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Review

Medicinal and therapeutic potential of Sea buckthorn (*Hippophae rhamnoides* L.)

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ABSTRACT

Ethnopharmacological context: This review explores the medicinal and therapeutic applications of Sea buckthorn (*Hippophae rhamnoides* L.) in curtailing different types of acute as well as chronic maladies. The plant is being used in different parts of the world for its nutritional and medicinal properties.

Materials and methods: Sea buckthorn based preparations have been extensively exploited in folklore treatment of slow digestion, stomach malfunctioning, cardiovascular problems, liver injury, tendon and ligament injuries, skin diseases and ulcers. In the recent years, medicinal and pharmacological activities of Sea buckthorn have been well investigated using various *in vitro* and *in vivo* models as well as limited clinical trials.

Results: Sea buckthorn has been scientifically analyzed and many of its traditional uses have been established using several biochemical and pharmacological studies. Various pharmacological activities such as cytoprotective, anti-stress, immunomodulatory, hepatoprotective, radioprotective, anti-atherogenic, anti-tumor, anti-microbial and tissue regeneration have been reported.

Conclusion: It is clear that Sea buckthorn is an important plant because of its immense medicinal and therapeutic potential. However, several knowledge gaps identified in this paper would give impetus to new academic and R&D activities especially for the development of Sea buckthorn based herbal medicine and nutraceuticals.

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Abbreviations: AIA, adjuvant induced arthritis; CHR, cold hypoxia restraint; CCl₄, carbon tetrachloride; FSH, flavonoids from seed residue of *Hippophae*; ICAM-1, intracellular cell adhesion molecule; LDL, low density lipoprotein; LPS, lipopolysaccharide; MDA, malondialdehyde; MMP, matrix metalloproteinases; RP-HPLC, reverse phase high performance liquid chromatography; R&D, research and development; SBT, Sea buckthorn; SFE, subcritical fluid extraction; ssp., sub species; tert-BOOH, tertiary butyl hydroperoxide; TFH, total flavonoids of *Hippophae*; VEC, vascular endothelial cells; VEGF, Vascular Endothelial Growth factor.

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1. Introduction

Herbal formulations have been in use for many years globally not only as therapeutic but also as prophylactic and health promotive agents. Sea buckthorn (*Hippophae rhamnoides* L.) Elaeagnaceae, a unique and valuable plant has recently gained worldwide attention, mainly for its medicinal and nutritional potential. Sea buckthorn (SBT) is a thorny nitrogen-fixing deciduous shrub of cold arid region native to Europe and Asia. It is currently domesticated in several parts of the world due to its nutritional and medicinal properties (Rousi, 1971; Li, 2003). It is a hardy plant, drought and cold resistant, useful for land reclamation and farmstead protection through its vigorous vegetative reproduction and strong, complex root system with nitrogen-fixing nodules (Rongsen, 1992). All parts of this plant are considered to be a good source of large number of bioactive substances like vitamins (A, C, E, K, riboflavin, folic acid), carotenoids (α , β , δ -carotene, lycopene), phytosterols (ergosterol, stigmasterol, lanosterol, amyryns), organic acids (malic acid, oxalic acid), polyunsaturated fatty acids and some essential amino acids (Beveridge et al., 1999; Yang and Kallio, 2001; Pintea et al., 2005).

Sea buckthorn has been used in traditional Chinese medicine since the Tang Dynasty, going back more than 1000 years. In-depth survey and documentation of indigenous ethnobotanical knowledge of SBT reveal that this plant was traditionally utilized by local people of Asia, Nordic countries and the Baltic region in multidimensional aspects of food, fuel, medicine, veterinary, agricultural tools and bio-fencing (Yang et al., 2000; Dhyani et al., 2010). This plant has been used extensively in oriental traditional system of medicine for treatment of asthma, skin diseases, gastric ulcers and lung disorders. Current research is now beginning to understand and support the traditional uses of SBT. A wide spectrum of pharmacological effects of SBT have been recently reported, including antioxidant, immunomodulatory, anti-atherogenic, anti-stress, hepatoprotective, radioprotective and tissue repair (Suleyman et al., 2001; Geetha et al., 2002a,b; Goel et al., 2002; Xing et al., 2002; Gao et al., 2003; Gupta et al., 2005; Basu et al., 2007; Chawia et al., 2007; Saggiu et al., 2007; Upadhyay et al., 2009, 2011). The present review juxtaposes the ancient and modern medical applications of SBT with relevant scientific studies pertaining to its medicinal as well as pharmacological activities.

2. Historical background and traditional uses

The word *Hippophae* has been derived from a Latin word 'Hippo' meaning horse and 'Phaos' which means 'shine'. In Greece, SBT leaves and twigs were used to feed animals which resulted in weight gain and shining coat, especially in horses. It has a rich history of use in treating numerous medical conditions. Many of its pharmacological effects have been recorded in classics such as *Sibu Yidian* from the Tang Dynasty and *Jing Zhu Ben Cao* from the Qing Dynasty. It was used as a medicinal plant in Tibet as early as 900 AD. The references to medicinal use of SBT 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) (Rousi, 1971; Bernath and Foldesi, 1992).

For centuries, the people of central and southeastern Asia have used SBT as an agent of traditional medicine to prevent various ailments. It has been considered to be one of the most important valuable bio-resource, being locally used for centuries as fuel, fodder, small timber, food and medicine. Every part of the plant such as fruit, leaf, twig, root and bark has been traditionally used as medicine, nutritional supplement, fire wood and fence. The SBT berries were used as a source of herbal medicines, health food and natural skin care in Europe and Asia. In Tibetan and Mongolian traditional medicines, SBT berries were used in the treatment of



Fig. 1. Sea buckthorn (*Hippophae rhamnoides* L.) in India, early September, branch bearing orange-red berries, thorn and leaves.

sputum and cough, and to improve the blood circulation and the function of the digestive system. In Russia and Indian Himalayan region, SBT was used for treatment of skin diseases, jaundice, asthma, for gastro-intestinal treatment, as laxative and for treatment of rheumatism (Singh, 2005). In the Central Asia (Pamirs of Tajikistan and Afghanistan), local people used SBT berries for treatment of hypertension, digestive system and skin diseases. The oil extracted from berries is used for treatment of gastritis, stomach ulcers, erosion of uterus and inflammation of genital organs. In addition, people used infusion of dried berries for skin diseases (Li and Wang, 1998; Li, 1999). In Germany, utilization of SBT started long back, for the ecological rehabilitation of degraded lands, particularly for the afforestation of industrial dumps and dumps from coal mining and control of soil erosion (Singh and Moersel, 2005).

