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THERAPEUTIC IMPLICATION OF SEA BUCKTHORN IN ALLEVIATING VASCULAR DEMENTIA ASSOCIATED WITH ESTROGEN DEFICIENCY IN POST-MENOPAUSAL WOMEN: PRE-CLINICAL TO CLINICAL PROGRESS

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ABSTRACT

Vascular dementia (VaD) is a neurological condition associated with estrogen insufficiency, especially in postmenopausal women, and is frequently brought on by cerebral ischaemia. It entails a steady loss in cognitive function brought on by inflammation, oxidative stress, and vascular dysfunction. Current therapies mostly deal with symptoms, which emphasises the need for creative approaches that focus on the underlying causes of the illness. With its abundance of bio actives such as flavonoids (isorhamnetin, quercetin), vitamins, and polyphenols, sea buckthorn (Hippophae rhamnoides) has the potential to be used as a natural remedy. These substances support vascular health and have neuroprotective, anti-inflammatory, and antioxidant qualities. Sea buckthorn is very promising for treating VaD-related disease because of mechanisms like nitric oxide increase, PI3K/Akt pathway Sea buckthorn's capacity to lower inflammation, enhance synaptic repair, and preserve cerebrovascular integrity is supported by preclinical data. Its function in modulating the gut-brain axis also emphasises its wider neuroprotective potential. Standardised formulations, improved bioavailability, and carefully planned human studies are necessary to translate these discoveries into practical practice. For postmenopausal women in particular, sea buckthorn offers a natural and safe way to manage vasodilator dysfunction. With more investigation, it might develop into a viable treatment option for this crippling illness.

KEYWORDS: Endothelial Function, Estrogen Deficiency, Hippophae rhamnoides, Inflammation, Isorhamnetin, Nitric Oxide (NO), Oxidative Stress, Phytoconstituents, PI3K/Akt Pathway, Polyphenols, Postmenopausal Women, Quercetin, Sea Buckthorn, Synaptic Repair, Vascular Dementia, Vasodilation.

INTRODUCTION

Vascular dementia mostly caused by cerebral ischaemia is a cognitive dysfunction combined with vascular disease.[1] It is a neurodegenerative disorder that can be related to estrogen deficiency specifically in post-menopausal women. Patients suffering from dementia die due to steady decline in neurocognitive functions, starting with short-term memory loss, further proceeding to long-term memory loss and the inability to perform daily tasks.[2] Known risk factors acting as vascular contributors for cognitive impairment including stroke, obesity and diabetes are less commonly experienced by women than men before menopause.[3]

Dementia currently has no known cure. Indeed, there is compelling molecular evidence that estrogen play a significant role in both neurotrophic and neuroprotective processes in the brain.[4] In numerous in vitro and in vivo models, estrogens have long been known to have antioxidant properties which have protective effects on vascular dementia

Many traditional medical systems have used herbal plants to treat illnesses. Currently there is a lack of an effective therapeutic strategy for vascular dementia. Pertaining to fewer adverse effects of herbal medicines than synthetic ones, use of medicinal plants could be a beneficial therapeutic approach in VaD as well.[5]

Given that VaD is a lifestyle disease, postmenopausal women may benefit from taking specific nutraceutical supplements.[6] In several traditional systems, sea buckthorn has long been used. It can be used as a potential treatment through a number of mechanisms, including anti-oxidant, anti-inflammatory, vascular and endothelial protection, neurogenesis and synaptic repair, and anti-atherosclerotic. These benefits are due to presence of a variety of phytoconstituents including flavanoids, phytosterols, and vitamins.[7]

The reported health benefits of sea buckthorn against obesity, metabolic syndrome, cardiovascular disorders etc. are thought to be due to presence of key polyphenolic flavonoids like isorhamnetin and quercetin. Along with potentially reducing ovarian cancer through apoptosis and hormonal (estrogen) release.[8] these sea buckthorn elements may mediate hormone release in VaD.

Pathophysiology of Vad

Cerebrovascular Lesions

Large Vessel Disease: Sudden cognitive deficits can result from severe cerebral artery occlusion or stenosis, which can cause large infarcts. Multi-infarct dementia can develop as a result of several cortical infarcts, frequently brought on by embolic events.

Small Vessel Disease (SVD): SVD causes pathological alterations such arteriolosclerosis and lipohyalinosis by affecting the capillaries, venules, arterioles, and small perforating arteries. Cognitive decline may ensue from these alterations, which can cause lacunar infarcts, white matter lesions,and microhaemorrhages.

