 4 weeks	TAG, total-C, HDL-C and LDL-C Platelet aggregation and maximum aggregation	No change between groups ↓ for SBo supplementation
Larmo et al., 2009	Effects of SB on CVD risk factors and circulating flavonols	229 Healthy men and women (age 19–50 years)	28 g/day of frozen SB berries puree (16.7 mg of flavonols/day) or placebo for 90 days	Total-, HDL-, LDL-C, TAG CRP	No change ↓ significant
Suomela, 2006	Effects of a nonglycosidic sea buckthorn (SB) flavonol extract on the potential risk factors of CVD (study 1)	14 Healthy, nonsmoking males (age 35–53 years)	185 g oatmeal porridge with 78 mg flavonol extract, with or without SB seeds oil (no flavonols) for 4 weeks	Plasma total cholesterol HDL-C, LDL-C, TAG, CRP, homocysteine, oxidized lipids	↓ not significant No change
Lehtonen et al., 2011	Effects of berries on associated variables of metabolic diseases	80 Overweight and obese women (age 44 ± 6 years)	Bilberries (BB), SB berries, SBo, SB phenolic extract (SBe). Amounts equivalent to average daily dose of 100 g fresh berries for 33–35 days	Plasma glucose sICAM-1 sVCAM-1 TNF-α IL-6	↓ significant for SB ↓ significant for SBe ↓ significant for BB and SBo ↓ significant for BB, SB and SBe No change
Larmo et al., 2013	Effects of berries on serum metabolome	77 Overweight and obese women (age 44 ± 6) divided in group A at lower risk and group B at higher risk for CVD	Dried SB berries (SBs), SB oil (SBo), SB phenolics ethanol extract (delivering18 mg flavonols/day) mixed with maltodextrin (SBe + MD) (1:1), and frozen bilberries in doses that corresponded to 100 g of fresh berries per day for 30 days	Overall metabolic profile Serum free C LDL and Total-C VLDL and TAG	Significant effect for all groups ↓ significant for SBo ↓ not significant for SBo ↓ not significant for SBs (more evident in group B)

sICAM-1, soluble intracellular adhesion molecule-1; LDL, low-density lipoproteins; HDL, high-density lipoproteins; TAG, triacylglycerol; C, Cholesterol; CRP, C-reactive protein; sVCAM-1 soluble vascular cell adhesion molecule-1; TNF-α, tumor necrosis factor-α; IL-6, interleukin-6.

Platelet aggregation

Only two studies have investigated the effects of SB consumption on platelet aggregation in healthy participants (Eccleston et al., 2002; Johansson et al., 2000). Platelet aggregation was determined *ex vivo* in both studies and SB was either given as a juice (300 ml/day) (Eccleston et al., 2002) or as oil capsules (10 capsules/day) (Johansson et al., 2000) for 8 and 4 weeks, respectively. Blood samples were taken at varying times, and the *ex vivo* platelet aggregation was determined using different agonists and techniques. The major bioactive compounds present in the SB juice include high concentration of vitamin C, tocopherols, tocotrienols, carotenoids, flavonoids, and fatty acids. In addition to these, SBo contains 1% sterols, where sitosterol is the most abundant. It is interesting to note that in the study by Eccleston et al. (2002), no effects were reported on the platelet aggregation after giving SB juice for 8 weeks; however, in the second study, where oil capsules were given for 4 weeks both the rate aggregation reaction (−3 to −4%) and maximum aggregation (−15%) were reduced (Johansson et al., 2000). This discrepancy in the outcomes could be associated to the different meal composition (juice and oil capsule) delivering different active compounds (mostly vitamin C and flavonoids in the juice and fatty acids in the oil).

Inflammation

Antioxidants are important in protecting cells of the immune system and modulating inflammation (González-Gallego et al., 2010). SB is high in antioxidants, quercetin, isorhamnetin, and kaempherol as well as vitamin C, E, and carotenoids, making it suitable as an anti-inflammatory fruit. Four out of six human clinical studies aimed at investigating the effects of SB berry and its fractions on markers of inflammation such as CRP, IL-6, IL-8 as well sICAM-1 and VCAM-1.