3. Botany

The exact number of species in the genus *Hippophae* is still unclear however, there are considered to be seven species. Three species i.e. *Hippophae rhamnoides*, *Hippophae salicifolia* and *Hippophae tibetana* have been described in India, of which *Hippophae rhamnoides* L. ssp. *Turkestanica* is the major one (Fig. 1). It is naturally distributed in dry temperate and cold desert areas in regions of the North-West Himalayas (2590–4175 m; above mean sea level). Sea buckthorn's natural distribution area includes China, Mongolia, India, Nepal, Pakistan, Russia, Latvia, Romania, Great Britain, France, Denmark, Netherlands, Germany, Poland, Finland, Sweden, Norway and Canada. *Hippophae rhamnoides* has been further divided into eight subspecies. In Finland, *Hippophae rhamnoides* L. ssp. *rhamnoides* and in China *Hippophae rhamnoides* L. ssp. *sinensis* is the most common subspecies reported. SBT cultivation can be carried out in a wide range of soil and adverse climatic conditions of temperate regions of Asia and Europe (Zubarev, 2008).

SBT is a deciduous, dioecious, branched, spiny shrub. SBT usually forms a shrub or a small tree 3–4 m in height. Its strong and complex root system with nitrogen-fixing nodules, having Frankia-actinorhizal symbiotic association, makes SBT an optimal pioneer plant for water and soil conservation in eroded areas. Leaves are alternate, narrow and lanceolate, with a silver-gray color. The male bud consists of four to six apetalous flowers, which produce wind-distributed pollen whereas, the female bud usually consists of one single apetalous flower with one ovary and one ovule. The female plants produce berry-like fruit 6–9 mm in diameter, soft, juicy and rich in oils. The ripe berries are drupe-like and orange/red in color, consisting of a single seed surrounded by a soft,

fleshy outer tissue. Seeds are dark brown, glossy, ovoid to elliptical in shape and 2.8–4.2 mm in size (Rousi, 1971; Bartish et al., 2002).

4. Phytochemistry

Various bioactive compounds in SBT berries and leaves are of special interest and the plant material is being screened for selected compounds. The content of carotenoids, tocopherols, tocotrienols, essential polyunsaturated fatty acids and other bioactive components in the berries and polyphenols in the leaves are being investigated by many researchers (Yang and Kallio, 2002; Zheng et al., 2009).

4.1. Fruits

SBT berries have a unique composition, combining a cocktail of components usually only found separately. The bioactive components vary with fruit maturity, fruit size, species, geographic locations, climate and methods of extraction (Zeb, 2004; Leskinen et al., 2010). The berries are orange-yellow to red color fruits which are a rich source of valuable compounds such as multiple vitamins (C and E), carotenoids (β -carotene, lycopene, lutein and zeaxanthin), flavonoids (isorhamnetin, quercetin, isorhamnetin-3- β -D-glucoside; isorhamnetin-3- β -D-glucosaminide; kaempferol, etc.) organic acids, amino acids, micro and macronutrients (Yang and Kallio, 2001; Kallio et al., 2002) (Table 1). Many bioactive compounds were isolated from the berries of SBT such as hippophae cerebroside, oleanolic acid, ursolic acid, 19- α -hydroxyursolic acid, dulcic acid, 5-hydroxymethyl-2-furancarbox-aldehyde, cirsiumaldehyde, octacosanoic acid, palmitic acid and 1-O-hexadecanolenin (Zheng et al., 2009). Isorhamnetin isolated from marc of SBT, showed significant antioxidant activity in several antioxidant assays (Pengfei et al., 2009). Zeaxanthin and beta-cryptoxanthin esters were identified by chromatographic analysis in SBT berries which can be used as food additives, cosmetic ingredients or nutraceuticals (Pintea et al., 2005; Andersson et al., 2009).

In addition to the plethora of antioxidants, the berries are also rich in fatty acids (saturated 13.7% and 86.3% unsaturated) including palmitic acid, oleic acid (ω -9), palmitoleic acid (ω -7), linoleic acid (ω -6), and linolenic acid (ω -3); and phytosterols. The most recognized product of SBT is comprised of seed oil that is enriched in essential fatty acids (ω -3 and 6) and pulp oil that contains high levels of ω -7 (Yang and Kallio, 2005). The oil of SBT is the only oil that naturally provides a 1:1 ratio of ω -3: ω -6 (linolenic and linoleic acid respectively). β -Sitosterol was identified as the major constituent of phyto-sterols in the SBT oil (Moersel et al., 2005; Sajfirtová et al., 2010). Carotenoid-lipoprotein rich complexes have been extracted from SBT berry pulp and studies showed that carotenoids and fatty acid esters are more stable in their supra-molecular lipoproteic complexes, stored in oleosome vesicles where their physiological functions are better kept (Socaciu, 1993; Pintea et al., 2001; Socaciu and Noke, 2003). In most of eastern and European countries, β -carotene content acts as quality indicator in SBT oils. Oil extracted from SBT fruit pulp and seeds absorb ultraviolet light and promote healthy skin and act as raw material for the pharmaceutical and cosmetic industries.

4.2. Leaves

SBT leaves contain nutrients and bioactive substances which mainly include flavonoids, carotenoids, free and esterified sterols, triterpenoids, and isoprenols. The leaves are an equally rich source of important antioxidants including β -carotene, vitamin E, catechins, elagic acid, ferulic acid, folic acid and significant values of calcium, magnesium and potassium. The polyphenolic compounds

in the leaves are represented by flavonols, leucoanthocyanidins, (–) epicatechin, (+) galocatechin, (–) epigallocatechin and gallic acid (Table 1). In the study by Shipulina et al. (2005), the tannin fraction was isolated from leaves and the principal components of which were hydrolysable gallo- and ellagi-tannins of monomeric type: strictinin, isostrictinin, casuarinin, casuarictin. Recently, antioxidant, cytoprotective and anti-bacterial effects of aqueous and hydroalcoholic leaf extracts of SBT have been studied using various *in vitro* systems and analysis of marker compounds by RP-HPLC. Some of its bioactive phenolic constituents, such as quercetin-3-O-galactoside, quercetin-3-O-glucoside, kaempferol and isorhamnetin were quantified in aqueous and hydroalcoholic SBT leaf extracts by RP-HPLC (Upadhyay et al., 2010).

