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Seabuckthorn Polyphenols: Characterization, Bioactivities and Associated Health Benefits

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Abstract

Sea Buckthorn (*Hippophae rhamnoides*) has a long history of use as food and medicine in Tibet and Northern Asia, where the plant has been associated with a wide range of health benefits. Sea buckthorn (SB) berry, seed and leaf have been reported to contain more than 190 bioactive compounds, including polyphenols (epicatechin, epigallocatechin, gallic acid, proanthocyanidins, chlorogenic acid) and flavonoids (quercetin, isorhamnetin, kampferol glycosides, luteolin, myricetin). SB represents a good source of phenolic compounds and flavonoids acting in synergy with PUFA such as omegas 3, 6, 7 and 9, vitamins (vitamin C), and organic acids. SB exerts antioxidant, anti-inflammatory, cytoprotective, anti-cancer, hepatoprotective properties, associated with improvement in various metabolic markers such as glycemic control and lipid profile. SB polyphenol fraction also demonstrated significant cardioprotective, antihypertensive and neuroprotective actions. SB acts as a natural stem cell mobilizer associated with significant regenerative properties. As a consequence, SB polyphenol consumption stimulates pancreatic regeneration in animal model of insulin-dependent diabetes. In conclusion, SB polyphenols exert a wide range of health benefits in metabolic health including obesity, diabetes and hypertension, as well as liver, kidney and brain health, positioning sea buckthorn berry extract as an interesting and valuable dietary supplement for natural complementary therapy and for antiaging.

Keywords: Polyphenols, flavonoids, proanthocyanidins, sea buckthorn, anti-inflammatory, antioxidant, stem cell enhancer, metabolic health, cardiovascular health

1. Introduction

Although it has been used for centuries in many parts of the world, especially in Northern Asia, sea buckthorn berry and its derivatives are relatively novel ingredients in the field of dietary supplements and functional foods. Sea buckthorn (SB) berry and leaf contain a variety of polyphenols, some of them being especially abundant in SB, that have been documented to bring a wide range of health benefits. This review is aimed at describing the composition of SB derivatives and the health benefits associated with their consumption.

2. Geographical origin

Sea Buckthorn is a deciduous, branched, spiny shrub belonging to genus *Hippophae* and family *Elaeagnaceae*. *Hippophae rhamnoides* L. is synonymous with *Elaeagnus rhamnoides* (L.) A. Nelson. SB usually forms a shrub or a small tree of 3–4 m in height, though it can reach up to 7 m when growing at low altitude and in moderate climate. The plant originally comes from the Northern Himalayan region where it naturally grows at altitudes ranging between 1600 and 5200 m and can resist to winter temperatures down to -40°C . Sea buckthorn's natural distribution area includes Northern China, Mongolia, India, Nepal, Northern Pakistan, and Russia, though over the centuries it has spread to Europe and North America. Seven species and 11 subspecies have been identified worldwide [1].

3. Botanical identity

Sea buckthorn is dioecious, with separate male and female plants. The male plants produce brownish flowers, which produce wind-distributed pollen and female plants produce an orange berry-like fruit. The leaves are narrow, alternate, lanceolate-linear and obtuse with peltate and stellate scales on the lower surface. The fruits are subglobose, spherical or oblate, succulent, and orange colored with a mean diameter of 5-8 mm. The seeds are solitary, uniquely lobed, light black, and stony. The seed kernel is white and oily, sour and astringent. The pulp of the fruit is oily and soft. The surface of the peel epidermal cells is polygonal with a slightly thicker vertical wall. The parenchyma cells of the pulp contain many orange-red or orange-yellow particles, along with bright yellow oil drops. The content in actives is respectively not less than 1.5% flavonoids, 0.1% isorhamnetin (Identification criteria by Chinese pharmacopeia).

Sea buckthorn has been reported to contain more than 190 bioactive compounds in the seeds, pulp, fruit, and juice. These compounds include fat-soluble vitamins (A, K, E), 22 fatty acids, 42 lipids, organic acids (malic acid, oxalic acid), amino acids, carbohydrates, vitamins C, B1, B2, B6, B12, folic acid, flavonoids (quercetin, isorhamnetin, kaempferol glycosides, luteolin, myricetin), polyphenols (epicatechin, epigallocatechin, gallic acid, proanthocyanidins, chlorogenic acid), terpenes, carotenoids (zeaxanthin, beta carotene, lycopene) and tannins [2]. Sea buckthorn berry also contains twenty mineral elements, including Ca, Cd, Cr, Cu, Fe, K, Mg, Mn, Na, Ni, Pb, Zn. It is a rich source of omega 3, 6, 7, and 9. It is the only plant that offers a wide variety of fatty acids and includes a beneficial amount Omega 7 (palmitoleic acid) [3].