Encouraging evidence of *in vivo* anti-inflammatory effects of SB products came from the large studies by Larmo et al. (2009) and Lehtonen et al. (2011). SB berry puree intervention for 3 months on 229 healthy participants led to small but significant reduction (−0.06 mg/l) of serum CRP concentrations (Larmo et al., 2009). Lehtonen et al. (2011) compared the effect of two berries (bilberry and SB berry) as well as of two edible fractions of SB, the phenolic alcohol extract, and SBo to assess their effectiveness on the reduction of alanine aminotransferase activity. They concluded that after only a month of SB intervention, sICAM-1 (−6 ng/l following SB extracts), sVCAM-1 (−66 and −50 ng/ml following SBo and bilberries consumption respectively), and TNF-α (−0.2 to −0.3 pg/ml for all interventions) were significantly reduced although no change in IL-6 was observed. On the other hand, other studies failed to detect anti-inflammatory effects. Eccleston et al. (2002) did not show any effect of SB berry juice on sICAM-1 levels; similarly Suomela et al. (2006) concluded that daily consumption of oatmeal porridge supplemented with SB flavonol extract had no effect on CRP levels. However, both these studies had short intervention period and small study population (Table 2), which may have not been enough to detect a difference on these markers of inflammation.

Limitations

The available body of evidence suggests that SB may have a potential effect on reducing CVD risk, through improvement of CVD markers, particularly platelet aggregation and inflammation, with only small effect on lipid metabolism. However, due to the relative paucity of available evidence and inconsistent results among different studies, the entity of this protective effect remains unclear, and to date, it is still not possible to state that SB berry plays a key protective role against CVD, although it has potential based on the beneficial composition of phytonutrients, vitamins, and fatty acids.

This paucity can be attributed to a number of evidence gaps that can be identified from the above mentioned studies including lack of controls, relatively short intervention periods, choice of healthy volunteers, and possibly inappropriate choice of CVD markers. Specifically, the variation in the number of participants shows a lack of adequate power calculation in each of these studies, which in turn can influence the entity of the measured effects and the reliability of results. Furthermore, Suomela et al. (2006) and Johansson et al. (2000) used unusual controls, oatmeal porridge and fractionated coconut oil, respectively. These studies did not specify the reason for choosing these controls and more importantly the potential effects that these controls had on the results of the study. As flavonoids have been reported to interact with other dietary components, such as proteins and fibres, the way in which these compounds are delivered in human intervention trials should be chosen to avoid potential confounding interactions. It also ought to be noted that compounds availability can change greatly according to the way the SB is consumed (whole fruit versus extracts). For example, lipids are mostly unavailable if the seed is ingested whole, so consistent differences may be expected if the entire berry or oil extracts are administered and this may explain variability in the results. Finally, the phytochemical composition of the study products were not always described and properly standardized (absolute concentration of each single compound in the daily portion), further limiting comparisons among the studies and making it difficult to identify possible underlying components.

Side effects

Among the studies included in Table 2, only one of them reported adverse events due to SB consumption. In the study by Eccleston et al. (2002), 10 of the 30 healthy male participants recruited dropped out because of gastrointestinal upset and diarrhea during the intervention with SB or placebo juice. It was reported that these side effects were possibly attributed to the acidity of the juices both the SB juice used as an intervention and the placebo juice. However, the number of drop outs from each group is not clear. Furthermore, a recent study by Grad et al. (2012) presented an isolate case where yellow staining of the skin had appeared after 6 months of SB chronic consumption. The side effects associated with SB ingestion are rare although the amount of consumption as well as the type of interventions chosen (SB capsules, juice, extract, or puree) can play a significant role in their development and manifestation.

Conclusion

Currently, SB has gained recognition worldwide as a high value functional food due to its valuable bioactive compounds. Although, there is some evidence for the beneficial effects of SB on CVD risk, the literature to date is limited and often inconsistent in terms of study design. Therefore, further well-designed and adequately powered placebo-controlled, randomised, controlled trials as well as explanatory/mechanistic experimental studies are required to confirm these observations as well as to clarify the mechanisms in a molecular and cellular level behind the evidence.

Acknowledgements

The authors thank David Eagle (British Sea Buckthorn association) for his continued support as well as Dr Gordon McDougall (The James Hutton

Institute), Elaine Evans (InterPharm Investments Ltd) and Celia Laur (NNEdPro) for their feedback and Professor Jill JF Belch (University of Dundee) for her encouragement to undertake this review.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper. The corresponding author, Dr S. Ray is funded primarily by the UK Medical Research Council.

References

Allmann S, Strass G, Kranl K, Frank T, Bitsch I, Bitsch R, Netzel M. 2006. Bioactivity and bioactive compounds of sea buckthorn fruit juice: a multipurpose wonder plant, vol. II. New Delhi, India: Daya Publisher House. p 402–412.

Andersson SC, Olsson ME, Johansson E, Rumpunen K. 2009. Carotenoids in sea buckthorn (*Hippophae rhamnoides* L.) berries during ripening and use of pheophytin a as a maturity marker. J Agric Food Chem 57:250–258.

Bal LM, Meda V, Naik SN, Santosh S. 2011. Sea buckthorn berries: a potential source of valuable nutrients for nutraceuticals and cosmoceuticals. Food Res Int 44:1718–1727.