5. Applications in health promotion and disease prevention

5.1. Antioxidant, immunomodulatory and anti-cancer activity

Oxidative damage to cells has been implicated in the pathogenesis of a wide variety of clinical disorders and its broad range of effects in biological systems has drawn attention of many experimental studies (Halliwell, 1987; Droge, 2002). The antioxidant and immunomodulatory properties of SBT were studied *in vitro* using rat splenocytes, macrophages and C-6 glioma cell line and *in vivo* using male albino rats. The alcoholic leaf extract of SBT (500 μ g/ml) inhibited chromium induced free radical production, apoptosis and restored the antioxidant status and mitochondrial transmembrane potential to that of control cells (Geetha et al., 2002a). The extract alone stimulated IL-2 and γ -IFN production in the absence of Con A and also inhibited chromium induced decline in IL-2 and γ -IFN production, but did not alter IL-4 production suggesting that SBT has significant immunomodulatory activity and specifically activates the cell-mediated immune response (Geetha et al., 2005). The SBT leaf alcoholic extract (100 mg/kg BW) protected the animals from chromium induced oxidative damage (Geetha et al., 2003). Besides providing protection against chromium induced oxidative injury, the SBT leaf extract also has the capability to protect the glial cells against hypoxia induced oxidative damage (Narayanan et al., 2005). Triterpenoids from SBT had significant inhibitory effect on nitric oxide production and enhanced radical-scavenging activities (Yang et al., 2007).

Kim et al. (2011) evaluated the antioxidant and α -glucosidase inhibitory activity of the extracts, fractions, and isolated compounds of SBT leaves. Six compounds, 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, were isolated from SBT leaf extracts. The butanol fraction which contained the highest amount of phenolic compounds showed higher radical-scavenging activity and also the most powerful α -glucosidase inhibitory effect.

In a study by Varshneya et al. (2011), different SBT extracts, were evaluated for antioxidant activity. The reducing power of the extracts increased in a dose-dependent manner and was highest in 70% methanol extract. Alcoholic fruit extract of SBT showed significant cytoprotection against sodium nitroprusside induced oxidative stress in the lymphocytes (Geetha et al., 2002b). The SBT extracts also attenuated the nicotine induced oxidative stress in rat liver and heart (Gumustekin et al., 2010; Taysi et al., 2010). SBT fruit flavones at the concentration of 100 μ g/ml significantly restricted tert-BOOH-induced apoptosis in lymphocytes by decreasing intracellular calcium levels, caspase activity and also decreased tert-BOOH-induced formation of DNA breaks (Geetha et al., 2009) (Fig. 2). The total flavones of *Hippophae rhamnoides*

Table 1**Major-phytochemicals in Sea buckthorn and their medicinal properties.**

SBT phytoconstituents	Medicinal properties	References
Tocopherols	Acts as antioxidant, minimizes lipid oxidation, helps to relieve pain	Kallio et al. (2002)
Carotenoids	Acts as antioxidant and helps in collagen synthesis and epithelialization	Andersson et al. (2009)
Vitamin K	Prevents bleeding; promotes wound healing; anti-ulcer effect	Jamyansan and Badgaa (2005)
Vitamin C	Acts as antioxidant and sustain cell membrane integrity	Kallio et al. (2002)
Vitamin B complex	Accelerates collagen synthesis	Jamyansan and Badgaa (2005)
Phytosterols	Stimulate cell repair and nerve regeneration	Yang et al. (2001)
	Improves microcirculation in the skin, anti-ulcer, anti-atherogenic, anti-cancer, regulate inflammatory process	Yang et al. (2001)
Polyphenolic compounds	Antioxidant, cytoprotective, cardioprotective, wound healing	Upadhyay et al. (2010)
Polyunsaturated fatty acids (PUFA)	Immunomodulatory, neuroprotective, anti-tumor	Yang and Kallio (2001)
Organic acids	Lower the risk of heart attack and stroke, anti-ulcer, wound healing, anti-arthritis	Yang and Kallio (2001)
Coumarins and triterpenes	Control of appetite, sleep, memory and learning	Grey et al. (2010)
Zinc	Strengthen the blood circulation, anti-tumor	Gupta and Singh (2005)
	Aids in cell proliferation, acts as a cofactor for enzymes, and enhances utilization of vitamin A	

(TFH) provided protection against H₂O₂ induced apoptosis on vascular endothelial cells (VECs) by lowering the caspase-3 expression (Cheng et al., 2011). The *in vitro* and *in vivo* antioxidant properties of SBT seed oil were evaluated by Ting et al. (2011) and their observations indicate that SBT oil has significant antioxidant activity. SBT seed oil also showed strong inhibition of oxidative damage induced by CCl₄ on mice, increased the activities of antioxidant enzymes and decreased the lipid peroxidation in liver.

The SBT leaf extract was found to have significant anti-inflammatory activity in adjuvant induced arthritis (AIA) rat model and lipopolysaccharide induced inflammatory response in murine macrophages (Ganju et al., 2005; Padwad et al., 2006). In another study, isolated casuarinin from the SBT leaves was studied for the effect on the TNF- α -induced ICAM-1 expression in a human keratinocytes cell line (Kwon et al., 2011). Pre-treatment with casuarinin inhibited TNF- α -induced protein and mRNA expression of ICAM-1 and subsequent monocyte adhesiveness in HaCaT cells. Casuarinin significantly inhibited TNF- α -induced activation of NF- κ B, ERK and p38 MAPK in a dose-dependent manner. Pretreatment with casuarinin decreased TNF- α -induced pro-inflammatory mediators, such as IL-1 β , IL-6, IL-8, and MP-1. Further, in the murine macrophage cell line, SBT leaf alcoholic extract significantly inhibited the enhanced production of NO induced by LPS in a dose dependent manner and by its inhibitory effect on iNOS activation (Padwad et al., 2006). Recently, SBT leaf alcoholic extract have shown up-regulated antigen presentation ability of macrophages in aged mice, which exhibited its immune boosting and anti-aging effect (Mishra et al., 2011). Sea buckthorn berries also showed immunoprotective effect against T-2 toxin-induced immunodepression in 15-day-old chicks (Ramamamy et al., 2010). SBT has been extensively used in oriental traditional medicines for treatment of many inflammatory disorders. Hence from these observations, the anti-inflammatory and immunomodulatory activities have been scientifically proved.