4. Traditional use of the plant

The genus name of Sea Buckthorn “*Hippophae*” originates from the Greek words “Hippo” (horse) and “Phaos” (to shine), meaning essentially “shining horse”. It is said that when Alexander the Great headed back from his Asian conquest, he travelled with his troops through a desert region near today's Northern Pakistan, where he had previously abandoned a group of horses wounded in battle. The area was abundant in sea buckthorn trees and the horses had the opportunity to feed on the berries and leaves. At one point they spotted the horses looking vibrant and with a shiny coat, which is a sign of health for horses. From there sea buckthorn was brought to Greece where it was used ever since of as horse feed to keep horses healthy and strong.

It was used as a medicinal plant in Tibet as early as 900 AD. The references to the medicinal use of SB were found in the ancient Tibetan medicinal texts, including “the RGYud Bzi” (The Four Books of Pharmacopoeia) dated to the times of Tang Dynasty (618–907) AD. In Tibetan and Mongolian traditional medicines, SB berries were used in the treatment of cough, wound healing and burns, blood circulation and digestive system support (constipation, stomach burn). Sea buckthorn berries are listed in the *Chinese Pharmacopeia* as an ingredient for the treatment of cough and for improving blood circulation and digestion. In Russia and the Indian Himalayan region, SB is used in a wide variety of therapeutical applications such as the treatment of skin diseases, jaundice, asthma, gastro-intestinal treatment, as laxative and for the treatment of rheumatism. In Central Asia, local people use SB berries for treatment of hypertension, gastric ulcers and skin diseases [4]. Sea buckthorn berries are normally not consumed as fresh fruits. However, they have become popular in jams, beverages, candies, and juices. Juice from sea buckthorn berries is a common drink in many parts of Asia and Europe. The juice is rich in protein, vitamins C and E, as well as organic acids. The leaves, either fresh or dried, can be steeped to yield a nutritional tea. The leaves were used in ancient Greece as a fodder for horses to promote weight gain and a shiny coat. Sea buckthorn has been used for centuries in both Europe and Asia as food (tea, beverages, jams...) and for its pharmaceutical properties [5, 6]. Chinese Pharmacopeia recommends for officinal use in humans a dose of 3-10 g of SB berries per day (Editorial Committee of Chinese Pharmacopeia, 2010, p184–185, 2015 (Vol1)).

5. Polyphenol composition in SB and phytochemistry

Polyphenols from SB have antioxidant [1], anti-inflammatory [7, 8], cardio-protective [9, 10] and anticancer [2] properties, associated with metabolic-health enhancement including weight management, improvement of lipid and glucose profiles, pancreatic regeneration, and reduction of hypertension (**Figure 1**) [11–16].

Figure 1.
Main mechanism of action and associated health benefits of Sea Buckthorn polyphenols.

	SB Berries Tibetan plateau	SB Berries*	SB berries defatted pomace ethanolic fraction
Method	UPLC-Q- Orbitrap MS (µg/g)	RP-HPLC (µg/g)	UPLC-Q/TOF MS** (µg/g)
Total phenolic acids		629	
Total phenolics		4730	
Total Flavones		309	
Total Flav-monoglycosides		1470	
Total Flav-diglycosides		2330	
Phloretin	310		
Gallic acid	80.9	198	
EGC			238.8
Protocatechuate	112.9	393	
Catechin	208.5	89.9	369.6
Epicatechin		21.4	123.2
Chlorogenic acid	14.04		
PAC-B2	99.12		
vanillic acid	31.7		
O-hydroxybenzene acetic acid	8.56		
coffeic acid	33.84		
P-coumaric acid	13.08		
Ferulic acid	11.28	376	
Salicylic acid	3.22		
Rutin	1,121.4		162.9
Ellagic acid	1.23		
Myricetin	39.96		
Naringenin	1.23		
Quercetin	36.6	55.1	
Kaempferol	117.48	12.3	
Isorhamnetin		131	195.1
Quercetin –3-rutinoside		329	
Quercetin-3-glucoside		397	
Isorhamnetin-3-rutinoside		586	
Isorhamnetin-3-glucoside		155	139.8
Quercetin-3-Sophoroside-7- Rhamnoside			1220
Kaempferol-3-Sophoroside-7- rhamnoside		450	1739
Isorhamnetin-3-Sophoroside-7- rhamnoside		397	1166
Isorhamnetin-3-glucoside-7- rhamnoside		1480	

	SB Berries Tibetan plateau	SB Berries*	SB berries defatted pomace ethanolic fraction
Method	UPLC-Q- Orbitrap MS (µg/g)	RP-HPLC (µg/g)	UPLC-Q/TOF MS** (µg/g)
Kaempferol-3-glucoside-7- rhamnoside			203.5
Reference	Jia et al. [17]	Guo et al. [18]	Dienaite et al. [19]
*Average of 4 sub-species <i>Sinensis</i> , <i>Yunnanensis</i> , <i>Mongolica</i> and <i>Turkestanica</i> . **Dry Weight extract.			