Hemodynamic Factors

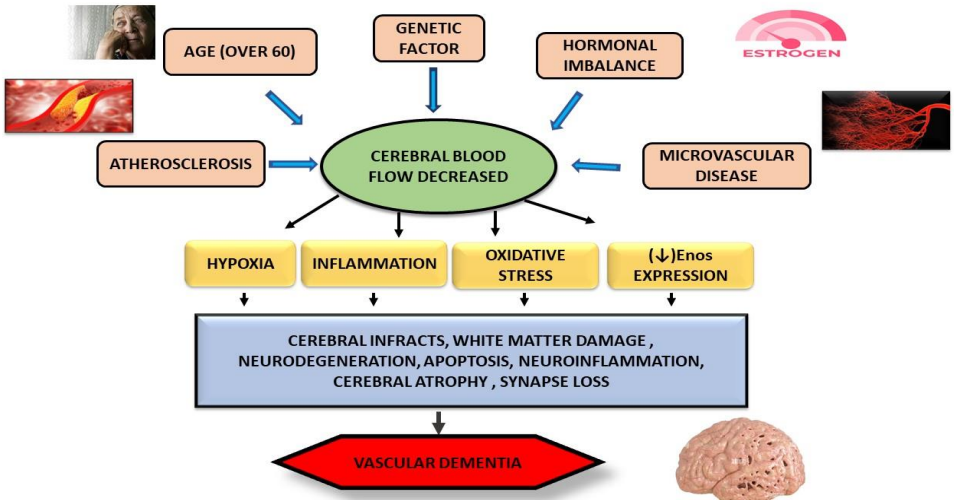
Chronic Hypoperfusion: White matter degeneration and ischaemic injury can result from reduced cerebral blood flow, which is frequently brought on by arterial stiffness or hypotension.

Dysfunction of the Blood-Brain Barrier (BBB): Endothelial damage can cause the BBB to malfunction, allowing plasma components to seep into the brain parenchyma and causing inflammation.

Amyloid Deposition

Cerebral Amyloid Angiopathy (CAA): Amyloid-beta build-up in cerebral blood arteries can cause microhemorrhages, vessel fragility, and further vascular dysfunction; these symptoms frequently accompany Alzheimer's disease pathology.

Genetic Elements: Mutations in the NOTCH3 gene cause CADASIL, or Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy, a genetic disorder that results in early-onset VaD and SVD. (Fig 1)



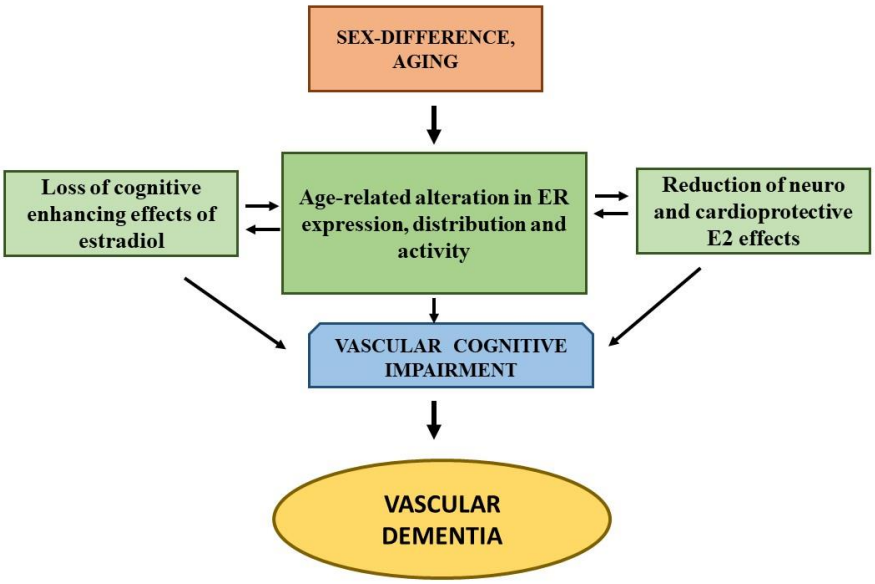
Role of Estrogen in Vascular Dementia

Estrogen deficiency has been reported in pre-menopausal and post- menopause females.

Protein tyrosine phosphatase has been shown to boost pro-apoptotic genes like caspase, BAD, and BCL-2, dephosphorylate the phosphoinositide-3 kinase (PI3K)/Akt pathway, and decrease the quantity and viability of endothelial progenitor cells, all of which reduce postnatal blood vessel repair.[9]

Estrogen quickly activates endothelial nitric oxide synthase (eNOS) through a PI3K-dependent pathway.[10]

Upregulation of endothelial nitric oxide (NO) production plays an important role in the vasoprotective effects of estrogen.[11,12] The cerebral vasculature is a significant target tissue for this hormone, and in vivo exposure to estrogen increases NO-mediated vasodilation in rodent cerebral arteries.[13,14] Long-term estrogen administration causes microglia in old female mice to exhibit a resting pattern, which is suggestive of a suppression of astrocytic and microglial activation.[15] An anti-inflammatory action is also suggested by estrogen's capacity to suppress phagocytic activity and microglial superoxide generation.[16](Fig 2)