Chemopreventive potential of SBT was evaluated in mice by Padmavathi et al. (2005) and the results showed that *Hippophae* fruit extract stimulated activities of both phase II and antioxidant enzymes in the mouse liver. The berry extract also had a positive effect on all antioxidant enzymes, and decreased the lipid peroxidation, indicating reduced levels of cellular oxidation processes. The study also found that SBT reduced tumor incidence of skin and forestomach papillomagenesis in mice. Yasukawa et al. (2009) isolated and identified three phenolic compounds, (+)-catechin, (+)-gallocatechin, and (–)-epigallocatechin and a triterpenoid, ursolic acid from the active fraction of the 70% ethanol extract of SBT

which exhibited remarkable anti-tumor activity. A recent study examined the comparative activities of SBT berry extracts having varying compositions against cell proliferation in the Caco-2 (colon) and Hep G2 (liver) cancer cell lines. Among the extracts, the ethyl-acetate soluble extract showed the strongest antiproliferative effects on Caco-2 cells. Phytochemical analysis showed that ursolic acid was much higher in this extract than the others (Grey et al., 2010). Induction of apoptotic activity and apoptotic morphological changes of the nucleus, including chromatin condensation were also observed in the HL-60 cells treated with some of the flavonols isolated from SBT such as quercetin, kaempferol and myricetin (Hibasami et al., 2005).

From the literature survey it has been observed that most of the research has been carried out using crude extracts of leaves and fruits of SBT. A limited number of studies have focused on identification and characterization of the bioactive components, which is an important area for the development of SBT based pharmaceuticals and nutraceuticals.

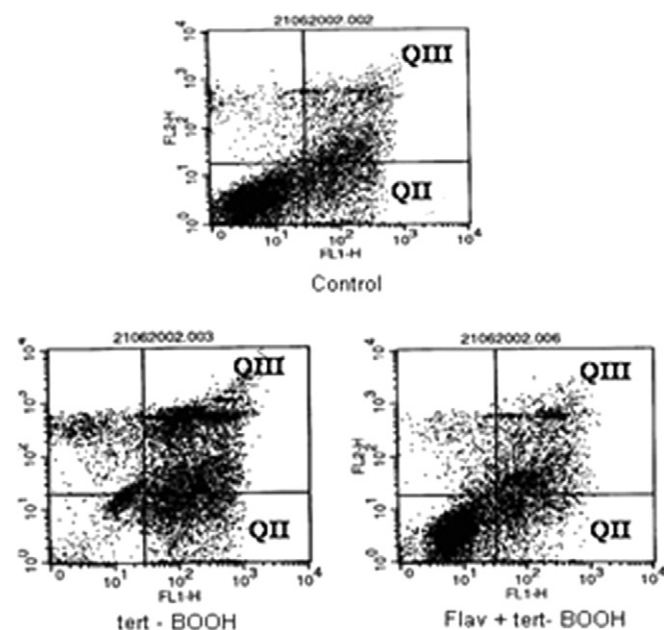


Fig. 2. Effect of Sea buckthorn flavonoids on tert-BOOH induced apoptosis. Apoptosis was determined by using fluorescein isothiocyanate-labeled annexin V antibody and counterstaining with propidium iodide and was analyzed by flow cytometry.

Source: Geetha et al. (2009), Journal of Medicinal Food 12, 151–158, with permission.

5.2. Hepatoprotective activity

The liver is often affected by a multitude of environmental pollutants and drugs, all of which place a burden on this vital organ that can damage and weaken the liver and eventually lead to hepatitis or cirrhosis (Zimmerman and Ishak, 1994). The hepatoprotective activity of SBT leaves and seed oil was evaluated using CCl₄ induced hepatic damage in animals (Geetha et al., 2008; Hsu et al., 2009), and the results showed that both SBT leaf alcoholic extract and seed oil ameliorated CCl₄-induced liver injury as evidenced by both histological and biochemical findings. In a recent study by Maheshwari et al. (2011), some of the phenolic constituents of leaves, such as gallic acid, myricetin, quercetin, kaempferol and isorhamnetin were identified in the phenol rich fraction (PRF) by RP-HPLC. Oral administration of PRF at dose of 25–75 mg/kg BW significantly protected from CCl₄ induced elevation in aspartate aminotransferase, alanine aminotransferase, γ -glutamyl transpeptidase and bilirubin in serum, enhanced the hepatic antioxidants. These observations suggest that PRF has potent antioxidant activity and protected against CCl₄ induced oxidative damage in the liver. However, more systematic studies on chronic liver injury should be carried out for the development of a product or a formulation. SBT may be a hopeful drug for prevention and treatment of liver fibrosis, but further well controlled clinical trials are required.

5.3. Anti-stress and adaptogenic activity

The herbal formulations which can enhance physical endurance, mental function and non-specific resistance of the body to stress have been termed as adaptogens (Brekhman, 1980). The adaptogenic activity of SBT leaf extract was studied in rats using a passive cold (5 °C)–hypoxia (428 mmHg)–restraint (C–H–R) animal model (Ramachandran et al., 1990). SBT leaf aqueous extract, administered orally in rats at a dose of 100 mg/kg BW both in single and five doses, 30 min before C–H–R exposure had significant anti-stress and adaptogenic activity (Saggu et al., 2007). The effect of the extract was studied on lipid peroxidation and antioxidant parameters in liver and gastrocnemius muscle of rats. Results suggested that supplementation with SBT leaf extract reduced the oxidative stress in liver and muscle of rats during C–H–R exposure and post-stress recovery (Saggu and Kumar, 2007a). During severe stressful exposure to C–H–R and post stress recovery, the aerobic metabolism as well as hexose monophosphate pathway is suppressed. The single and five doses of SBT extract treatment restricted the decrease or better maintained tissue glycogen and enzyme activities, such as hexokinase, phosphofructokinase, citrate synthase and glucose-6-phosphate dehydrogenase, in blood, liver and muscle, during C–H–R exposure. The studies suggested that SBT leaf aqueous extract treatment caused a trend for shifting anaerobic metabolism to aerobic during multiple stress C–H–R exposure and post stress recovery (Saggu and Kumar, 2007b, 2008).