Table 1.
Identification and quantification of the main polyphenolic compounds present in SB; taken from [17–19].

Particularly, kaempferol, quercetin, and their derivatives, proanthocyanidins (PAC), catechins, phenolic acid and tannins demonstrated significant health-promoting benefits. Isorhamnetin, kampferol, quercetin, catechins and procyanidins represent some active molecules with well-known health benefits.

SB represents a good source of phenolic compounds acting in synergy with PUFA such as omegas 3, 6, 7 and 9, vitamins (vitamin C), organic acids, making SB a suitable candidate for dietary supplement and food fortification. SB polyphenols are mainly phenolic acids and flavonoids. Polyphenolic content ranges from 29 to 38.8 mg/g (GAE), with more than 100 polyphenolic compounds identified (**Table 1**). The estimated content in polyphenols is higher than in mulberry, blueberry, raspberry or pomegranate [1]. Polyphenol content varies from species to species, geographical origin, the degree of maturity at the harvest, and the production process, such as drying temperature, method of extraction and storage. Comparing species, flavonoid content was the highest in *H. rhamnoides L subsp sinensis* and *yunnanensis*. Phenolic acids are divided into hydroxybenzoic acid, hydroxycinnamic acid, and their derivatives. The main phenolic acids naturally occurring in SB fruit are gallic acid, protocatechuic acid, salicylic acid, vanillic acid, caffeic acid, ferulic acid, P-coumaric acid and chlorogenic acid (**Table 1**). Flavonoids commonly found in SB include isorhamnetin, quercetin, kaempferol, myricetin, catechin, epicatechin and rutin. Condensed tannins or PAC constitutes the third category of polyphenols in SB. There is also a significant amount of carotenoids (including β -carotene, zeaxanthin and lycopene) in SB. **Table 1** summarizes the main polyphenols identified and quantified in SB berry preparations in recent publications.

6. Effects of SB polyphenols on cellular function

Ethanolic extract of SB berry (SBB) exerts significant cytoprotective properties against sodium nitroprusside induced oxidative stress in lymphocytes [20]. SBB extract also attenuated nicotine-induced oxidative stress in rat liver and heart [21]. Moreover, the total flavones of SB provided protection against H2O2-induced apoptosis on vascular endothelial cells with the lowering the caspase-3 expression [22]. SBB also showed immunomodulating effect against T-2 toxin-induced immunodepression in 15-day-old chicks [23]. The SBB extract also had a protective effect on antioxidant enzyme levels and contributed to the reduction of lipid peroxidation, leading to reduced levels of cellular oxidation processes. Furthermore, Yasukawa et al.

reported that an ethanolic fraction of SB containing (+)-catechin, (+)-gallocatechin, (–)-epigallocatechin and ursolic acid exhibited anti-tumor activity [24]. When tested on cell proliferation in the Caco-2 and HepG2 cancer cell lines, SBB extracts induced apoptotic activity and apoptotic morphological changes of the nucleus. This included chromatin condensation in HL-60 cells treated with flavonols isolated from SB such as quercetin, kaempferol and myricetin [25–27].

A flavonoid extract of SB containing isorhamnetin and quercetin exerted protective effects on myocardial ischemia and reperfusion, on microcirculation and on the regulation of thyroid function [2]. Isorhamnetin isolated from SB has also been investigated for its cytotoxicity and its influence on human hepatocellular carcinoma cells. The cytotoxic effect of isorhamnetin was showed to be dose and time-dependent against hepatocellular carcinoma cells after treatment with isorhamnetin for 72 h [28].

Polyphenolic compounds in SBB juice at different phases of digestion exerts beneficial effects on colonic microbial diversity, with an increase in total phenolic content and in total antioxidant activity during gastric and small intestine digestion, and the release of quercetin from the food matrix in the colon. Colonic fermentation resulted in an increase in quercetin and caffeic acid, along with a decrease in rutin and chlorogenic acid after 36 h of fermentation. The Shannon diversity index of beneficial groups including Lactic acid bacteria, Bacteroides/Prevotella and Bifidobacteria was increased by 35%, 71% and 17%, respectively. As a consequence, SB juice seems to represent a good source of prebiotic substrate for the proliferation of beneficial gut microbiota [29].

