



## Therapeutic potential of Seabuckthorn (*Hippophae rhamnoides* L.) in medical sciences

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### Abstract

Seabuckthorn is multiple use properties. This review explores the medicinal applications of *Hippophae rhamnoides* in healing ailments. The plant is being used in different parts of the world for its nutritional and medicinal properties. 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 Seabuckthorn have been well investigated using limited clinical trials. Homeopathy is well-respected modality to assist wellness. Traditional and modern medicinal experts have been applied this plant to treat various diseases. It is clear that Seabuckthorn 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. Its full application in the dermatology may be attributed to the presence of a variety of flavonoids, vitamins, and unsaturated fatty acids. Great use of plant in the traditional system for dermatological aspect, demands further comprehensive phytochemical work based on its actual use by the traditional population. Anti-inflammation is the most important applicable ingredient of this miracle berry.

**Keywords:** Hippophae, Medicinal, Traditional, Seaberry

## INTRODUCTION

### BACKGROUND

Sea Buckthorn (*Hippophae rhamnoides* L.) from Elaeagnaceae family has become a crop of interest for the food processing industry. Accepted name in the plant list org of this species is *Elaeagnus rhamnoides* (L.) A. Nelson (1935). The exact number of species in the genus *Hippophae* is still unclear however, there are considered to be seven species and *Hippophae rhamnoides* has nine subspecies (Lu and Ahani, 2013). *Hippophae rhamnoides*, also known as common sea buckthorn is a species of flowering plant, native to the cold-temperate regions of Europe and Asia. It is a spiny deciduous shrub. The plant is used in the cosmetic industry, in traditional medicine (useful for the treatment of skin disorders resulting from bed confinement, stomach and duodenal ulcers cardiovascular diseases and perhaps growth of some tumors), as animal fodder and for ecological purposes. The plants have a very developed and extensive root system, and the roots live in symbiosis with nitrogen fixing *Frankia* bacteria. The roots also transform insoluble organic and mineral matters from the soil into more soluble states (Lu, 1992). Vegetative reproduction of the plants occurs rapidly via root suckers (Kondrashov and Kuimov, 1987). *E. rhamnoides* has a strong ability to maintain leaf water and can increase chlorophyll content, reduce the photosynthesis and water relations during drought stress (Ahani et al., 2014, 2015). Seed germination at its lowest point of origin China with 32% and the most was in East Azerbaijan with 95% (Ahani et al., 2016). Means of germination percent in seed pretreatments (control, cold, ice water, hot water, lime juice and Gibberellin acid) were 7.5, 23.75, 21.25, 0, 15, and 42.5 in field (Ahani et al., 2014<sup>2</sup>) and 3.75, 43.75, 17.5, 1.25, 15 and 37.5 in greenhouse (Ahani et al., 2014<sup>1</sup>) and in laboratory were 33, 12, 41, 4, 9 and 32, respectively (Ahani et al., 2015).

The DNA weight and the mean A260 and A280 values of the samples from China were found to be statistically significantly higher than those of the samples from Iran, whereas the mean A260/280 ratio of the samples from Iran was higher than that of the sample/isolate from China albeit by a non-significant difference (Ahani et al., 2015).

Despite of decrease in morphological characteristics encountered to drought, this species has been able to tolerance this amount of salt and no died that showed comparative tolerance this species. Therefore offers for *Elaeagnus rhamnoides* species resistance threshold electrical conductivity ( $EC= 12.03dS m^{-1}$ ) of the lower levels used to determine which however need to do other tests because the morphological indicators studied here were not able to clearly explain the differences in salt tolerance and Physiology parameter (i.e. Water Use Efficiency (WUE), Relative Water Content (RWC), Water Potential (WP), Water Saturation Deficit (WSD), Chlorophyll content and Photosynthetic of leaves (Ahani et al., 2018).