5.4. Modulation of hypoxia-induced transvascular leakage

Cerebral and pulmonary syndromes may develop in unacclimatized individuals shortly after ascent to high altitude resulting in high altitude illnesses like high altitude pulmonary edema and high altitude cerebral edema which may occur due to extravasation of fluid from intra to extravascular space in the brain, lungs and peripheral tissues. The hypoxia induced increase in vascular permeability may be due to increased generation of reactive oxygen and nitrogen species, which in turn may increase oxidative damage of lipids, proteins and DNA as exposure to hypoxia has been demonstrated to decrease the activity and effectiveness of antioxidant enzyme system (Bakonyi and Radak, 2004). The SBT leaf alcoholic extract and seed oil provided significant protection

against hypobaric hypoxia induced transvascular fluid leakage in the lungs and brain of rats by reduction in Vascular Endothelial Growth factor (VEGF) expression (Fig. 3) (Puroshothaman et al., 2008, 2011). The SBT seed oil pretreatment also resulted in the significantly improved hypoxic tolerance as evidenced by increased hypoxic gasping time and survival time and decreased plasma catecholamine levels (Puroshothaman et al., 2008). SBT has been recommended in the traditional medicines for treatment of pulmonary disorders and from the above observations, the scientific findings prove that SBT leaf extract and seed oil were able to protect against hypoxia induced pulmonary edema in the lungs. However, still there is a lack of clinical studies to evaluate the effect of SBT extracts as a therapeutic agent for high altitude related maladies.

5.5. Cardioprotective and anti-atherogenic effects

Curative effect of SBT preparations on cardiovascular diseases are known and well documented in Tibetan traditional medical literature. Some studies on human and animals have been carried out to evaluate the effect of flavonoids of SBT on cardiovascular diseases, as some flavonoid compounds are known to have positive ionotropic effects. Flavonoids in SBT fruit and leaves are well known to improve the functioning of cardiovascular system. The total flavonoids of *Hippophae* (THF), extracted from its leaves and fruit, is a group of compounds containing seven kinds of flavonoids. Among them, the main components are isorhamnetin and quercetin. THF treatment exhibited protective effects on myocardial ischemia and reperfusion, tumors, oxidative injury and aging (Eccleston et al., 2002). In another study, the flavonoids of SBT were shown to reduce the production of pathogenic thromboses in mouse (Cheng et al., 2003). Flavonoids from SBT protected endothelial cells from oxidized low-density lipoprotein induced injuries via regulation of LOX-1 and eNOS expression (Bao and Lou, 2006).

The study by Pang et al. (2008) demonstrated the anti-hypertensive effect of total flavones extracted from seed residues of SBT in chronic sucrose fed rats by regulating its insulin and angiotensin II levels. The hypertension, hyperinsulinemia, dyslipidemia and activated angiotensin II provoked by the high-sucrose diet could be ameliorated by total SBT flavones and the optimal effect was observed at the dose of 150 mg/kg/day. SBT supercritical CO₂-extracted seed oil have been shown to possess anti-atherogenic and cardioprotective activities. In a study using rabbit as an animal model, administration of SBT seed oil along with high cholesterol diet restricted further rise of total cholesterol and caused a significant decline of triglyceride and LDL-cholesterol as compared to animals fed on high cholesterol diet only. The rise in HDL-cholesterol over the basal values in seed oil treated animals was significantly higher than the non-treated animals. SBT seed oil also caused a significant vasorelaxation (Basu et al., 2007). The hypolipidemic and hypoglycaemic effects of total flavonoids from seed residues of *Hippophae rhamnoides* L. (FSH) were evaluated in a high-fat diet fed mouse model (Wang et al., 2011). FSH significantly lowered total cholesterol and triglyceride concentrations in liver, and the results were corroborated by transmission electron microscope findings. The rise in serum glucose was significantly suppressed by FSH treatment while improving impaired glucose tolerance.

5.6. Anti-bacterial and anti-viral effects

A systematic chemical investigation of active fractions from the SBT leaves has led to the discovery of a new phytochemical drug-Hiporamin, possessing a wide spectrum of anti-viral and anti-microbial activities. Hiporamin is a purified fraction of polyphenol fraction, containing monomeric hydrolysable gallo-ellagi-tannins