Sea Buckthorn (Hippophae rhamnoides)

Sea buckthorn is used for both medical and nutritional purposes all over the world. Typically growing 2–6 meters tall, sea buckthorn trees have robust juvenile branches and rough bark that emerge as tiny, pointed spines from the main trunk. Its lance-shaped or linear leaves are dark green on the adaxial surface and silvery grey on the abaxial surface, measuring 3 to 8 cm in length and less than 7 mm in breadth. It yields berries that are spherical, 3–8 mm in diameter, yellow or orange, and densely covered in sharp spines. The ovoid, 3–4 mm long, brown or grey seeds are encased in a glossy shell. Products made from sea buckthorn contain bioactive compounds such as vitamins, fatty acids, phytosterols, and polyphenols.[17] (Fig 3)

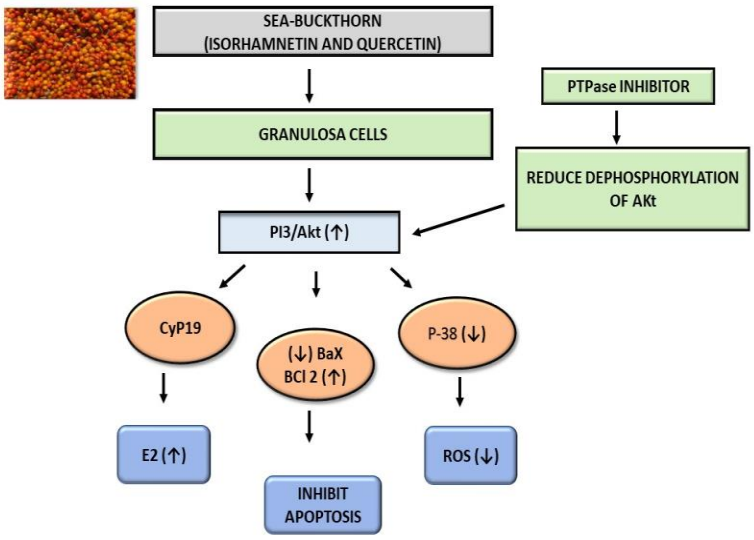
SEA BUCKTHORN FRUIT
(Hippophae rhamnoides)

Mechanistic Insights into Sea Buckthorn Therapeutic Potential

Sea buckthorn berries consist of variety of phytoconstituents that may have beneficial effect on VaD. Based on previous studies it can be suggested that SBBE have variety of anti-inflammatory, anti-oxidant, anti-atherosclerotic, neuroprotective activities. Thus, it can serve as a good therapeutic candidate for VaD. The components of sea buckthorn seem to mediate the proliferation, death, and hormone production of healthy ovarian cells. They also appear to reduce ovarian cancer, presumably by apoptosis and the release of hormones (estrogen).[8]

Additionally, its oil—which contains sterol, hypericin, and carotenoid—has been proposed as a substitute for estrogen replacement therapy in postmenopausal women, specifically to enhance the integrity of the vaginal epithelium.[18] Isorhamnetin a flavonoid present in SBBE has the potential to stimulate estrogen release which can be helpful with

post-menopausal women.it has the potential to stimulate the PI3/AKt signalling pathway that enhance phosphorylation of AKt which can stimulate SOD2 and decrease the ROS production hence showing the anti-oxidant effect. It can inhibit apoptosis stimulate the Enos and increase NO production and increase the cerebral blood flow which can help with hypoperfusion associated with vascular dementia. Quercetin act as the PTP inhibitor that can reduce dephosphorylation of AKt and maintain PI3/AKt activation.[19] **(Fig 4)**