7. Safety of SB extracts

The safety of SB leaf and berry extracts was assessed in several studies [30–32]. In a sub-acute study, the absence of any sign of toxicity at the highest dose used established the LD50 at >10 g/kg bw for SB leaf extract. In a chronic 90-day repeated gavage administration study, no changes were observed at any of the doses used with regard to body weight and organ weight for animal of both sexes, when compared to control rats [31]. Moreover, no significant changes in biochemical parameters were noticed relative to lipid metabolism as well as renal or hepatic function. The absence of histopathological lesions in the main organs at any dose suggests a NOAEL superior to 500 mg/kg bw. In addition, the safety of herbal antioxidants composed of SB pulp and extract thereof was studied [32]. There were no significant alterations in hematological and biochemical parameters at any dose. Histopathological analysis of vital organs showed normal architecture and absence of lesions in all treated groups, which was associated with no difference in weight gain and relative organ weight in treated groups compared to controls. Even at high dose of 2,000 to 8,000 mg/kg bw [32], an absence of toxicity and side effects was reported, confirming that SBB extract is a safe product.

8. Health benefits of SB leaf and seed polyphenols

8.1 Lead intoxication model

The efficacy of SB leaf aqueous extract (SLE) was assessed in a model of lead toxicity in Wistar rat model, at a daily dose of 100 mg/kg bw for 60 days [33]. Administration of SLE to lead intoxicated Wistar rats resulted in normalization of almost all the safety

parameters studied - albumin, creatinine, blood urea, total proteins. Significant improvement in total protein levels after SLE treatment in lead intoxicated animals may be due to its antioxidant properties and its hepatoprotective effect, normalizing protein synthesis. SLE treatment of lead intoxicated rats resulted in normalization of serum urea and creatinine levels, suggesting a normalization of glomerular filtration rate in kidney. Supplementation of SLE in lead intoxicated rats resulted in normalization of elevated cholesterol levels, that may due to the presence of flavonoids, terpenoids, carotenoids.

8.2 Cardiometabolic risk improvement, anti-obesity and hepatoprotective effects

SB leaf tea (SBLT) included at levels of 1 and 5% of total diet, in a high fat diet (HFD) for 6 weeks, suppressed body weight gain in a dose-dependent manner and significantly reduced visceral fat, plasma levels of leptin, triglyceride, total cholesterol and ALT activity compared with high-fat-fed control mice [34]. SBLT also decreased hepatic triglyceride, serum cholesterol and lipid accumulation. Moreover, its consumption normalized the expression of several hepatic lipid metabolic markers such as glucose-6-phosphate dehydrogenase, phosphatidate phosphohydrolase, beta-oxidation, and carnitine palmitoyltransferase. Intra-abdominal deposition of visceral adipose tissue is a major risk factor for the development of hypertension, insulin resistance, metabolic syndrome, diabetes mellitus and hyperlipidemia. SBLT supplementation seemed to have a direct effect on lipid metabolism, and it exhibited significant anti-visceral obesity property, while also reducing hepatic lipid accumulation when compared with the high-fat-fed control animals. The hypolipidemic effect of SBLT supplementation seemed likely to be due to a decrease in hepatic triglycerides synthesis through a modulation of the fatty acid esterification pathway. Compared to high-fat-fed control mice, SBLT lowered CYP2E1 activity which participates to the production of reactive oxygen species and overall oxidative stress. Both 1% and 5% SBLT supplementation effectively improved ALT activity. SBLT supplementation may prevent hepatic damage of HFD by enhancing the antioxidant defense system and the attenuation of microsomal CYP2E1 induction. Therefore, SBLT exerts antioxidant, anti-obesity and hepatoprotective effects by modulating hepatic lipid metabolism.

Total flavones from SB fruit seed residues were administered at the daily concentrations of 50, 100 or 150 mg/kg/day for 8 weeks in sucrose-fed rats model [35]. Sucrose-fed rats displayed increases of 25.6% in systolic blood pressure, 114% in plasma insulin, 85% in triglycerides (TG), as well as an increase in activated angiotensin in both heart and kidney. SB flavones significantly suppressed the elevated hypertension, hyperinsulinemia and dyslipidemia. It also led to the normalization of systolic blood pressure by at least improving insulin sensitivity and the increase in plasma angiotensin II after 8 weeks of SB consumption, especially at the daily dose of 150 mg/kg. The antihyperinsulinemia abilities of SB total flavones from fruit seed residues and irbesartan were comparable. SB flavones reversed the abnormalities in plasma triglyceride, cholesterol and FFA levels and low content of HDL. Administration of SB seed residues at a daily dose of 400 mg/kg bw for 4 weeks significantly decreased serum glucose, TG and nitric oxide levels in diabetic rats and increased serum superoxide dismutase activity and glutathione level [36]. Therefore, SB seed extract has hypoglycemic, hypolipidemic and antioxidant effects in diabetic rats.