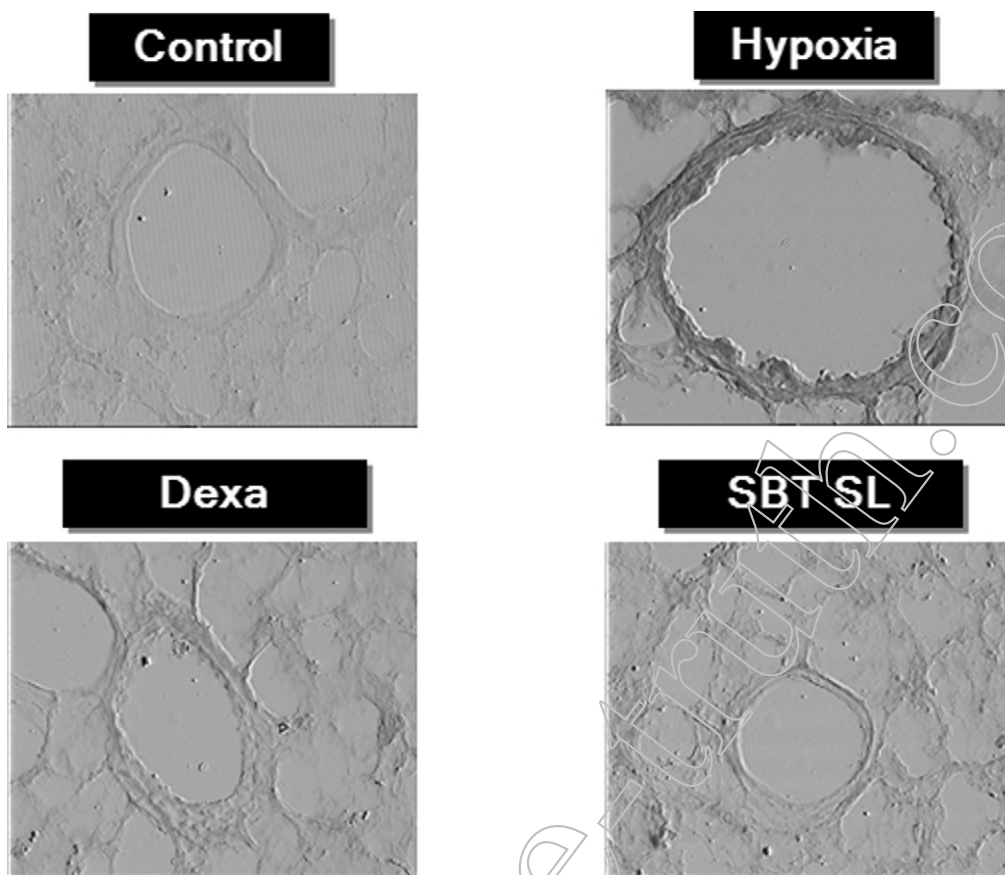


Fig. 3. VEGF immunohistochemistry in the lungs reduction of VEGF immunohistochemical staining after pretreatment with dexamethasone (DEXA) and seabuckthorn (SBT) leaf extract (LE) (100 mg/kg BW) in rats exposed to simulated high altitude of 9144 m for 5 h.

Source: Puroshothaman et al. (2011), eCAM (doi:10.1093/ecam/nep199) with permission.

(preferably strictinin, isostrictinin, casuarinin, casuarictin pedunculagin, stachyurin according to the NMR spectra). It was found to possess a very strong anti-virus activity and wide range of action against Influenza and Herpes viruses (Shipulina et al., 2005). Anti-viral activity of Hiporamin in respect of Influenza virus was observed by its inhibitory effect on the viral neuraminidase. It also showed inhibitory effect in a HIV infection in the cell culture and antimicrobial activity. The SBT leaf extract also has a significant anti-dengue activity when evaluated in Dengue virus type-2 infected blood-derived human macrophages with a decrease and increase in TNF- α and IFN- γ respectively (Jain et al., 2008). The aqueous extract of SBT seeds was screened for antioxidant and antibacterial activities. The extract was also found to possess antibacterial activity against *Listeria monocytogenes* and *Yersinia enterocolitica* (Chauhan et al., 2007). The antioxidant and antimicrobial effects of the extract implicate its potential for natural preservation. In another study, aqueous and hydroalcoholic leaf extracts of SBT showed growth inhibiting effect against *Bacillus cereus*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Enterococcus faecalis* (Upadhyay et al., 2010).

5.7. Anti-radiation effects

SBT leaf extracts, both aqueous and alcoholic, were reported to render more than 80% survival at lethal doses (10 Gy), in the mice. The extract showed high antioxidant potential when tested under *in vitro* condition. The leaf extract countered the radiation damage to hemopoietic system and restored the ferric reducing activity of plasma (Goel et al., 2002; Prem Kumar et al., 2002). The whole

extract of the fresh berries of SBT has been reported to provide protection to whole mice, various tissue, cells and cell organelles against lethal irradiation. More than 50% protection was observed at a dose range of 15–40 mg/kg BW given intra-peritoneal. It is suggested that pre-irradiation treatment of animals with SBT extracts protect the functional integrity of mitochondria from radiation-induced oxidative stress (Goel et al., 2005; Chawla et al., 2007). Agrawala and Adhikari (2009) reported that SBT extracts act as an antioxidant preventing cellular and mitochondrial free radical generation that could contribute to its ability to inhibit radiation-induced apoptosis and cytotoxicity. However, clinical studies must be carried out to investigate the radioprotective activity of SBT extracts.

5.8. Healing effect on acute and chronic wounds

SBT based preparations have been widely used for treating skin radiation lesions, burn of different etiology, gastric and duodenal ulcers. The protective and curative effects of SBT against wounds, burns, scalds, ulcers and mucosal injuries have been extensively investigated using different animal models and by clinical trials (Zhao, 1994; Suleyman et al., 2001; Xing et al., 2002; Gupta et al., 2005, 2006, 2008; Upadhyay et al., 2009, 2011; Gupta and Upadhyay, 2011). In the recent years, SBT leaf extract has been scientifically investigated and shown that it enhances acute and chronic dermal wound healing (burns and diabetic) in rats. The SBT treated animals showed faster reduction in wound area in comparison with control and silver sulfadiazine (standard care) treated animals. The topical application of SBT increased neovascularization, collagen synthesis and stabilization at wound site, as

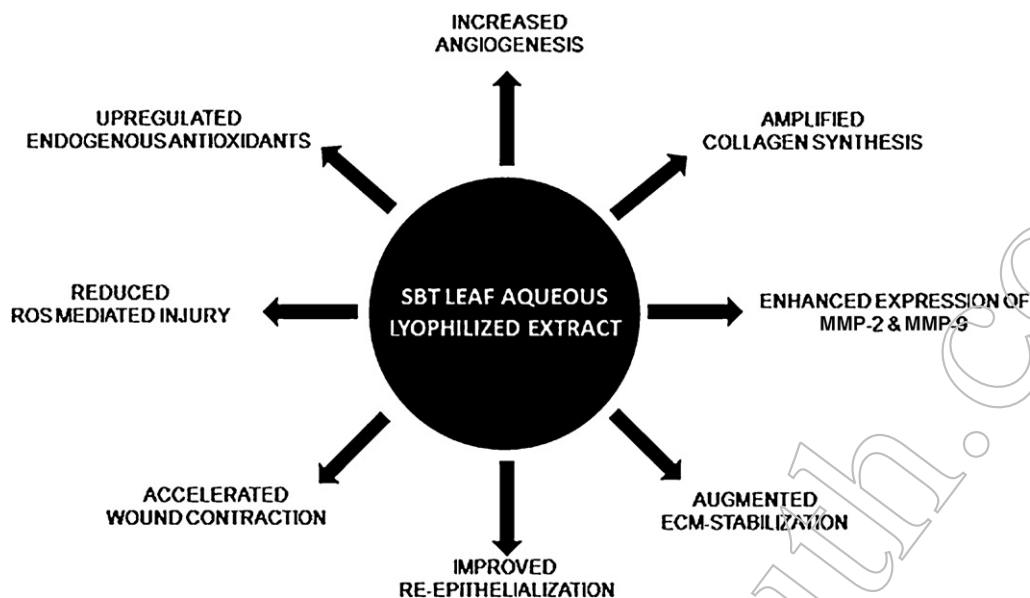


Fig. 4. The schematic diagram showing the possible effect of the Sea buckthorn leaf extract in promoting wound-healing activity.