## Ecological review

Seabuckthorn is multiple use properties. It is very rich in its biodiversity. The exact number of species in the genus *Hippophae* is still unclear however, there are considered to be seven species *Hippophae rhamnoides* L. has 9 subspecies. According to the latest study, there are 15 species and subspecies in *Hippophae*. *H. rhamnoides* subspecies which has been widely used for ecological restoration and producing a series of products. In Europe, *Hippophae rhamnoides* subsp. *rhamnoides* is used in many countries like Germany, Italy, Switzerland, Sweden, Finland etc. Several improved varieties have been cultivated in these counties. In the Central Asia and South Asia, a widely distributed subspecies is *Hippophae rhamnoides* subsp. *turkestanica*. Due to its rich wild resources this subspecies is being used for producing a lot of products in India, Pakistan, Turkmenistan, Kirghizstan etc. Since seabuckthorn are rich in wild resources, so they are directly being used for various purpose. But wild seabuckthorn have only disadvantages like small berries, many thorns for processing. Few studies have been done on these species and subspecies. Since many countries are awareness of seabuckthorn is a very important plant in economy and ecology, it is believed that more attention and more studies will be given to those genetic resources of *Hippophae*, including that have been used and that have not been touched but very promised. It is estimated that more than 20 countries have their own breeding programs on seabuckthorn.

Each country has its localization of genetic resources so it is needed to make an international cooperation on exchange of genetic resources of *Hippophae*. It is believed that the favourite varieties will be produced through wide international cooperation (Lu and Ahani, 2013).

**Table\_1: The Distribution and the Status of Utilization of *Hippophae*\***

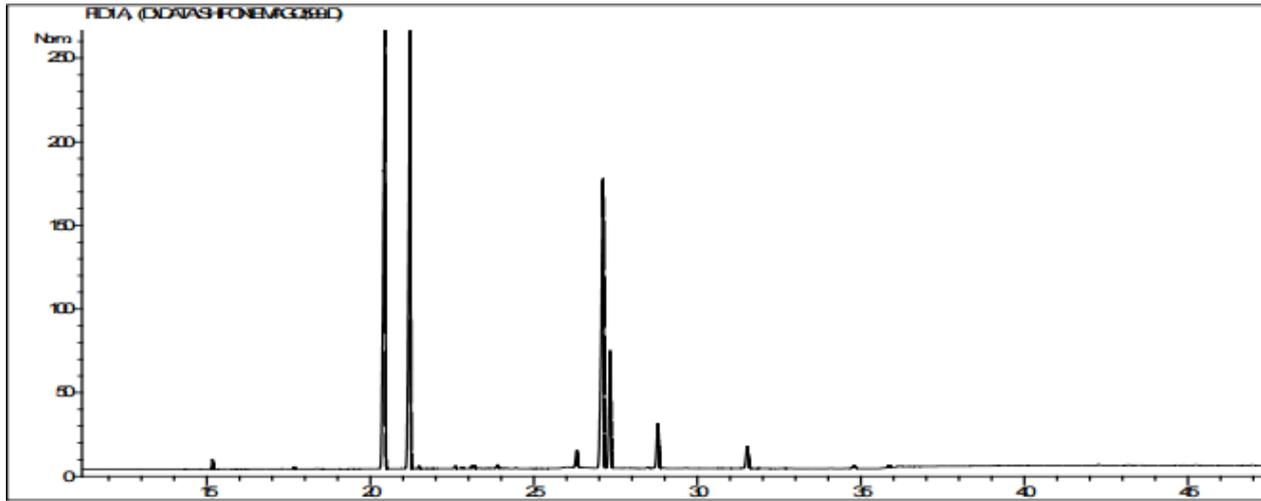
Taxons	The Areas of Distribution	The Status of Utilization
1. <i>H. rhamnoides</i> . subsp. <i>rhamnoides</i>	Scandinavian countries, Baltic Sea countries, Germany, Belgium, Netherlands, Ireland, Poland, U.K. France, Russia	Many varieties are cultivated in some European countries and Canada.
2. <i>H. rham.</i> subsp. <i>sinensis</i>	The North, Northwest, Southwest of China	Wild resources are used for ecological restoration and berries are processed for products. Some new varieties are in tests.
3. <i>H. rham.</i> subsp. <i>yunnanensis</i>	Sichuan, Yunnan, Tibet of China	Wild resources are used for ecological restoration only.
4. <i>H. rham.</i> subsp. <i>mongolica</i>	Siberia of Russia, Mongolia, Xinjiang of China	More than 60 varieties are cultivated in Russia, Mongolia, many East European counties. Many West European counties, Canada and China introduced the varieties for test
5. <i>H. rham.</i> subsp. <i>turkestanica</i>	India, Pakistan, Afkhanistan, Turkmenistan, Kirghizstan, Uzbekistan, Kazakhstan, Iran, Turkey, Xinjiang, Tibet of China	Wild resources are used for ecological restoration and berries are processed for various products
6. <i>H. rham.</i> subsp. <i>fluviatilis</i>	Around Alps Mountains: Germany, France, Switzerland, Austria, Czech, Slovakia, Italy,	Most of wild resources are protected as forest species. Some berries are collected for processing products
7. <i>H. rham.</i> subsp. <i>carpatica</i>	The Capathinan Mountains, Transsylvanian Alps, the valley and the mouths of the Donube and its tributary.	Most of wild resources are protected as forest species. Some varieties are cultivated for processing products
8. <i>H. rham.</i> subsp.	The Caucasus Mountains, Georgia, Azerbaijan, Armenia, Ukraine, Romania, Turkey, Bulgaria,	Most of wild resources are protected as forest species. Some selected varieties are cultivated