These findings were confirmed in another study where an ethanolic extract of SB leaves (SBLE) at daily doses of 500 and 1,000 mg/kg was administered for 13 weeks to mice fed high-fat diet (HFD) [37]. Oral administration of SBLE significantly reduced

energy intake, body weight gain, epididymal fat pad weight, hepatic triglyceride, hepatic and serum total cholesterol levels, as well as serum leptin levels when compared to control HFD mice. Glucose tolerance assessed by OGTT was significantly improved at both daily doses of SBLE. Lipid droplet infiltration in the liver was significantly reduced at the lower dose of SBLE and absent at the higher dose of SBLE, confirming hepatoprotective action against triglycerides accumulation in the liver, as well as steatosis. SBLE modulates liver lipid metabolism by the upregulation of PPAR α , PPAR γ and CPT1 and downregulation of acetylCoA carboxylase.

8.3 Stress reduction and cytoprotective effect

The anxiolytic properties of water and ethanolic extract of SB leaves (SBLE) at daily doses ranging from 50 to 300 mg/kg bw for 17 days were compared to L-theanine as positive control and saline in a model of electric foot shock stress in mice [38]. Corticosterone-induced impairment model was also studied in SH-SY5Y neuroblastoma cell line. Corticosterone-induced decrease in cellular viability was restored by different SB extracts at the concentration of 30 μ g/ml. The group receiving SBLE exhibited a significantly reduced stress-induced increase in immobility times compared with the mice in the EFS group. Moreover, SBLE consumption increased climbing times in forced swim tests induced by electric foot shocks in the stressed mice. The levels of CORT, dopamine, and norepinephrine were increased, and the level of serotonin in the hippocampus was decreased in the electric foot shock stress model. The standardized SB extract effectively restored abnormal CORT and monoamine levels in the hippocampus to normal levels. These findings suggest anti-stress and neuroprotective properties of SB leaf extract *in vivo*.

8.4 Hepatoprotective effect

Phenolic-rich fraction of SB leaves (319.33 mg gallic acid equivalent; SBLE) was administered at doses of 25, 50 and 75 mg/kg bw for 7 days in a model of carbon tetrachloride (CCl $_4$)-induced oxidative stress and liver injury in Sprague Dawley rats [39]. SBLE significantly protected against CCl $_4$ -induced increase in serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ -glutamyl transpeptidase (GGT), bilirubin, hepatic lipid peroxidation, hydroperoxides, protein carbonyls, as well as depletion of hepatic reduced glutathione (GSH) and decrease in the activity of hepatic antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPX), glutathione reductase (GR) and glutathione-S-transferase (GST). SBLE protected against histopathological alterations induced by CCl $_4$ such as liver necrosis, fatty changes, and vacuolation. SBLE demonstrated antioxidant and hepatoprotective effects against CCl $_4$ liver injury. These observations were confirmed in another model of CCl $_4$ -induced liver injury in male albino rats fed SBLE at doses of 50, 100 and 200 mg/kg-bw for 5 days [40]. SBLE at doses of 100 and 200 mg/kg significantly restricted the CCl $_4$ -induced increase of glutamate oxaloacetate transferase, glutamate pyruvate transferase, alkaline phosphatase and bilirubin. SBLE also enhanced GSH and decreased MDA levels. SBLE (100 mg/kg) protected against CCl $_4$ -induced hepatotoxicity, as hepatic cells showed well-preserved cytoplasm and the liver showed a marked decrease in inflammatory cells. These results confirm the antioxidant and hepatoprotective effect of SBLE against CCl $_4$ liver injury model.

9. Health benefits of SB berry polyphenols (in powders, purees, and extracts)

9.1 Anti-inflammatory effect

Two grams of frozen SBB puree containing 16.7 mg of flavanol glycosides or a placebo was consumed for 3 months in a study including 254 healthy volunteers [41]. The objective was to assess the efficacy and safety of SBB for common cold (CC), digestive tract infections (DTI), and urinary tract infections (UTI). While no difference was reported in CC and DTI frequency or duration, consumption of SBB reduced both the number and duration of UTI. A small but significant decrease in CRP was also observed in the SBB group. The decrease in the inflammatory marker CRP was confirmed in another study in which a dose of 28 g of SBB or placebo was given to 220 healthy volunteers for 90 days. SBB did not affect serum total HDL and LDL cholesterol, nor serum triacylglycerol concentrations. However, compared with placebo, there was a significant reduction in blood concentrations of CRP in the SBB group [9].