Source: Upadhyay et al. (2011) eCAM (doi:10.1093/ecam/nep189), with permission.

evidenced by up-regulated expression of VEGF, collagen type-III, matrix metalloproteinases (MMP-2, 9) and increased contents of hydroxyproline and hexosamine (Fig. 4) (Upadhyay et al., 2011). SBT treatment also increased the endogenous enzymatic and non-enzymatic antioxidants and decrease in lipid peroxide levels in wound granulation tissue (Gupta et al., 2005, 2006, 2008; Upadhyay et al., 2009). Further, it has been reported that SBT leaf has no cytotoxic, heavy metal contamination and adverse effect after oral administration (Saggu et al., 2007; Upadhyay et al., 2009). Flavonoids are one of the important biologically active substances present in SBT leaves and fruits. The positive healing effect of topical application of SBT flavone (isolated from fruit pulp) (1.0%, w/v) has been observed on dermal wounds in experimental rats (Gupta et al., 2006).

Traditional use of SBT oil to promote recuperation of skin injuries and support the healing of skin diseases well agrees with the data of modern preclinical and clinical studies. SBT oil extracted from fruits and seeds combine high levels of beneficial unsaturated fatty acids (omega-3, 6, 7), natural antioxidants and vitamins (E, K), carotenoids, as well as phytosterols (Li and Schroeder, 1996; Beveridge et al., 1999). These phytochemicals make it ideal for medicinal and cosmetic industries for giving synergistic power to protect cell membrane and enhance cell regeneration. One ingredient, palmitoleic acid, is a component of skin that is considered a valuable topical agent in treating burns and healing wounds. The preventive and curative effects of SBT seed oil have been reported in different types of gastric ulcers, chronic cervicitis and atopic dermatitis (Zhang et al., 1988; Yang et al., 2000; Xing et al., 2002). A systematic pre-clinical study conducted by Upadhyay et al. (2009) demonstrated the safety and wound healing efficacy of SBT CO₂-SFE seed oil co-administration by both route i.e. topical (200 μ l) and oral (2.5 ml/kg BW) on experimental burn wounds in rats. Treatment promotes significant re-epithelialization and wound closure and enhances formation of granulation tissue and collagen biosynthesis in burn wounds. SBT seed oil has been observed to possess mitogenic potential and is involved in fibroblasts and keratinocytes proliferation at the wound site. It has the capability to increase new blood capillaries formation and thus contributes to structural repair through the formation of granulation tissue. Seed oil treatment showed an increase in endogenous antioxidant and decrease in free radical production in burn wounds. SBT seed oil absorbs

strongly in the UV-B range (290–320 nm) and may be used as a natural sunscreen absorber (Beveridge et al., 1999). A survey of the most common pharmacological activities of SBT is presented in Table 2.

6. Clinical studies

The majority of the medicinal uses of SBT in humans are based on historical reports or anecdotal evidence with only few reports coming from modern clinical investigations. SBT was traditionally used for the treatment of gastric ulcers and laboratory studies confirm the efficacy of seed oil for this application. SBT seed oil has been used clinically to treat chronic cervicitis and ulcers. Wang (1995) treated 30 patients suffering from partial erosion of the cervix with topically sprayed SBT seed oil. All the patients were cured after 90 days of treatment. SBT seed oil was used topically (3–4 times a day) to treat 60 children (aged 4 months–12 years) with ulcerative stomatitis; 55 cases were cured after 3–5 days of treatment and two severe cases were cured after 8 days of treatment (Wang, 1992). The positive effect of seed oil on mucosal injuries may be related to its high content of natural carotenoids and tocopherols. Treatment with SBT seed oil led to increased levels of α -linolenic acid, linoleic acid and eicosapentaenoic acid in plasma phospholipids, resulting in improved atopic dermatitis (Yang et al., 2000).

In the study by Eccleston et al. (2002), the objective was to characterize the antioxidant profile of SBT juice and to evaluate its effect on plasma lipids, LDL oxidation, platelet aggregation and plasma soluble cell adhesion protein concentration. Twenty healthy male volunteers were given either a placebo or SBT juice for 8 weeks. Additional daily intakes of vitamin C, α -tocopherol, β -carotene and flavonoids through SBT juice supplementation were 462, 3.2, 1.0 and 355 mg respectively. Results of the study found that SBT juice affects the risk factors (plasma lipids, LDL oxidation, platelet aggregation and plasma soluble cell adhesion protein concentration) for coronary heart disease in humans possibly due to the high antioxidant levels. In another study, patients with ischemic heart disease were given total flavonoids of SBT, 10 mg, 3 times daily for 6 weeks (Chai et al., 1989). The patients had a decrease in cholesterol level and improved cardiac function. The cardioprotective mechanism of action of SBT flavonoids may be due to reduced stress of cardiac muscle tissue by regulation of inflammatory mediators.

Table 2
Pharmacological activities of different parts of Sea buckthorn (*Hippophae rhamnoides* L.).

Plant part	Pharmacological action study	Type of the study	Reference
Leaves	Antioxidant, immunomodulatory, cytoprotective	<i>In vitro</i> , rat	Geetha et al. (2002, 2005)
	Anti-stress and adaptogenic	Rat	Saggu and Kumar (2007)
	Protection against hypobaric hypoxia, modulate transvascular fluid leakage in lungs	Rat	Puroshothaman et al. (2011)
	Hepatoprotective	Rat	Gao et al. (2003) and Geetha et al. (2008)
	Healing activity in acute and chronic burn wounds	Rat	Gupta et al. (2005, 2006) and Upadhyay et al. (2010, 2011)
	Anti-inflammatory activity	Rat	Ganju et al. (2005) and Padwad et al. (2006)
Fruit	Anti-bacterial and anti-viral	Mouse, rat	Shipulina et al. (2005), Jain et al. (2008) and Upadhyay et al. (2010)
	Antioxidant and cytoprotective	<i>In vitro</i>	Geetha et al. (2002)
	Anti-stress	Rat	Tulsawani (2010)
Seed oil	Radioprotective	Rat, mouse	Prem Kumar et al. (2002) and Goel et al. (2002)
	Protection against hypoxia-induced transvascular leakage in brain	Rat	Puroshothaman et al. (2008)
	Anti-atherogenic activity	Rabbit	Basu et al. (2007)
	Hepatoprotective	Hsu et al. (2009)	
Flavones	Enhanced healing activity in burn wound, atopic dermatitis and mucosal injury	Rat	Upadhyay et al. (2009) Yang et al. (2000)
	Protection against sulphur dioxide inhalation		Ruan et al. (2003)
	Dermal wound healing activity	Rat	Gupta et al. (2006)
Isolated from fruit	Anti-apoptotic and antioxidant	Rat	Mishra et al. (2008) and Geetha et al. (2009)
	Immunomodulatory		

