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FOOD SCIENCE & TECHNOLOGY | REVIEW ARTICLE

Bioactive profile, health benefits and safety evaluation of sea buckthorn (*Hippophae rhamnoides* L.): A review

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Abstract: Sea buckthorn (*Hippophae rhamnoides* L.) contains a large number of versatile compounds with antioxidant and hence medical properties that have been reported from time to time. Intensive work on the medical properties of sea buckthorn has concluded incredible results like the effects on atherosclerosis, anti-visceral obesity, platelet aggregation, inflammation, adverse stressful situations, and that of liver injury. Only a few studies have been conducted on the safety evaluation of the plant extract but importantly no study has deemed it unsafe for animal or human consumption till date. Considering the fact that no significant changes have been observed in organ weight/body weight ratios, of any vital organ studied (except liver and kidney in 1 g/kg and 2 g/kg body weight doses, respectively) and biochemical and hematological parameters in different animal trials with an lethal dose for 50% reduction of population (LD₅₀) of >10 g/kg when given orally, there is scope for further investigations regarding its safety in the daily diet as a protective medicine.

Subjects: Bioscience; Food Science & Technology; Health and Social Care

Keywords: Sea buckthorn; *Hippophae rhamnoides*; antioxidant activity; medical value; safety evaluation

1. Introduction

Sea buckthorn (*Hippophae rhamnoides* L., family: Elaeagnaceae) is a thorny, deciduous shrub that grows widely at high altitudes of 7,000–15,000 foot of the northwest Himalayan region, native to Eurasia. It is also been domesticated and used in traditional medicine in several countries, which has long been used for relieving cough, aiding digestion, invigorating blood circulation, and alleviating pain since ancient time (Rousi, 1971; Zheng, Dong, & Yu, 1997). Recently, sea buckthorn has been planted as a new berry crop for obtaining important bioactive compounds. Its good adaptability,

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PUBLIC INTEREST STATEMENT

Different parts of Sea buckthorn plant are excellent sources of bioactive compounds. Over the years, different studies have concluded various medical properties and health benefits of this plant. As a nonconventional source of bioactive compounds and medical food, it has been evaluated for safety in the human body and the results consider its use safe.



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rapid growth, ability to act as protection against wind and sand drift, assistance in soil and water conservation, and improvement of soil by efficient nitrogen fixation allow sea buckthorn to be widely used in vegetation and restoration of degenerated ecosystems (Chen & Chen, 2003; Hou, Bai, & Cao, 1995; Li, 2004; Ruan & Li, 2002; Ruan, Xie, & Li, 2000; Wei, Yu, & Zhu, 1998). Sea buckthorn with diverse uses such as, controlling soil erosion, a source of horse fodder, nutritious foods, drugs, and skin-care products, also contains bioactive compounds with antioxidant properties that are preferred over the synthetic antioxidants simply because the latter have quite often been found to be carcinogenic (Fan, Ding, & Gu, 2007; Rodríguez-Meizoso et al., 2006).

Oil from sea buckthorn has shown effectiveness in skin therapy for sunburns, chemical burns, radiation burns, and eczema (Goel et al., 2002; Seven et al., 2009; Yang et al., 2000; Zeb, 2004b). Furthermore, sea buckthorn oil has shown positive results in treating health problems related to damaged mucous membranes of the gastrointestinal tract including mouth ulcers, gastric ulcers, and stress ulcers (Suleyman, Buyukokuroglu, et al., 2001; Suleyman, Demirezer, et al., 2001; Xu et al., 2007). Of particular interest, the berries, the oil, and the seeds of sea buckthorn have been shown to possess antiatherogenic, hypocholesteromic, hypotensive, and anti-inflammatory properties (Eccleston et al., 2002; Ganju et al., 2005; Wu, Yu, Ma, Li, & Liu, 1994; Yang, 1995; Zhang, 1987) and could therefore be successfully exploited to prevent or treat cardiovascular disease.

Sea buckthorn has been used mostly in the Tibetan and Chinese traditional medicines for so long, which is supported by a lot of both ancient and recent literature on the use of different parts of sea buckthorn, such that the plant is also commonly known as Chinese medicinal plant. The fact that all parts of the plant possess bioactive compounds with antioxidant properties, the literature on its antioxidant activity, impact on the medical lines, and its safety evaluation are reviewed in the present manuscript.