9.2 Regenerative effect for improvement of pancreatic function

SBB pulp at a daily dose of 1 or 2 ml/kg bw for 3 weeks was administered to streptozotocin-nicotinamide (STZ) induced diabetes in rats [42]. A decrease of more than 50% of fasting hyperglycemia was observed in diabetic rats, at both 1 and 2 ml/kg. Pancreatic glutathione content increased significantly in SBB treated diabetic rats. Moreover, a decrease in HbA1c was reported at the highest dose. SBB decreased all histopathological changes induced by STZ, such as degenerative and lytic changes were reduced, beta cells depletion was decreased, as well as fibrosis. SBB pulp had a regenerative and protective effect on pancreatic beta cells.

9.3 Metabolic health improvement

The beneficial effect of flavonoid-rich extract of SBB was assessed in high-fat diet-induced obesity (HFDO) at daily doses of 100 and 300 mg/kg bw for 9 weeks, and compared to placebo [43]. SBB administration significantly reduced body weight gain, inhibited macrophage infiltration into adipose tissues, and downregulated TNF α mRNA expression in adipose tissue. A decrease in TG was observed but not in total cholesterol. At the highest dose of 300 mg/kg, hepatic TG was decreased by 49.56% when compared to HFDO control mice. Blood glucose concentration was 14.55% lower in the SBB treatment group (300 mg/kg), compared to the HFDO control. SBB alleviated the glucose intolerance induced by HFD, as determined by Oral Glucose Tolerance Test (OGTT). The sizes of adipocytes were considerably lower at both doses of SBB, compared to the HFDO control. Therefore, the anti-obesity activity of SBB may be attributed partly to a decrease in the volume of fat cells. Decrease in adipose tissue inflammation, anti-obesity properties, improvement of glucose tolerance and glycemia, and the decrease in hepatic TG accumulation all points to an improvement of cardiometabolic profile.

The efficacy of SBB was also evaluated in a model of spontaneously hypertensive stroke-prone rat, using a daily dose of 0.7 g/kg-bw for 2 months [44]. Mean and diastolic blood pressure, heart rate, total plasma cholesterol, triglycerides, and glycated hemoglobin were significantly decreased by the SBB treatment when compared to hypertensive control group. The number of AP-containing capillary portions fell

while the number of those containing DPPIV increased. The expression of these 2 enzymes is modulated by inflammation enhanced by hypertension. Antihypertensive and cardioprotective properties measured by heart rate, blood pressure, total plasma cholesterol, TG levels improvement were thus confirmed.

The efficacy of SBB, and SBB phenolic extract on metabolic health was compared to bilberry berries (BB) in 110 overweight women [45]. The daily doses were all equivalent to 100 g of fresh berries. Each product was consumed for 35 days in a cross-over study. Decrease in waist circumference and $\text{TNF}\alpha$, and a small decrease in fasting plasma glucose was observed after SBB consumption. A decrease in ICAM and $\text{TNF}\alpha$ was observed after consumption of SB extract. No significant difference in BP, percentage of fat mass, fasting plasma cholesterol, TG, and IL6 levels was observed. Therefore, SB products brought mild but significant improvement in metabolic, inflammatory and endothelial markers in overweight volunteers. Another clinical study demonstrated the efficacy of SB juice (SBJ) on platelet aggregation. Placebo or 300 ml of SBJ was consumed by 20 healthy volunteers for 8 weeks [46]. No difference in platelet aggregation and LDLox levels was seen between placebo and SBJ group. A non-significant increase of 20% was observed in plasma HDL-C. In another study, a crude flavone extract from SBB prevented thrombogenesis in an *in vivo* model of thrombosis in mouse femoral artery, probably by inhibition of platelet aggregation. It prolonged occlusion time at a dose of 300 $\mu\text{g}/\text{kg}$ had a similar effect to aspirin at 10 mg/kg [47].

This cardioprotective effect and improvement in metabolic profile has been confirmed in clinical studies. Eighty overweight women were given either 20 g of dried SBB, or 14.6 g of sea buckthorn phenolic extract for 35 days, in a randomized cross-over study. All these daily doses represent 100 g of fresh SBB [16]. All groups using the various SB products showed significant improvement in metabolic profile, especially in individuals with higher baseline cardiometabolic risk. SB-induced effects were mainly on serum TG and very-low-density lipoprotein (VLDL) and its subclasses, which decreased in participants with higher baseline cardiometabolic risk. During SB consumption, a significant decrease in TG and creatinine was observed. To conclude, a meta-analysis including 11 RCT which enrolled 514 patients confirmed that supplementation with SBB and extracts significantly reduced total cholesterol, LDL-cholesterol and significantly increased HDL-cholesterol in subjects with cardiovascular risks [6].