caucasica	Iran, Russia.	for test.
9. H. goniocarpa	Sichuan, Qinghai of China	Most of wild resources are protected as forest species. Very few studies have been don on it.
10. H. goniocarpa subsp. litangensis	Sichuan, Qinghai of China	Most of wild resources are protected as forest species. Very few studies have been don on it.
11. H. neurocarpa	Sichuan, Qinghai, Gansu of China	Most of wild resources are protected as forest species. Very few studies have been don on it.
12. H. neurocarpa subsp. stellatopilosa	Sichuan, Qinghai, Tibet of China	Most of wild resources are protected as forest species. Very few studies have been don on it.
13. H. tibetana	Sichuan, Qinghai, Gansu, Tibet of China, Nepal, India	Most of wild resources are protected as grassland species. Very few studies have been don on it.
14. H. gyantsensis	Tibet of China	Most of wild resources are protected as forest species. Some berries are collected for producing Tibetan medicine.
15. H. salicifolia	The southern slope of Himalayan Mt. Tibet of China, Bhutan, Nepal, India	Most of wild resources are protected as forest species. Some berries are collected for producing products.

Drived from Lu and Ahani, 2013

### Medicinal advantages

Valuable substances contained in sea-buckthorn oil play an important role in the proper functioning of the human body and give skin a beautiful and healthy appearance. A balanced composition of fatty acids give the number of vitamins or their range in this oil and explains its frequent use in cosmetic products for the care of dry, flaky or rapidly aging skin. Moreover, its unique unsaturated fatty acids, such as palmitoleic acid (omega-7) and gamma-linolenic acid (omega-6), give sea-buckthorn oil skin regeneration and repair properties. Sea-buckthorn oil also improves blood circulation, facilitates oxygenation of the skin, removes excess toxins from the body and easily penetrates through the epidermis. Because inside the skin the gamma-linolenic acid is converted to prostaglandins, sea-buckthorn oil protects against infections, prevents allergies, eliminates inflammation and inhibits the aging process. Immune system of this plant can prevent some viruses spread. Modern cosmetic and pharmaceutical companies search for natural substances which display unique properties such as sea-buckthorn oil, which added to a product even in a small quantity will undoubtedly ensure its uniqueness. (Zielińska and Nowak, 2017). 14Noreudesmanes and a phenylpropane heterodimer from seabuckthorn berry inhibit Herpes simplex type 2-virus replication, therefor; these bioactives exhibited an antiviral effect (Redei et al., 2019). Seabuckthorn extract may make restriction for Dunge virus (Jain, 2008). Seabuckthorn decreases fever of some diseases (Guliyeva et al., 2004). Extraction of leaves can limit lung cancer. In addition, seabuckthorn prevent some viruses such as victoria and influenza viruses (Enkhtaivan et al., 2017). Seabuckthorn and several plants could limit spreading of HIV (Nikolaeva et al., 2008). Adeno, HIV, HPV viruses can limit by seabuckthorn (Shipulina et al., 2005). Sea buckthorn has also shown unique biological properties against viral diseases, anti-viral activity against the influenza virus and herpes virus. The suppressing effect on the influenza virus is provided by inhibition of viral neuraminidase present in the virus. Seabuckthorn properties were evaluated with the help of humoral immune reaction against NCD (Newcastle disease virus). Hexane extract from sea buckthorn acts positively against indomethacin, stress, and ethanol which contribute to the development of gastric ulcer (Krejcarová et al., 2015). Treatment with SBT bud extract reduced the virus titer to 2.0 TCID50/ml at 50 µg/ml, while the HA titer was reduced from 1431 (control) to 178. Concentrations lower than 50µg/ml displayed an inhibitory effect in the HA assay, but not in the TCID50 virus titration (Torelli et al., 2015).