Antiinflamatory activity

The study investigated effect of Sea buckthorn Leaf Supercritical Extract on endotoxemia in mice. Findings showed that it prevented peritoneal macrophages from producing NO in response to LPS. The decrease in IL-6 and TNF-α production affected cytokines' ability to mediate effector functions, and the extract groups also showed a significant decrease in CD40 expression.[20] The present study investigated the preventive effects, mechanisms of SB berry polysaccharide extracts against acute liver failure in mice caused by lipopolysaccharide (LPS) and d-galactosamine hydrochloride (d-GalN). According to this study, pre-treatment shields mice's livers from LPS/d-GalN-induced damage via inhibiting the TLR4-NF-κB signalling pathway.[21] This study investigated effect of seabickthorn in edema It demonstrate that Paw volume and edema significantly decreased after receiving sea-buckthorn orally and topically in vivo in the Carrageenan-stimulated paw oedema paradigm.[22] This study investigated the effect of sea buckthorn berries on the frequency and length of common cold (CC) illnesses. Additionally, the effects on serum C-reactive protein (CRP) levels and urinary tract infections (UTI, DTI) were examined as secondary goals. Berries from sea buckthorn did not stop DTI or CC. Nonetheless, a decrease in CRP, an indicator of inflammation and a risk factor for heart conditions, was noted.[23] The study investigated the effect of sea-buckthorn in individuals with periodontitis in terms of clinical parameters (pocket depth, gingival bleeding index, plaque index, and clinical attachment degree). SBT was a successful adjuvant in improving the clinical and microbiological parameters in patients with periodontitis.[24] This study investigated the role of supplementing with sea buckthorn fruit oil in individuals with active rheumatoid arthritis. added sea buckthorn fruit oil (1800 mg/day) as a supplement.. Sea buckthorn fruit oil is a promising supplementary treatment option for rheumatoid arthritis.

Anti-Cancer Activity

This study investigated effect of sea buckthorn seed residue hydroalcoholic extract (HYD-SBSR) to reduce oxidative stress damage and stop cell apoptosis. The protective and reparative effects of HYD-SBSR on cells have been examined utilising the H2O2-induced oxidative stress a framework with B16F10 cells. The findings showed that HYD-SBSR had cytoprotective benefits, as shown by moderate cell repair qualities, increased resistance to oxidative stress, and decreased apoptotic rates.[25] This study investigated effect of 70% ethanol extract of sea buckthorn branches (1 mg of plant extract/mouse) on cancer. The indicator was 7,12-dimethylbenz[a]anthracene. Potent anti-oxidant activity was seen.[26] The present study investigated its anticancer and immunostimulating effects, Lewis's lung cancer in mice might It showed that in tumor-bearing animals, this substance increased natural killer cell activity, lymphocyte proliferation, and macrophage activity.[27] No CT has yet been reported on anti-cancer activities of sea-buckthorn.

Cardiovascular Activity

The current investigation, sea buckthorn berries, were collected for the current investigation and given orally at a dose of 7–28 mg/kg. The level of circulating TNF-α and IL-6 decreased, antioxidant enzyme activity was increased, and serum lipids were significantly reduced. By reducing the expression of eNOS, ICAM-1, and LOX-1 mRNA and proteins in the aortas of rats with excessive lipid levels, SVP also lessens vascular impairment.[28] The effectiveness of sea buckthorn (Hippophae rhamnoides) and a grape extract (antioxidative) in oxidative stress was examined, along with the cytoarchitecture of the rats' organs. The results showed that sea buckthorn significantly reduced the oxidative stress in the kidney, liver, and heart.[29] The study examines how SBSO (Sea buckthorn seed oil) affects the gut flora and blood cholesterol in hamsters with hypercholesterolaemia in four hamster groups, by intestinal excretion of cholesterol and encouraging the development of bacteria that produce SCFA. Showed beneficial effects in improving the cholesterol.[30] investigated role of Sea buckthorn on cholesterol. Sea buckthorn berry or extract supplements dramatically lowered total cholesterol in cardiovascular risk subjects, but not in healthy subjects. Consuming sea buckthorn may have cardio-protective effects since it contains phytochemicals, including flavonoids and β-sitosterol.[31] The present study investigated role of sea buckthorn puree to lower blood cholesterol and other CVD risk factors. In this study, 111 hypercholesteraemic patients were treated with SBP. The results showed that ingestion of sea buckthorn puree has effects on a high cholesterol level in patients with hypercholesteremia. Nevertheless, there was no impact on the level of lipid signals in the circulation.[32] The present study investigated role of sea buckthorn seed oil on 74 hypertensive and hypercholesteraemic human beings and 32 normal subjects took part in the double-blind, chosen, controlled longitudinal studies. For 30 days, an oral supplement of 0.75 ml of sea buckthorn seed oil or a placebo of sunflower oil was given daily. The effectiveness of sea buckthorn seed oil in lowering cardiovascular risk factors, hypertension, and dyslipidaemia in the general population. The inclusion of vitamin E and beta carotene in sea buckthorn seed oil is responsible for the improvement in antioxidant status.[33]

Reproductive Health Support

This experiment was aimed at investigating the effects of supplementing sea buckthorn extract on laying ducks with on their egg quality and lipid accumulation. By adding SBE, the yolk lipid decreased.[34] This study investigated ability of sea buckthorn promote osteogenic differentiation in ovariectomised mice may be used to treat osteoporosis. According to these results, the active fractions of H. rhamnoides fruit enhanced osteogenic gene expression and markedly accelerated osteoblast development in mesenchymal stem cells, improving bone mineral density in the osteoporosis mouse model.[35] A novel vaginal gel made by Alfa sigma, was evaluated for its safety and effectiveness in treating

vulvovaginal atrophy (VVA) in this randomised, placebo-controlled, single-center trial. Aloe vera, hyaluronic acid, 18β-glycyrrhetic acid, sea buckthorn (Hippophaë rhamnoides) oil, and glycogen make up the gel. This experiment suggests that the gel is a viable option for treating VVA symptoms and enhancing sexual function locally, with good compliance.[36]