2. Bioactive compounds and antioxidant properties

Bioactive substances like vitamins (A, C, E, riboflavin, folic acid, and K), carotenoids (α , β , δ -carotene, and lycopene), flavonoids, organic acids (malic acid and oxalic acid), sterols (ergosterol, stigmasterol, lanosterol, and amyryns) and some essential amino acids have been found in all parts of the plant (Häkkinen, Kärenlampi, Heinonen, Mykkänen, & Törrönen, 1999; Upendra et al., 2008). In general, the major components of the seed are vitamin C, large amount of carotenoids and vitamin E, flavonoids and kaempferol, fatty acids, triacylglycerol, phytosterols, sugar, organic acids, proanthocyanidins, and phenolic compounds (Fan et al., 2007; Li, Beveridge, & Drover, 2007). The ripe fruit has been reported to be a source of exceptionally high contents of vitamins (A, C, E, and K), carotenoids, flavonoids, and organic acids (Geetha, Sai Ram, Singh, Ilavazhagan, & Sawhney, 2002). Oil from sea buckthorn contains several bioactive components such as vitamin E, vitamin K, carotenoids, and β -70 sitosterol (Zeb, 2004a). Oil extracts obtained from the berries of sea buckthorn in recent studies have been found to be rich in monounsaturated fatty acids (MUFA) (Yang & Kallio, 2001), tocopherols, tocotrienols (Kallio, Yang, Peippo, Tahvonen, & Pan, 2002), carotenoids, and other bioactive compounds (Guliyev, Gul, & Yildirim, 2004). The leaves of sea buckthorn are rich in kaempferol-3-O- β -D-(6''-O-coumaryl) glycoside, 1-feruloyl- β -D-glucopyranoside, isorhamnetin-3-O-glucoside, quercetin-3-O- β -D-glucopyranoside, quercetin-3-O- β -D-glucopyranosyl-7-O- α -L-rhamnopyranoside, and isorhamnetin-3-O-rutinoside. Nine fractions, four monomeric flavan-3-ols, catechin, epicatechin, gallocatechin, and epigallocatechin, along with two dimeric procyanidins, catechin(4 α -8)catechin and catechin(4 α -8)epicatechin, have been reported from the extracts of sea buckthorn seeds (Fan et al., 2007; Kim, Kwon, Sa, & Kim, 2011; Nitin, Upadhyay, Kumar, & Gupta, 2010) (Table 1).

The assays like 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) diammonium salt (ABTS), 1,1-diphenyl-2-picrylhydrazyl (DPPH), and ferric reducing antioxidant power (FRAP), which are often used to test the antioxidant activity, have revealed that the antioxidant activity of seed and root extracts is better than that of leaf and stem extracts (Michel, Destandau, Le Floch, Lucchesi, & Elfakir, 2012; Nitin et al., 2010). Gallic acid, which is also present in sea buckthorn, has been reported to be the most effective antioxidant (Pandurangan, Bose, & Banerji, 2011). The antioxidant potential of

Table 1. Antioxidant compounds present in different parts of sea buckthorn

Part of the plant	Antioxidant compounds	References
Leaves	Kaempferol-3-O-β-D-(6"-O-coumaryl) glycoside, 1-feruloyl-β-D-glucopyranoside, isorhamnetin-3-O-glucoside, quercetin-3-O-β-D-glucopyranoside, quercetin-3-O-β-D-glucopyranosyl-7-O-α-L-rhamnopyranoside, and isorhamnetin-3-O-rutinoside	Nitin et al. (2010)
Fruit	Carotenoids, flavonoids, and organic acids	Geetha et al. (2002)
Seed	Catechin, epicatechin, gallo catechin, and epigallo catechin	Kim et al. (2011)
	Catechin(4α-8)catechin and catechin(4α-8) epicatechin	Fan et al. (2007)
Oil	Carotenoids and β-sitosterol	Zeb (2004a)
	MUFA	Yang and Kallio (2001)
	Tocopherols and tocotrienols	Kallio et al. (2002)