Basu A, Rhone M, Lyons TJ. 2010. Berries: emerging impact on cardiovascular health. Nutr Rev 68:168–177.

Beattie J, Crozier A, Duthie GG. 2005. Potential health benefits of berries. Curr Nutr Food Sci 1:71–86.

Beveridge T, Li TSC, Oomah BD, Smith A. 1999. Sea Buckthorn products: manufacture and composition. J Agric Food Chem 47: 3480–3488.

Boivin D, Blanchette M, Barrette S, Moghrabi A, Béliveau R. 2007. Inhibition of cancer cell proliferation and suppression of TNF-induced activation of NFkappaB by edible berry juice. Anticancer Res 27: 937–948.

Cenkowski S, Yakimishen R, Przybylski R, Muir WE. 2006. Quality of extracted sea buckthorn seed and pulp oil. Can Biosyst Eng 48: 3.9–3.16.

Chong MFF, Macdonald R, Lovegrove JA. 2010. Fruit polyphenols and CVD risk: a review of human intervention studies. Br J Nutr 104: S28–S39.

Christaki E. 2012. *Hippophae rhamnoides* L. (Sea Buckthorn): a potential source of nutraceuticals. Food Public Health 2:69–72.

Dauchet L, Amouyel P, Hercberg S, Dallongeville J. 2006. Fruit and vegetable consumption and risk of coronary heart disease: a meta-analysis of cohort studies. J Nutr 136:2588–2593.

Eccleston C, Baoru Y, Tahvonen R, Kallio H, Rimbach GH, Minihane AM. 2002. Effects of an antioxidant-rich juice (sea buckthorn) on risk factors for coronary heart disease in humans. J Nutr Biochem 13: 346–354.

Erkkola R, Yang B. 2003. Sea Buckthorn oils: towards healthy mucous membranes. Agrofood Industry Hi-Tech 3:53–57.

Erlund I, Koli R, Alfthan G, Marniemi J, Puukka P, Mustonen P, et al. 2008. Favorable effects of berry consumption on platelet function, blood pressure, and HDL cholesterol. Am J Clin Nutr 87:323–331.

Gao ZL, Gu XH, Cheng FT, Jiang FH. 2003. Effect of sea buckthorn on liver fibrosis: a clinical study. World J Gastroenterol 9:1615–1617.

Gao XQ, Ohlander M, Jeppsson N, Bjork L, Trajkovski V. 2000. Changes in antioxidant effects and their relationship to phytonutrients in fruits of sea buckthorn (*Hippophae rhamnoides* L.) during maturation. J Agric Food Chem 48:1485–1490.

González-Gallego J, García-Mediavilla MV, Sánchez-Campos S, Tuñón MJ. 2010. Fruit polyphenols, immunity and inflammation. Br J Nutr 104:S15–S27.

Grad SC, Muresan I, Dumitrascu DL. 2012. Generalized yellow skin caused by high intake of sea buckthorn. Forsch Komplement med 19: 153–156.

Habauzit V, Morand C. 2012. Evidence for a protective effect of polyphenols-containing foods on cardiovascular health: an update for clinicians. Ther Adv Chronic Dis 3:87–106.

Halliwell B. 2008. Are polyphenols antioxidants or pro-oxidants? What do we learn from cell culture and in vivo studies? Arch Biochem Biophys 476:107–112.

Johansson AK, Korte H, Yang B, Stanley JC, Kallio HP. 2000. Sea buckthorn berry oil inhibits platelet aggregation. J Nutr Biochem 11: 491–495.

Larmo P, Alin J, Salminen E, Kallio H, Tahvonen R. 2008. Effects of sea buckthorn berries on infections and inflammation: a double-blind, randomized, placebo-controlled trial. Eur J Clin Nutr 62: 1123–1130.

Larmo PS, Yang B, Hurme SA, Alin JA, Kallio HP, Salminen EK, Tahvonen RL. 2009. Effect of a low dose of sea buckthorn berries on circulating concentrations of cholesterol, triacylglycerols, and flavonols in healthy adults. Eur J Clin Nutr 48:227–282.

Larmo PS, Järvinen RL, Setälä NL, Yang B, Viitanen MH, Engblom JR, Tahvonen RL, Kallio HP. 2010. Oral sea buckthorn oil attenuates tear film osmolarity and symptoms in individuals with dry eye. J Nutr 140: 1462–1468.

Larmo PS, Kangas AJ, Soininen P, Lehtonen HM, Suomela JP, Yang B, Viikari J, et al. 2013. Effects of sea buckthorn and bilberry on serum metabolites differ according to baseline metabolic profiles in overweight women: a randomized crossover trial. Am J Clin Nutr 98: 941–951.