HEPATOPRPTECTIVE ACTIVITTY

The present study investigated Hepatoprotective effect of Sea buckthorn, on male albino rats' liver damage caused by carbon tetrachloride (CCl4) and it was found that the extract improved blood protein levels and considerably reduced the rise in GOT, GPT, ALP, and bilirubin brought on by CCl4.Further, it can be used as a food supplement or nutraceutical to treat liver ailments as it lowered MDA levels and increased GSH. by its antioxidant activity. It can be used as a food supplement or nutraceutical to treat liver ailments.[37] The present study investigated, the hepatoprotective effect of Sea buckthorn, on harm to the liver brought on by peritoneal tetracycline injection. Sea buckthorn flavonoids extracted by MCAE were found to significantly boost biomarkers in body fluid of (NAFLD) mice, according to biochemical and histological observations.[38] This study evaluated the oil from SB berries' protective qualities against aflatoxin B1 (AFB1)-induced toxicity in broiler chickens. These results imply that SB oil has strong hepatoprotective properties, lowering the levels of aflatoxins in the liver and lessening their negative effects on health[39] The goal of the study was to see if sea buckthorn berry seed oil (SBO) might mitigate the alterations in liver enzymes and liver histology caused by cyclophosphamide in BALB/c mice. SBO co-administration reduced the increase in hepatic damage biomarkers and sinusoidal injury.[40]The study aimed to assess the clinical effectiveness of sea buckthorn (SBT), a traditional Chinese medicine, in treating patients with non-alcoholic fatty liver disease (NAFLD). The results showed that SBT improved serum lipids, transaminase, the liver/spleen ratio, and liver stiffness in NAFLD patients. SBT may be further developed as a promising therapy for NAFLD.[41]

Anti-microbial and Oral Health Benefits

Tests of antimicrobial activity were conducted against clinical and food-borne bacteria. The findings demonstrated the effectiveness of crude extracts of sea buckthorn against strains of Gramme − and + bacteria.[42] The purpose of this study was to create a herbal intracanal medicine based on sea buckthorn (SBT) extract and assess its antibacterial efficacy against Enterococcus faecalis. It had antibacterial effect.[43] This study aimed to analyse the phytochemicals of sea buckthorn pulp oil and assess the mouthwash form's antibacterial, anti-biofilm, and antioxidant properties. Sea buckthorn mouthwash shown anti-biofilm properties against specific oral bacterial species, both single and multiple.[44]

Neuroprotective Effects on Cognitive Function

The purpose of this study was to examine , the antidepressant-like effects of an aqueous fruit extract of sea buckthorn (Hippophae rhamnoides L. ssp. turkestanica). Accordingly, it is hypothesised that sea buckthorn aqueous fruit extract had notable antidepressant-like effects in animal models of depression and could be used as a natural remedy.[45]

The goal of the current investigation was to examine how oral supplementation of SB fruit extract affected behavioural abnormalities and alterations in brain serotonin (5-hydroxytryptamine; 5-HT) metabolism in rats given haloperidol on a regular basis. Showed potential in improving the behaviour abnormalities.[46] This study sought to determine how sea buckthorn polysaccharide (SBP) affected the cognitive dysfunctions of mice fed a high-fat diet (HFD). SBP's reversd gut dysbiosis and improved the cognitive function.[47] The present study evaluated role of SBT leaf extract in Scopolamine-induced cognitive impairment in rats administered three different oral doses (50, 100, and 200 mg/kg

body weight). The results indicate that it may be useful in treating cognitive disorders by promoting the antioxidant system and controlling the activity of the cholinergic marker enzyme (AChE).[47] The present study investigated role of Seabuckthorn's flavonoid-enriched fraction, known as SBF, in the treatment of major depressive illness in mice. The findings point to the potential benefits of seabuckthorn flavonoids as a dietary supplement for the treatment of serious depressive disorders.[48]