**Identification results – SEA BUCKTHORN PULP OIL BATCH N° YI180228**

Peak	RT(min)	Component	%
1	15,2	MYRISTIC ACID C14 : 0	0,39
2	17,7	PENTADECANOIC ACID C 15 : 0	0,10
3	20,4	<b>PALMITIC ACID C16 : 0</b>	<b>32,03</b>
4	21,2	<b>Z-PALMITOLÉIC ACID C16 :1 ω7</b>	<b>28,05</b>
5	21,5	E-PALMITOLEIC ACID C 16 : 1	0,11
6	22,6	HEXADECENEDIOLIC ACID C 16 : 2	0,11
7	22,8	TRICOSANE	0,09
8	23,1	MARGARIC ACID C 17 : 0	0,10
9	23,2	TRICOSENE	0,12
10	23,9	8-HEPTADECENOIC ACID	0,20
11	24,4	HEPTADECENOIC ACID ISOMER	0,03
12	26,3	STÉARIC ACID C18 : 0	1,20
13	27,1	<b>OLÉIC ACID C 18 : 1 ω9</b>	<b>23,83</b>
14	27,3	<b>cis-VACCÉNIC ACID C 18 : 1 ω7</b>	<b>7,90</b>
15	28,8	<b>LINOLÉIC ACID C 18 : 2 ω6</b>	<b>3,29</b>
16	31,5	<b>LINOLÉNIC ACID C 18 : 3 ω3</b>	<b>1,84</b>
17	34,8	ARACHIDIC ACID C 20 : 0	0,27
18	35,9	GONDOÏC ACID C 20 : 1 ω9 (GADOLÉIC)	0,23
19	42,3	BEHENIC ACID C 22 : 0	0,04
20	52,0	LIGNOCERIC ACID C 24 : 0	0,05
		<b>TOTAL</b>	<b>99,98</b>

**Table- ingredients of seabuckthorn fruits (derived of sinensis subspecies)**

In traditional Chinese medicine and the former Soviet Union for inflammation of the mouth, stomach ulcers, radiation injuries and burns have been used (Lu, 1992). Anti-bacterial and antioxidant support and protection of the natural seeds of this plant species is recommended. Methanol fruit and leaves of the plant are also antioxidant and help prevent cell necrosis (Geetha *et al.*, 2002). The oil extracted from berries is used for treatment of gastritis, stomach ulcers, erosion of uterus and inflammation of genital organs. Seabuckthorn leaves contain nutrients and bioactive substances which mainly include flavonoids, carotenoids, free and esterified sterols, triterpenols, and isoprenols. The leaves are an equally rich source of important antioxidants including carotene, vitamin E, catechins, elagic acid, ferulic acid, folic acid and significant values of calcium, magnesium and potassium (Geetha and Asheesh, 2011). Bone-breaking fever virus in the blood of substances extracted from sea-buckthorn leaves is inhibited (Jain, 2008). Total phenolic content of root and seed

extracts were significantly higher than leaf and stem extracts. No significant differences were seen between root and seed, or between leaf and stem (Michel *et al.*, 2012).

## New approaches

Sea buckthorn can act as promising functional food. Sea buckthorn extract can effectively inhibit prostate cancer growth and proliferation in vitro. Sea buckthorn extract effectively downregulates prostate specific antigen with other androgen responsive genes in vitro. Differential extraction using various solvents based on polarity revealed that the end phase aqueous cocktail extracted from leaves of *Hippophae rhamnoides* L. (SKICDDL-3) can effectively target AR and downregulate androgen responsive genes, PSA, ELL2, EAF2 and CALR significantly in vitro. Colony formation Unit assay and Wound healing assay further shows that SKICDDL-3 can effectively inhibit proliferation and migration of castration resistant C4-2 prostate cancer cells in vitro. Sea buckthorn (*Hippophae rhamnoides* L.) has recently attained worldwide recognition, for its pharmaceutical and nutraceutical potential and is currently cultivated in several parts of the world (Masoodi *et al.*, 2020)

The findings of flavonol suggest that mechanisms of growth inhibition by pentamethylquercetin, syringetin and isorhamnetin are different from the apoptosis caused by quercetin, kaempferol and myricetin. (Hibasami *et al.*, 2005).