9.4 Hepatoprotective effect

Sea buckthorn extract (SBE) was administered at the daily dose of 15 g, 3 times a day for 6 months, to 50 cirrhotic Child-Pugh grade A and B patients [48]. The rate of normalization in AST and ALT, was significantly higher in the groups treated with SBE: 80% in the treated group and 56% in the control group. Parameters of liver fibrosis such as serum laminin, hyaluronic acid, total bile acid (TBA), collagen types III and IV were decreased after treatment, when compared with control group. SBE decreased markers of liver fibrosis and improved the rate of AST/ALT normalization, suggesting hepatoprotective properties.

9.5 Regenerative effect

Stemberry®, a SBB aqueous extract standardized in 30% of proanthocyanidins was consumed by 12 healthy participants at a daily dose of 500 mg, compared to a placebo in one single dose. Rapid and highly selective stem cell mobilization was observed, as quantified by an increase in the number of circulating CD45dim C D34^+

CD309⁻ progenitor stem cells by 24%, CD45⁻ CD31⁺ CD309⁺ endothelial stem cells by 33%, and CD45⁻ CD90⁺ mesenchymal stem cells by 20%. All these types of stem cells are involved in regenerative and reparative functions. Moreover, a mild significant increase was observed in the number of CD45dim CD34⁺ CD309⁺ pluripotent stem cells [49]. SB PAC-rich extract supports the natural ability of the body to repair and renew, suggesting regenerative properties.

9.6 Acute lung injury protection

The efficacy of SBB paste (SB total polyphenols 191.5 mg/g and SB total flavonoids 130.9 mg/g) was studied in a mouse model of LPS-induced acute lung injury [50]. SBB paste was consumed for 7 days at daily doses of 200, 400 and 800 mg/kg bw, and at day 8 LPS challenge was carried out. The loss of body weight, microstructure lesions in the lung tissue, increase in MDA, and reduction of SOD and glutathione peroxidase levels caused by LPS challenge were all significantly reduced by SB treatment in a dose dependent manner. As a consequence, SBB paste improved lung lesions such as alveolar thickness caused by edema, hemorrhage alveolus collapse, inflammatory cell inflammation were greatly reduced in the SB-treated group compared with the group acute lung injury. SB treatment provided significant protection against protein transvascular leakage. As lung lesions, oxidative stress markers are decreased, SB provides protection against acute lung injury, via partly the activation of Nrf2 pathway and redox homeostasis due its high content in polyphenols.

9.7 Cytoprotective and antioxidant effect

SBB flavones at the concentration of 100 µg/mL exert cytoprotective and antioxidant properties in a tert-Butyl hydroperoxide-induced cytotoxicity (BOOH) model in lymphocytes [51]. SBB flavones significantly inhibited tert-BOOH-induced cytotoxicity and free radical production, restored the antioxidant status, significantly maintained ATP levels comparable to control and protected the cells from tert-BOOH-induced lipid peroxidation. Treatment with SBB flavones reduced tert-BOOH-induced apoptosis and a decreased tert-BOOH-induced formation of DNA breaks by 30%. Cytoprotective and antioxidant effects suggest safety of SB berries extracts.

9.8 Anti-inflammatory and neuroprotective effect

The efficacy of a SBB extract rich in flavonoids was demonstrated in a model of high-fat high-fructose diet (HFFD) induced cognitive impairment [11]. The extract was consumed for 14 days at 2 daily doses of 100 and 500 mg/kg-bw. Compared to HFFD placebo mice, SBB consumption resulted in a reduction in body weight gain by 8.8% and a decrease in glucose intolerance. It also improves insulin sensitivity. More specifically, SBB consumption resulted in a 45–48% decrease in HOMA-IR value, a 20–30% decrease in fasting hyperglycemia, a 12–20% decrease in fasting insulinemia, a reduction in TG and total cholesterol levels, a prevention of neuronal loss and working memory impairment in behavioral tests, and a suppression of HFFD-induced synaptic dysfunction and neuronal damages. Dietary supplementation SF significantly improved the length by 37.91% and width by 10.07% of postsynaptic density in the hippocampus when compared with the HFFD group mice. SBB flavonoids also increased the levels of BDNF, NT-3, NT-4 and NGF involved in the growth, survival, and synaptic plasticity of brain neurons. SBB flavonoids also reversed HFD-induced

overexpression of iNOS, and the up-regulation of p38 phosphorylation and NFkB expression, which are markers of neuro-inflammation.