aqueous extract of sea buckthorn leaves varies within the range of 76.44–88.82% while as the total polyphenols vary in the range of 67.91–88.69 GAE/g (Wani, Wani, Shah, & Masoodi, 2013). Sea buckthorn leaf evaluation using maceration, soxhlet, and subcritical water extraction techniques showed the antioxidant potential of 86.35, 133.31–255.87, and 164.03–343.86 Trolox equivalents per gram (TE/g), respectively, while as the respective total phenolic content was reported to be 28.35, 43.77–77.85, and 60.22–86.70 mg/g (Kumar, Dutta, Prasad, & Misra, 2011). The phenolic rich fraction (PRF) of sea buckthorn leaves showed a total phenolic content of 319.33 mg gallic acid equivalents (GAE) per gram while as in the berries, it ranged from 21.31 to 55.38 mg GAE/g on dry weight basis. It showed the highest antioxidant activity of 93.54% and the lowest of 80.38% with no correlation between the total phenolic content and the antioxidant activity. The DPPH radical scavenging activity of sea buckthorn leaf extract (50% effective concentration (EC₅₀) = 1.81 μg/mL) is higher than the butanol fraction (EC₅₀ = 1.86 μg/mL), and quercetin-3-O-β-D-glucopyranoside. It showed stronger reducing power (OD₇₀₀ = 1.83, and 1.78, respectively), with the highest amount of phenolic compounds (477 mg GAE/g) contained in the butanol fraction (Ercisli, Orhan, Ozdemir, & Sengul, 2007; Kim et al., 2011; Maheshwari, Yogendra Kumar, Verma, Singh, & Singh, 2011). The EC₅₀ values of sea buckthorn seed oil from the hydrogen peroxide, superoxide radical, and hydroxyl radical scavenging assays were 2.63, 2.16, and 0.77 mg/ml, respectively (Ting et al., 2011). Taken together, sea buckthorn seed oil, leaf, branches, and root extracts have significant potential as natural antioxidants and could be used potentially for food additives and the development of useful natural compounds (Table 2).

Table 2. Phenolic content and antioxidant properties of sea buckthorn

Type of extract	Phenolic content	Antioxidant potential	References
Leaves (Aqueous extract)	67.91–88.69 GAE/g	76.44–88.82%	Wani et al. (2013)
Leaves (Butanol fraction)	477 GAE/g	–	Kim et al. (2011)
Leaves (maceration)	28.35 mg/g	86.35 TE/g	Kumar et al. (2011)
Leaves (soxhlet)	43.77–77.85 mg/g	133.31–255.87 TE/g	
Leaves (subcritical)	60.22–86.70 mg/g	164.03–343.86 TE/g	
Leaves (PRF)	319.33 GAE/g	–	Maheshwari et al. (2011)
Berries (PRF)	21.31–55.38 GAE/g	80.38–93.54%	

3. General medical properties

The branches of sea buckthorn contain (-)-epigallocatechin and ursolic acid that exhibit anti-inflammatory effects and the leaves are used in the treatment of diarrhea, gastrointestinal, and dermatologic disorders (Yasukawa, Kitanaka, Kawata, & Goto, 2009). The leaf extracts of sea buckthorn are rich in flavonoids, tannins, and triterpenes (Kallio et al., 2002), which as well as the extracts of its branches are used to treat colitis and enterocolitis in humans and animals in Mongolia (Tsybikova, Rasputina, Zalykeeva, Darzhapova, & Kundanova, 1983). The leaves have also been applied as compress form in rheumatoid arthritis in the Middle Asia. Flowers of sea buckthorn have been used as skin softener in Tajikistan. The extracts of whole fruit, fruit pulp, pulp oil, and seed oil of ripe fruits have been reported to be useful in treating various diseases such as gastric ulcers (Suleyman, Demirezer, et al., 2001; Xing et al., 2002), skin disorders (Yang et al., 2000), coronary heart disease (Eccleston et al., 2002), radiation-induced oxidative damage (Goel, Gupta, Gupta, Garg, & Bala, 2005), wound healing (Gupta & Flora, 2005), thrombosis, and platelet aggregation in Indian and Tibetan medicine (Cheng et al., 2003).