Lehtonen HM, Lehtinen O, Suomela JP, Viitanen M, Kallio H. 2010a. Flavonol glycosides of sea buckthorn (*Hippophaë rhamnoides* ssp. sinensis) and lingonberry (Vaccinium vitis-idaea) are bioavailable in humans and monoglucuronidated for excretion. J Agric Food Chem 58: 620–627.

Lehtonen HM, Suomela JP, Tahvonen R, Vaarno J, Venojärvi M, Viikari J, Kallio H. 2010b. Berry meals and risk factors associated with metabolic syndrome. Eur J Clin Nutr 64:614–621.

Lehtonen HM, Suomela JP, Tahvonen R, Yang B, Venojärvi M, Viikari J, Kallio H. 2011. Different berries and berry fractions have various but slightly positive effects on the associated variables of metabolic diseases on overweight and obese women. Eur J Clin Nutr 65: 394–401.

Mente A, de Koning L, Shannon HS, Anand SS. 2009. A systematic review of the evidence supporting a causal link between dietary factors and coronary heart disease. Arch Intern Med 169:659–669.

Olsson ME, Gustavsson KE, Andersson S, Nilsson Å, Duan RD. 2004. Inhibition of cancer cell proliferation in vitro by fruit and berry extracts and correlations with antioxidant levels. J Agric Food Chem 52: 7264–7271.

Ranjith A, Sarin Kumar K, Venugopalan VV, Arumughan C, Sawhney RC, Singh V. 2006. Fatty acids, tocols, and carotenoids in pulp oil of three sea buckthorn species (*Hippophae rhamnoides*, *H. salicifolia*, and *H. tibetana*) grown in the Indian Himalayas. J Am Oil Chem Soc 83: 359–364.

Riihinen K. 2005. Phenolic compounds in berries [dissertation]. Natural Environ Sci 187. Kuopio University Publications C. Available at: http://wanda.uef.fi/uku-vaitokset/vaitokset/2005/isbn951-27-0345-9.pdf. Accessed on September 2013.

Rosch D, Bergmann M, Knorr D, Kroh LW. 2003. Structure – antioxidant efficiency relationships of phenolic compounds and their contribution to the antioxidant activity of sea buckthorn juice. J Agric Food Chem 51:4233–4239.

Sabir SM, Maqsood H, Hayat I, Khan MQ, Khaliq A. 2005. Elemental and nutritional analysis of sea buckthorn (*Hippophae rhamnoides* ssp. turkestanica) Berries of Pakistani origin. J Med Food 8:518–522.

Serafini M, Crozier A. 2003. Milk and absorption of dietary flavonols. Nature 426:788.

Suomela JP, Ahotupa M, Yang B, Vasankari T, Kallio H. 2006. Absorption of flavonols derived from sea buckthorn (*Hippophae rhamnoides* L.) and their effect on emerging risk factors for cardiovascular disease in humans. J Agric Food Chem 54: 7364–7369.

Tiitinen KM, Hakala MA, Kallio HP. 2005. Quality components of sea buckthorn (*Hippophae rhamnoides*) varieties. J Agric Food Chem 53: 1692–1699.

Upadhyay NK, Kumar R, Siddiqui MS, Gupta A. 2011. Mechanism of Wound-Healing Activity of *Hippophae rhamnoides* L. Leaf Extract in Experimental Burns. Evid Based Complement Alternat Med 2011: 659–705.

Wang LJ. 1992. Sea buckthornoil andchymotrypsinare effective intreatingulcerative stomatitis of children. Hippophae 5:32–34.

Yang B, Kalimo KO, Mattila LM, Kallio SE, Katajisto JK, Peltola OJ, Kallio HP. 1999. Effects of dietary supplementation with sea buckthorn (*Hippophaë rhamnoides*) seed and pulp oils on atopic dermatitis. J Nutr Biochem 10:622–630.

Yang B, Kallio HP. 2001. Fatty acids composition of lipids in Sea Buckthorn (*Hippophae rhamnoides* L.) berries of different origins. J Agric Food Chem 49:1939–1947.

Yang B, Kallio H. 2002. Composition and physiological effects of sea buckthorn (Hippophae) lipids. Trends Food Sci Tech 13:160–167.

Yildiz H, Sengul M, Celik F, Ercisli S, Duralija B. 2012. Bioactive content of Sea Buckthorn (*Hippophae rhamnoides* L.) berries from Turkey. Agric Cons Sci 77:53–55.

Zeb A. 2004. Important therapeutic uses of Sea Buckthorn (Hippophae): a review. J Biol Sci 4:687–693.