The consumption of SBT berries in 229 healthy participants significantly increased the fasting plasma concentration of quercetin and isorhamnetin indicating that it is a good dietary source of flavonols. However, this did not convert to affecting the circulating concentrations of lipid markers in healthy, normolipidemic adults having healthy diets (Larmo et al., 2009). In another study, Lehtonen et al. (2011) evaluated the effect of SBT berry phenolic extract and oil in a randomized order for 33–35 days in 110 female volunteers. There was a statistically significant decrease in waist circumference and vascular cell adhesion molecule in subjects fed with SBT berry oil. These results show that SBT berry fractions have positive effects on the associated variables of metabolic diseases.

In another clinical study, SBT was used in cirrhotic patients to determine its effect on the changes of fibrotic parameters, improvement of liver function and whether it could be used as a therapeutic anti-fibrotic agent (Gao et al., 2003). The study indicates that SBT may help prevent progression of liver fibrosis, due to the vitamin A content and precursors and their role in the progression of liver fibrosis.

7. Safety and toxicity studies

The fruit extract of SBT has a significant protective role against arsenic-induced oxidative injury. However, it lacks the ability to remove arsenic from the binding sites, suggesting that the herbal extract could be co-administered with a chelating agent of known efficacy during treatment of arsenic to achieve the optimum effect of chelation treatment (Gupta and Flora, 2006). In another study, Ruan et al. (2003) have reported the protective effects of SBT seed oil against injury induced by sulphur dioxide inhalation. Administration of SBT extracts also significantly protected from the lethality of sulphur mustard by curtailing oxidative damage induced by sulphur mustard (Vijayaraghavan et al., 2006).

Toxicity studies in animals were carried out using SBT based formulations and extracts. All the biochemical parameters related to fuel metabolism, liver function and renal function and hematological parameters remained within normal limits following acute or subacute (30 days) administration of the SBT leaf aqueous extract. In sub-acute toxicity studies of 10 and 20 times of maximal effective dose, administration for 14 days, the body weight gain and biochemical parameters related to toxicity namely serum bilirubin, creatinine, were unaltered and comparable to controls (Saggu

et al., 2007). No adverse effects of SBT leaf aqueous extracts were observed at a dose of 100 mg/kg Bw/day in rats administered for 90-days (Tulsawani, 2010). In another study, safety and toxicological studies of CO₂-SFE extracted SBT seed oil were performed. In acute and sub-acute oral toxicity studies, no adverse effects were observed in any of the groups administered with SBT SFE-seed oil (Upadhyay et al., 2009).

8. Other applications

Sea buckthorn leaves contain considerable protein (averaging 15%), and can be used as livestock and pet food, and the fruits are among the most nutritious of all berries. SBT is useful in reclaiming and conserving soil, especially on fragile slopes due to its extensive root system. SBT has been developed into a major resource for China. During the past ten years, large areas of land have been afforested by SBT and at the same time established more than 200 SBT processing factories producing a range of the foods, beverage, health protecting products, medicines and cosmetics (Li and Zhang, 2008). The main organization overseeing and promoting its utilization is the China Research and Training Centre on SBT, which has given rise to the International Center for Research and Training on Sea buckthorn. India has recently embarked on a major national initiative for commercial cultivation of SBT, pledging to bring an area of one million hectare under the crop's ambit by 2020 to reach the level achieved by China. China has 1.1 million hectares under SBT cultivation; while India has only 11,500 hectares of land Mongolia has 30,000 hectares and Russia is cultivating the valuable plant in the 47,000 hectares.

9. Conclusions

Currently, Sea buckthorn has gained the status of one of the most sought after plant in the pharmaceutical and cosmetic based industries, besides health food processing industries the world over. Several countries are commercially and ecologically harnessing the potential of SBT for livelihood enhancement and environmental conservation. The amount of experimental data evidencing important properties and bioactive substances from SBT is vast and continues to increase rapidly. The presence of valuable chemicals and nutritionally important constituents in SBT, and from the scientific knowledge of their importance, it is clear that SBT should

be used as alternative nutritional sources in the commercial market. However, in depth investigation on the effect of processing on the total nutrient content of SBT species growing in different agro-ecological regions needs to be carried out (Bal et al., 2011). SBT shows multiple pharmacological and therapeutic activities such as antioxidant, immunomodulatory, anti-inflammatory, anti-atherogenic, anti-stress, cardioprotective and wound healing from its different parts (leaves, fruits and seeds). Due to immense antioxidant activities, SBT and its various products ensure the human and animal body's equilibrium through the action of its various effective components. Evidence of these uses originated in traditional knowledge and recent scientific investigations. SBT based formulations can be developed as plant drug or functional food and nutraceutical to increase the antioxidant status and strengthen the immune system which in turn may be useful in enhancing the resistance of the organisms subjected to multiple stresses.

However, there are a limited number of studies describing the bioactivities of SBT in relation with their phytochemical compositions. Since the plants and plant products are subjected to wide variation in their phytochemical profile due to variety, geo-climatic conditions, maturity, post-harvest processing, storage and stability, it is extremely important to conduct detailed investigations on the composition and physiological significance of medicinal plants and standardize the formulations based on ingredients. Further systematic studies are necessary to evaluate the efficacy using standardized extracts of SBT, and to identify the bioactive molecules responsible for the biological activities so that cost effective, potential herbal drug can be established at large scale. There is no doubt that the future holds great promise for SBT bio-actives.

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