Sea buckthorn can increase the production of plasma leptin and of neuropeptide Y in children with functional dyspepsia. The overall effect of sea buckthorn is improvement of gastric emptying, gastric mobility, gastrointestinal digestive function, and promotion of children's growth (Xiao, Qiu, Yue, Cai, & Mo, 2013). Sea buckthorn berry oil is reported to play a potential role in treating atopic dermatitis and thrombosis (Cheng et al., 2003; Yang et al., 2000). Juice, syrup, and oil of the fruits have been used as pain killer, to heal wounds, in ulcer and other diseases of the stomach, disantharia, cancer, and as a metabolism regulator in traditional medicine. The freshly pressed juice is used in the treatment of colds, febrile conditions, and exhaustion (Yang et al., 2000). Oil from seeds and fruits is used in the treatment of eczema, lupus erythematosus, chronic wounds that are difficult to heal, inflammatory diseases, erosion of the cervix uteri, in the treatment of burns and frozen parts of the body, and in ophthalmology. Besides, they are used in the treatment of keratitis, trachoma, injuries or burns of eyelid, and conjunctivitis (Guliyev et al., 2004). Isorhamnetin isolated from sea buckthorn has been investigated for its cytotoxicity and its influence on human hepatocellular carcinoma cells. The cytotoxic effects of isorhamnetin showed dose and time dependency against hepatocellular carcinoma cells ($IC_{50} = 74.4 \mu\text{g/ml}$) after treatment with isorhamnetin for 72 h. The cytotoxicity of isorhamnetin on tumor cells depends on cellular accumulation of the drug that permeates the cell membrane into the cell (Teng, Lu, Wang, Tao, & Wei, 2006). Cytotoxicity studied in murine macrophages induced by tertiary-butyl hydroperoxide was controlled up to >95% using a pretreatment of the cells with sea buckthorn extract of concentration as low as 25 $\mu\text{g/ml}$ (Kumar et al., 2011). Sea buckthorn leaf tea supplementation suppressed body weight gain in a dose-dependent manner and significantly reduced visceral fat, plasma levels of leptin, triglyceride and total cholesterol, and alanine aminotransferase activity as compared to high-fat-fed control mice studied for six weeks (Lee et al., 2011). The leaf tea supplementation also decreased hepatic triglyceride and cholesterol concentrations, and lipid accumulation, whereas fecal lipid excretion elevated. The hepatic cytochrome P450 2E1 activity and hepatic and erythrocyte lipid peroxides were significantly lowered with the leaf tea supplements. The hepatic and erythrocyte superoxide dismutase and catalase activities were also increased with the leaf tea supplements in a dose-dependent manner induced by high-fat feeding, which indicate that sea buckthorn leaf tea supplementation has potential anti-visceral obesity properties and antioxidant activity mediated by the regulation of lipid and antioxidant metabolism in high-fat diet-induced obese mice.

4. Anti-inflammatory properties

Sea buckthorn leaf extract acts as an immunosuppressant during the acute phase of inflammation by selectively inhibiting T-cell activation as a treatment against adjuvant-induced arthritis in rats (Ganju et al., 2005). The inducible nitric oxide synthase (iNOS) induced by microbial products like lipopolysaccharide accounts for the sustained generation of nitric oxide (NO) and is well known for its role in immunological responses such as inflammation and autoimmunity. Many flavanoids and phenylethanoids are antioxidants protecting biological system against oxidative stress. This is mainly due to their redox properties, which can play an important role in adsorbing and neutralizing free

radicals, quenching singlet and triplet oxygen or decomposing peroxidase (Rice-Evans, Miller, & Pagana, 1996; Wang et al., 1996). Sea buckthorn leaf extract increased cell viability against dexamethasone (control) and NO scavenging activity as compared to four (amla, bahera, sacred basil, and shankhpushpi) extracts of known medicinal value. Pretreatment of macrophages with sea buckthorn leaf extract showed the maximum significant inhibition as compared to different extracts (Padwad et al., 2006). Treatment of cells with sea buckthorn leaf extract reduced iNOS expression with respect to the lipopolysaccharide-treated cells, whereas dexamethasone-treated cells showed almost a minimal expression (Wang et al., 1996). Sea buckthorn berries caused a reductive effect on C-reactive protein (marker of inflammation and a risk factor for cardiovascular diseases) in a study carried out as a randomized, double-blind, placebo-controlled trial, over an observation period of 90 days (Larmo, Alin, Salminen, Kallio, & Tahvonen, 2008). The branches of sea buckthorn contains (-)-epigallocatechin and ursolic acid that exhibit anti-inflammatory effects (Yasukawa et al., 2009).

5. Effects on adverse stressful situations

Alcoholic leaf extract of sea buckthorn (70% ethanol) has been analyzed to inhibit hypoxia-induced cytotoxicity, mitochondrial integrity, reactive oxygen species (ROS) production, and DNA damage better than vitamin C (Narayanan et al., 2005). In a study of effect of dry sea buckthorn leaf (aqueous lyophilized) extract, untreated rats exposed to cold-hypoxia-restraint (C-H-R) up to fall of rectal temperature (T_{rec}) 23°C, blood hexokinase (HK) activity decreased, liver phosphofructokinase (PFK) activity increased, and muscle PFK activity decreased (Saggu & Kumar, 2007). During cold exposure of 20°C for 8 h in rat, liver glycolysis activated at the regulatory step catalyzed by PFK/fructose-1,6-biphosphatase (Churchill et al., 1994). Acute hypoxic exposure of 7,000 m was found to increase heart HK activity in rats (Bass et al., 1989). Another study by Saggu and Kumar (2008) on the effect of sea buckthorn dry leaves (aqueous lyophilized extract) showed improvement in anaerobic generation of energy during C-H-R exposure and post-stress recovery, enabling the organism to adapt successfully in such a severe stressful situation (Table 3).