The antiproliferative effect of *Hippophae rhamnoides* L. leaves extract on acute myeloid leukemia cells was at least partially determined by activation of the S phase checkpoint, which probably led to deceleration of the cell cycle and apoptosis induction. (Zhamanbaeva *et al.*, 2014)

Sea buckthorn may represent a “golden mean” for the treatment of cancers: It has anti-proliferation properties and can induce apoptosis and stimulate the immune system, and sea buckthorn oil counteracts many side effects of chemotherapy by restoring kidney and liver function, increasing appetite, and keeping patients in general good health. Although the anticancer activity of sea buckthorn has been confirmed by many in vitro and animal in vivo studies, the treatment and prophylactic doses for humans are unknown (Olas *et al.*, 2018).

Seabuckthorn (*Hippophae rhamnoides* L.) constitutes thorny nitrogen fixing deciduous shrub. Sea buckthorn (SBT) is primarily valued for its very rich vitamins A, B1, B12, C, E, K, and P; flavonoids, lycopene, carotenoids, and phytosterols. and therapeutically important since it is rich with potent antioxidants. *Hippophae* sp has high-nutritional and medicinal values due to its very rich antioxidant property. It is a widely used plant in traditional medicine for various clinical conditions. Scientifically evaluated pharmacological effects of it are like antiulcerogenic effect, in vitro and in vivo antioxidant effects, cardiac disease, anti atherogenic effect, radio protective effects, beneficial effects on experimental injury and clinical diseases of the liver, inhibition of platelet aggregation. Lot of research work is still needed to find cellular and molecular mechanisms of these activities (Chirag *et al.*, 2012).

In vitro, Cytotoxic and anti-proliferative effect of hydro-alcoholic extract of *Hippophae rhamnoides* Linn (HEHR) seeds was investigated on human leukemia (HL-60) and normal (BHK21) cells while in vivo anti-proliferative effect of HEHR was evaluated on Ehrlich ascite carcinoma (EAC) induced Swiss albino mice. anti-proliferative effect of HEHR due to its interference with the cell kinetics which was indicates the reduction in the GSH levels and colony growth. The cytotoxic effect of HEHR is produced by apoptosis mechanism which involved DNA fragmentation (Divakar *et al.*, 2010).

Accumulation of cholesterol in the aorta was studied using Sudan-IV staining technique. SBT seed oil feeding to normal rabbits for 18 days caused a significant decline in plasma cholesterol, LDL-C, atherogenic index (AI) and LDL/HDL ratio. The HDL-C levels, HDL-C/TC ratio (HTR) and vasorelaxant activity of the aorta were significantly increased. In cholesterol-fed animals the TC, TG, LDL-C and AI were significantly increased and showed a decline following seed oil administration. The increase in HDL-C was more marked in seed oil treated hypercholesterolemic animals. The acetylcholine-induced vasorelaxant activity was significantly decreased in cholesterol-fed animals and could be restored to that of normal values by seed oil administration. These observations suggest that supercritical CO<sub>2</sub> extracted SBT seed oil has significant anti-atherogenic and cardioprotective activity (Basu *et al.*, 2007).

sea buckthorn powder (SBP) was administered at varying concentrations (0.6, 0.9, 1.2, 1.5 and 1.8  $\mu\text{g mL}^{-1}$ ) to cell cultures (BE(2)-M17) with 20 mm A $\beta$  for 72 h. MTS test indicated that SB significantly increased cell viability in A $\beta$ -induced cells up to 95%. Results of Western blot showed maximum 38% inhibition of A $\beta$  compared to the control (A $\beta$  only). ELISA demonstrated significantly lower amyloid- $\beta$  level (6672  $\text{pg mL}^{-1}$ ) than the control (10189  $\text{pg mL}^{-1}$ ). These findings suggest that this plant warrants further investigation as potential therapeutic agent in the treatment of AD (Dong *et al.*, 2020).