Other CT Studies on Sea buckthorn

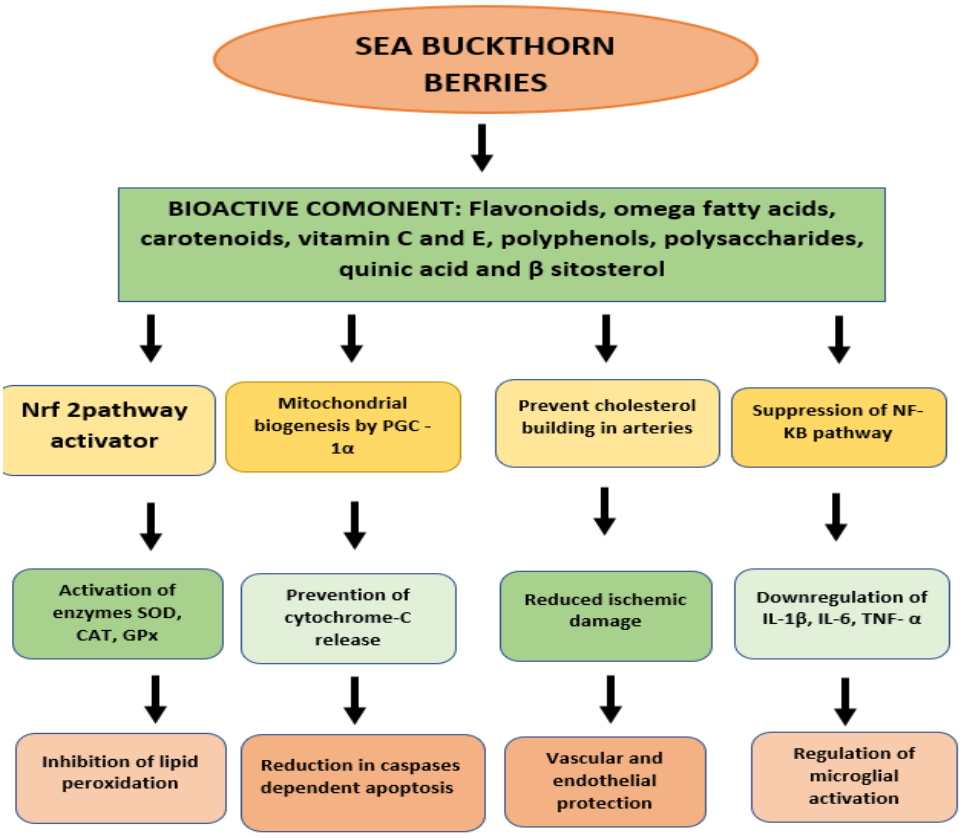
This study sought to determine how sea buckthorn oil (SBO) extract, which is high in vitamins, phytochemicals, and polyunsaturated fatty acids, affected haemodialysis patients' oxidative stress, salivary flow, and inflammation. Following SBO administration, the data revealed no appreciable changes in inflammation, salivary flow rates, oxidative DNA damages, or DNA breaks. However, iron plasma levels dropped while sodium and phosphate plasma levels rose***[50]*** The study investigated sea- buckthorn for second-degree burns, assess the healing time using sea buckthorn dressings and compare the outcomes with 1% silver sulfadiazine. The findings showed that 1% SSD was not as clinically effective as sea buckthorn cream. applying SB dressing can speed up the healing process of second-degree burns and lessen the strain on medical services by lowering the healing period.[51] The effects of oral supplementation with sea buckthorn oil on serum phospholipid fatty acids (PLFAs) were investigated. In metabolically healthy individuals, supplementing with sea buckthorn oil boosted in 16:1n–7 and unmodified sea buckthorn oil moderately raised concentrations of their respective PLFAs, indicating that supplementing with these fatty acids could be used to study possible clinical benefits in people.[52] The purpose of this study was to assess how a sea buckthorn berry extract rich in proanthocyanidins (SBB-PE) affected the quantity of several kinds of adult stem cells in the bloodstream of healthy human participants. Stem cell types engaged in reparative and regenerative processes were selectively mobilised upon consumption of SBB-PE. These findings could further knowledge of SBB's historical applications in preventing disease, promoting regeneration, and delaying the ageing process.[53]

Clinical Trial on Sea-Buckthorn: - (Table 1)

S. No.	Year of Study	Disease	Formulation Used	Type of Study	Conclusion	Refrence
1	2018	Psoriasis	Sea buckthorn extract (berry oil)	Clinical trial (single blind)	Improvement in psoriasis was seen	(54)
2	2014	Vaginal Atrophy	Sea buckthorn oil (3g/day)	Clinical Trial (double blind)	Improvement in vaginal epitheliumin	(55)
3	2024	Skin, ocular and vaginal health	Sea buckthorn oil (Omegia™ capsules)	Clinical trial (randomized)	Showed antioxidant activity improved skin health	(56)
4	2022	Hypercholesteromia	Sea buckthorn puree	Clinical trial (double blind)	Increased HDL Showed anti- inflammatory and anti hypertensive effects on hypercholesteromia	(32)
5	2014	Serum metabolome in overweight women	Dried sea buckthorn berries, sea buckthorn oil and sea buckthorn extract	randomized crossover trial	SB has overall good metabolic effects	(57)
6	2025	Skin inflammation, anti-bacterial, whitening effect	Sea buckthorn extract	Tested in 4 subjects	Skin lightened and roughness improved	(58)
7	2021	Impaired glucose regulation (IGR)	sea buckthorn fruit puree (90 mL/day)	Clinical Trial (double blind)	Fasting Plasma Glucose (FPG) decreased	(59)
8	2017	Cardiovascular risk	Sea buckthorn seed	Clinical trial	Showed anti-oxidant	(33)