Table 3. Medical 6 properties of the different parts of sea buckthorn

Part of the plant	Used for the treatment of	References
Leaves	Rheumatoid arthritis	Suleyman, Demirezer, et al. (2001)
	Over weight, visceral fat, leptin, triglyceride, and total cholesterol	Lee et al. (2011)
	Inflammation	Padwad et al. (2006)
	Hypoxia-induced cytotoxicity and DNA damage	Narayanan et al. (2005)
	Cold-hypoxia-restrain	Saggu and Kumar (2007, 2008)
	Cytotoxicity	Kumar et al. (2011)
Branches	Inflammation and diarrhea	Yasukawa et al. (2009)
	Colitis and enterocolitis	Tsybikova et al. (1983)
Fruit	Gastric ulcers	Xing et al. (2002)
	Skin disorders	Yang et al. (2000)
	Cardiovascular diseases	Eccleston et al. (2002), Larmo et al. (2008)
	Radiation-induced oxidative damage	Goel et al. (2005)
	Wound healing	Gupta and Flora (2005)
	Thrombosis and platelet aggregation	Cheng et al. (2003)
Seed and berry oil	Dermatitis and thrombosis	Cheng et al. (2003), Yang et al. (2000)
	Eczema, lupus erythematosus, chronic wounds, inflammatory diseases, erosion of the cervix and uterus, keratitis, trachoma, and conjunctivitis	Guliyev et al. (2004)

6. Safety evaluation

In rats exposed to C-H-R, aqueous extract of sea buckthorn leaf administered for 14 days (single oral dose of 1 g/kg and 2 g/kg once daily) and 30 days (single oral dose of 100 mg/kg once daily) showed that the maximal effective adaptogenic dose of the extract was 100 mg/kg body weight. No significant changes were observed in organ weight/body weight ratios, of any vital organ studied (except liver and kidney in 1 g/kg and 2 g/kg body weight doses, respectively) and biochemical and hematological parameters of the sub-acute drug-treated animals in comparison to control rats. In acute toxicity study, LD₅₀ of the extract was observed to be >10 g/kg when given orally (Saggu et al., 2007). Safety and efficacy of supercritical CO₂-extracted sea buckthorn seed oil on burn wound model revealed no adverse effects in acute and sub-acute oral toxicity (Upadhyay et al., 2009). Sub-chronic toxicity and efficacy study of sea buckthorn oil showed no significant changes in various physiological, hematological, biochemical (AST, ALT, ALP, uric acid, urea, and creatinine) and histopathological parameters in three groups of New Zealand white rabbits (0.5, 1, and 1.5 ml/kg body weight) with no mortality in any of the treatment groups (Rashid et al., 2011). Aqueous extract of sea buckthorn fruit administered in four groups of rats (0, 100, 250, or 500 mg/kg in a single dose/day for 90 days) showed no treatment-related change in mean body weight, organ/body weight ratio, histological, hematological, and biochemical parameters (Tulsawani, 2010).

7. Scope for further investigations

Analysis of the published literature on sea buckthorn reveals a lot of health-promoting properties *in vitro* and *in vivo*. However, the safety concerns regarding the use of sea buckthorn extract in the daily diet is still in its early days. Although only a few studies have been performed on the safety evaluation of different sea buckthorn extracts on different trial animals, yet no study has deemed its use deleterious for human consumption to the best of the knowledge of the authors. Therefore, further studies on the safety evaluation of sea buckthorn extracts find a great scope and are needed to authenticate the area of incorporation of sea buckthorn extracts in the daily diet of human beings as a protective medicine.

8. Conclusion

Different parts of sea buckthorn plant have been widely used in traditional medicine in various countries (India, China, Nepal, Pakistan, Myanmar, Russia, Britain, Germany, Finland, Romania, France, etc.) of the world. Among the various studies conducted on the effects of different parts of the plant are cardiovascular effects, effect on atherosclerosis and platelet aggregation, effect on diabetes, anti-inflammatory effect, antitumor effect, effect on clinical diseases of the liver, anti-visceral obesity, antiulcerogenic effect, effect on adverse stressful situations, etc. The different pharmacological effects of sea buckthorn are attributed to the various bioactive components with antioxidant properties of which sea buckthorn is a good source. These bioactive components include kaempferol, isorhamnetin, quercetin, catechin, epicatechin, gallic acid, epigallocatechin, procyanidins, carotenoids, organic acids, etc. Sea buckthorn offers an excellent source of functional and therapeutic food whose safety evaluation although is in its infancy, yet the trails till date deem its use safe.

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Competing interests

The authors declare no competing interest.

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