As a consequence, SBB flavonoids displayed neuroprotective effects against chronic neuro and systemic inflammation observed in diabetes-induced obesity and is associated with an improvement of metabolic parameters (namely lipid and glucose profiles).

9.9 Beneficial effect in idiopathic nephrotic syndrome

Hydroalcoholic extract of leaves and fruits of SB at a daily dose of 350 mg twice daily for 12 weeks, in addition to other standard drugs, was administered to 52 patients with Idiopathic Nephrotic Syndrome [52]. Beneficial effects were reported in symptoms like anorexia and oedema. There was no statistically significant change in creatinine, phosphorous and blood urea after 12 weeks of treatment when compared to control subjects. Improvement in cholesterol, triglyceride, albumin and 24-hour urinary protein excretion in the SB group was observed. Decreased CRP and IL6 levels were also noticed in the group treated with SB, confirming a nephroprotective role of SB.

10. Conclusion

Sea buckthorn can be considered as a functional ingredient for use in cosmetics, dietary supplements, general foods and fortified foods due to its richness in anti-oxidant molecules, in vitamins C, A and E, in omega 3, 6, 7 and 9, and a diversity of bioactive molecules. Its polyphenolic compounds include phenolic acids, flavonoids, carotenoids associated with antioxidant, anti-inflammatory, antibacterial and anti-cancer properties. SB exerts cardioprotective effect including antiatherogenic properties, hepatoprotective and neuroprotective effect, improves metabolic profile (lipid profile, glycemic control, blood pressure, fat mass and waist circumference), protects against acute lung injury, and supports tissue regeneration (Table 2).

As a consequence, sea buckthorn offers an excellent source of bioactive molecules [3] that could enter in the formulation of nutritional beverages, yogurts, muesli, healthy snacks and bars, in dietary supplements or instant powder mixes as a superfood ingredient. SB polyphenolic extracts such as Stemberry® standardized for polyphenols and

Health benefits of sea buckthorn	Mechanism of action and main outcomes
Cardioprotective effect	Anti-hypertensive effect [35, 44] Improvement of lipid profile [6, 16, 43] Inhibition of atherosclerotic plaque formation [47] Preservation of cardiac function, decrease in ischemic zone, reduction of progression of infarction [2] Preservation of structural integrity of myocardium [2]
Improvement of metabolic profile	Decrease in hyperglycemia and Hb1ac [36, 42, 43] Decrease in hyperinsulinemia [11, 35] Improvement of insulin resistance [11] Anti-obesity effect [34, 37, 43] Anti-inflammatory effect (CRP, TNFa) [9, 45] Antioxidant effect (SOD, GSH, GPx) [39, 40, 50, 51]
Hepatoprotective effect	Decrease in ALAT/ASAT/GGT [34, 37, 39, 40] Decrease in histopathological lesions and markers of fibrosis [34, 37, 39, 40] Decrease in hepatic lipid accumulation [34, 37, 39, 40]

Health benefits of sea buckthorn	Mechanism of action and main outcomes
Antiatherogenic effect	Improvement in lipid profile [6] Decrease in VCAM, ICAM endothelial markers [45] Decrease in platelet aggregation [46, 47]
Tissue regeneration	Selective mobilization of several stem cell types participating to tissue renewal and repair [49]
Neuro and cytoprotective effect	Prevention of neuronal loss and memory impairment in behavioral tests Suppression of synaptic dysfunction and neuronal damages [11] Decrease in neuroinflammation [11]
Protection against acute lung injury	Preservation of lung tissue microstructure, body weight loss reduction, transvascular leakage increase reduction, MDA decrease, and increase in SOD and glutathione peroxidase levels [50]
Protection against acute intestinal injury	Decrease in injury/ulcer area size [4] Decreased in apoptotic cells [4]
Prebiotic effect and gut health support	Colonic microbial diversity increase of beneficial groups of bacteria [29]
Kidney function support	Improvement of creatinine, phosphorous, blood urea, 24 h urinary protein excretion and albumin in idiopathic nephrotic syndrome patients [52] Reduction of oedema [52]

Table 2.
Summary of health benefits of sea buckthorn berry, seed and leaf.

more specifically proanthocyanidins, demonstrated significant regenerative properties through a stimulation of endogenous stem cell mobilization, which has demonstrated therapeutical benefits in neurodegenerative disease, heart diseases, diabetes, and chronic inflammatory diseases by supporting the body’s natural repair system. Additional studies on the regenerative effect of SB polyphenol fraction in several diseases such as diabetes, neurodegenerative, cardiovascular diseases could open new complementary therapeutical strategies in order to improve patients’ quality of life [53].

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