		factor	oil (0.75 ml for 30 days)	(double blind)	activity and reduced cholesterol	
9	2021	Second degree burns	Sea buckthorn cream	Clinical trial (triple blind)	Better results were seen in comparison with sulfadiazine	(51)
10	2003	Liver fibrosis	Sea buckthorn extract 15g 3 times a day	Clinical trial (single blind)	Showed potential in treatment of liver fibrosis	(60)
11	2018	postprandial glycaemia and insulinemia in overweight or obese male subjects	Sea buckthorn berries	Clinical trial (single blind)	Improved glycaemic profile	(61)
12	2008	Common cold, digestive and urinary tract infections (DTI, UTI)	Sea buckthorn berries	Clinical trial (double blind)	Did not prevent CC or DTI. Reduced CRP	(23)
13	2019	Dry eyes	Sea buckthorn oil spray	Clinical trial (randomized)	Relieved the symptoms of dry eyes	(62)
14	2021	vulvovaginal atrophy	Vaginal gel composition containing SB	Clinical trial	Improved VVA symptoms and sexual wellbeing	(36)
15	2010	Dry eyes	Oral administration of sea buckthorn oil	Clinical trial (randomized)	Improved symptoms of dry eyes in cold season	(63)
16	2011	Tear film Fatty acids dry eye	Sea buckthorn oil	Clinical trial (double blind)	No direct effect on tear film fatty acid was seen	(64)
17	2013	Chronic kidney disease	Sea buckthorn oil (capsules)	Clinical trial(double blind)	Did not protect against inflammation and oxidative damage in CKD patients	(65)
18	2019	Effect on adult stem cell	proanthocyanidin-rich extract of sea buckthorn berry (SBB-PE)	Clinical trial (double blind)	Selective mobilization of stem cell types involved in regenerative and reparative functions.	(53)
19	1999	Atopic dermatitis	Oil of sea buckthorn seed and pulp	Clinical trial (double blind)	Symptomatic improvement was seen	(66)
20	2008	Type 1 diabetic children	Sea buckthorn and blueberry concentrate		Proven beneficial in treatment of type 1 diabetes in children	(67)
21	2015	Traumatic perforation of tympanic membrane	Sea buckthorn oil	Prospective study	Shortened the healing time and helped patient to avoid operation	(68)
22	2013	Idiopathic nephrotic syndrome	Sea buckthorn extract	Pilot study	oedema, anorexia, oliguria symptoms improved	(69)
23	2014	Senile dementia in Alzheimer patients (SDAT)	Polyherbal drug product containing sea buckthorn extract	Clinical trial (double blind)	Potential in treating SDAT	(70)
24	2013	Functional dyspepsia	Sea buckthorn		increases the levels of appetite factors, leptin and neuropeptide Y, increases gastric emptying	(71)

SEA-BUCKTHORN MULTI-MECHANISTIC APPROACH IN TREATING VaD: - (Fig 5)



Pharmacological Activity	Bioactive	Activity	Reference
Anti-Oxidant	Isorhamnetin/ quercetin	DPPH Radical scavenging activity	(72)
	Isorhamnetin	improves cellular antioxidant defences and prevents the overproduction of superoxide.	(73)
Anti-Inflammatory	Isorhamnetin/ quercetin	Prevent LPS and INFc-induced RAW264.7 cells from synthesising NO,	(74)
	Isorhamnetin	Reduce the synthesis of interleukin 6 and TNF-a in RAW264.7 cells, as well as the expression of iNOS and COX-2.	(75)
Anti-Cancer	Isorhamnetin/ quercetin	Profilerator inhibitor	(76)
	Isorhamnetin/ quercetin	By stimulating the transcription factor p53 and repressing its promoters, cyclin B1 and MAPK/ERK1/2, it can result in cell cycle arrest.	(77)
	Quercetin	Influences the intrinsic apoptotic process and prevents the growth of human metastatic ovarian cancer cells.	(78)
	Isorhamnetin	The ability to promote the release of estrogen and the growth of ovarian cells.	(79)
	Isorhamnetin	PI3K AKT adaptive autophagy mediated by mTOR The apoptotic response of MKN-45 gastric cancer cells in a hypoxic environment	(80)
	Isorhamnetin/ quercetin	Relative percentage of all PC-12 cells that undergo apoptosis is decreased	(81)
	Isorhamnetin	Increase in the memory T cell and plasma cell	(82)
Anti-Coagulant and Anti-Platelet	Isorhamnetin	Isorhamnetin inhibited the thrombin-induced human platelet aggregation at, but had no influence on ADP- or collagen-activated platelets	(83)

	Isorhamnetin/ Quercetin	In three models of non-activated platelets, platelets activated by 10 µM adenosine diphosphate (ADP), and platelets triggered by 10 µg/mL of collagen were demonstrated to suppress the production of PAC-1. This could be because of the inhibition of platelet aggregation brought on by reduced GPIIb/IIIa expression.	(84)
Anti-Hyperglycemic and Anti-Hyperlipidemic Activit	Isorhamnetin/ Quercetin	As demonstrated by in vitro and in vivo studies, SB may be helpful in the treatment of type 2 diabetes and metabolic syndrome.	(72)
		In mice given a high-fat diet (HFD), g decreased the levels of liver and blood triglycerides by 49.56% and 16.67%, respectively. By reducing adipose tissue inflammation, increasing PPARα expression, and inhibiting peroxisome proliferator-activated receptor gamma (PPARγ) expression, FSH may enhance lipid metabolism.	(85)
		Caused by lipid peroxidation, oxidative damage is reduced	(86)
		Reduce vascular damage in hyperlipidemics rats by lowering the expression of intercellular adhesion molecule-1 (ICAM-1), lectin-like oxLDL receptor-1 (LOX-1), and endothelial nitric oxide synthase (eNOS) in the aorta at both the mRNA and protein levels.	(28)
Anti-Viral	Isorhamnetin	The SARS-CoV-2 spike pseudo typed virus was also prevented from entering ACE2-overexpressing cells	(87)

Marketed Formulations and Applications (Table 3)

CATEGORY	PRODUCT NAME	Brand Name	USAGE
Capsules & Tablets	Sea Buckthorn Capsules	Himalayan wellness	Skin, heart, immunity
	Sea Buckthorn Capsules	Patanjali	Skin, Antioxidant, Digestion
	Sea buckthorn Capsules	Sovum	Antioxidant, skin
Juices & Beverages	Sea buckthorn juice	Stockholm	Wellness, immunity, Heart health
	Sea buckthorn juice	Nutriorg	Digestive, heart health
	Pure sea buckthorn pulp	Patanjali	Boost immunity
Oils & Topical Applications	Sea buckthorn oil	Veda-oils	Skincare, anti-aging
	Sea Buckthorn oil	Organic harvest	Wound healing, skin nourishment
	Sea Buckthorn oil (Aroma Magic)	Aroma magic	Skin and hair health
Other Healthcare Products	Ayurvedic Sea Buckthorn Extract Powder	Nature Sum	General Wellness
	Sea – Buckthorn dried berries	Azzyvero	General wellness

CONCLUSION AND FUTURE DIRECTIONS

Sea buckthorn has strong antioxidant, anti-inflammatory, neuroprotective, and vascular-endothelial protective qualities due to its rich phytochemical composition, which includes flavonoids like isorhamnetin and quercetin, vitamins, phytosterols, and polyphenols. These bioactives target important VaD-related processes. Estrogen has a well-established role in reducing VaD. Vascular dysfunction, inflammation, and oxidative damage are all accelerated by estrogen shortage and are major causes of cognitive decline. Sea buckthorn provides a natural substitute for hormone replacement treatments, which are frequently associated with serious risks and adverse consequences, by inducing the production of estrogen and imitating its neuroprotective properties. Because of this, sea buckthorn is a strong contender to treat estrogen-deficient diseases including postmenopausal vasodilation.

Abbreviation list

AChE – Acetylcholinesterase

Akt – Protein Kinase B

ALT – Alanine Aminotransferase

AST – Aspartate Aminotransferase

BBB – Blood-Brain Barrier

COX – Cyclooxygenase

ER – Estrogen Receptor

GPx – Glutathione Peroxidase

HFD – High-Fat Diet

IL – Interleukin

LDL – Low-Density Lipoprotein

MDA – Malondialdehyde

NF-κB – Nuclear Factor kappa-light-chain-enhancer

NO – Nitric Oxide

NOS – Nitric Oxide Synthase

PI3K – Phosphoinositide 3-Kinase

PTP – Protein Tyrosine Phosphatase

ROS – Reactive Oxygen Species

SOD – Superoxide Dismutase

TNF-α – Tumor Necrosis Factor-alpha

VaD – Vascular Dementia

Competing Interests

The authors declare that they have no competing interests.

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