Naturally occurring vitamin B12 is only found in animal products such as meat, milk, dairy products, fish, oysters and clams, but it is well-known for its absence in plant-based foods. Significant amounts of vitamin B12 were detected only in

*Hippophaes rhamnoides* (37 µg/ 100 g dry weight). These initial findings provide the basis for detection of vitamin B12 also in other plants, and can be a good measure of prevention for the vitamin B12 deficiency in vegetarians (Nakos et al., 2015). There have been numerous bioactives in *Hippophae* sp. some of which are rare in the plant kingdom e.g., the ratio of palmitoleic or Omega 7 to  $\gamma$ -linolenic acid or Omega 6. Vitamin C is present in very high amounts (up to 900 mg%). In comparison with citric fruits, sea buckthorn berries have about a 14-times higher amount of vitamin C than oranges. The oil used internally has positive effects on the digestive system lowering inflammation. Oral application is adjuvant in the treatment of gastric, duodenal, and intestinal ulcer. It has been shown to reduce inflammation processes in the vagina and cervix. A high amount of vitamin C makes it suitable for immune deficiencies; due to its antioxidant activity, it removes free radicals and strengthens the immune system. *Hippophae* oil lowers blood cholesterol, which helps to prevent atherosclerosis. Seabuckthorn was tested and shown to significantly increase the level of beneficial high-density lipoprotein (HDL) cholesterol fraction. It reduces the risk of thrombophlebitis and is enrolled in the control of bleeding. Febrile states respond positively to oil, as well as symptoms of rheumatoid disease. Some of the lipophilic components ( $\alpha$ - and  $\gamma$ -linolenic acids) of Seabuckthorn oil positively influence brain functions and the central nervous system by an antidepressant effect. Its advantage as an adjuvant in cancer therapy is that fastens regeneration after use of chemotherapy.

The favoring feature of oil is that it is considered safe, with no potential harmful effects. It can be consumed by pregnant and breastfeeding women. The suggested pharmaceutical form that would be ideal for the application of oil is capsules, because of the problem with rancidity (presence of unsaturated fatty acids). Different fractions of fruits were investigated for antioxidant activity and its relationship to different phytonutrients. The capacity of the crude extracts, such as the phenolic and ascorbate extracts, to scavenge radicals decreased significantly with increased maturation. The antioxidant capacity of the lipophilic extract increased significantly and corresponded to the increase in total carotenoids (Koskovic et al., 2017). Seabuckthorn is primarily found in cold-temperate regions of Eurasia and was first located in China. Berries are the most prominent feature of the plant. Phytochemical studies reveal the presence of a wide variety of compounds like flavonoids, carotenoids, polyunsaturated fatty acids, minerals, vitamins, Omega 3, 6, 9 and rarest Omega 7 and about 190 bioactive compounds. The pharmacological studies demonstrated, sea buckthorn to exhibit antibacterial, anti-sebum, antifungal, anti-psoriasis, anti-atopic dermatitis and wound healing activities. Besides, it has also been included in various cosmeceuticals for its use in skin-eventone, smoothening, rejuvenation, removal of wrinkles, scars, and pigmentation, and also in hair related problems. Pharmacological evaluation confirmed the ethnomedically claimed biological actions and other beneficial effects on the skin of *H. rhamnoides* using scientifically accepted protocols and controls, although some of the studies require more elaborative studies. Its full application in the dermatology may be attributed to the presence of a variety of flavonoids, vitamins, and unsaturated fatty acids. Great use of plant in the traditional system for dermatological aspect, demands further comprehensive phytochemical work based on its actual use by the traditional population. Demonstration of the plant in the traditional system, pharmacology, cosmeceuticals not only demands its further therapeutic studies but also warrants focus towards its cultivation and propagation across the globe. (Pundir et al., 2021).

Signs of irritation (corneal epithelial inflammation/corrosion, dilatation of blood vessels in the bulbar conjunctiva, conjunctival chemosis, dots on the margin of the cornea, oedema on the margin of the conjunctiva/cornea, eyelid irritation, and other possible signs of irritation) were evaluated and scored from photographs taken of the eyes and eyelids at study visits. In part one, the *Hippophae* spray was well tolerated. In part two, OSDI decreased significantly ( $P=0.022$ ) in the Seaberry spray eye compared to the reference spray, indicating a beneficial effect on symptoms. In part three, OSDI in the SB spray eye decreased significantly compared to the untreated control ( $P=0.0007$ ). Symptom sums and frequencies of dryness (sum  $P=0.0046$ , frequency  $P=0.0016$ ) and watering (sum  $P=0.0003$ , frequency  $P=0.013$ ) in the daily logs were lower in the eye treated with Seaberry spray (Larmo et al., 2019). Aqueous extract of Seabuckthorn (*Hippophae rhamnoides* L.) leaves and evaluation of its therapeutic role in oxidative stress-induced cataract in isolated goat lenses using Vitamin E as reference compound. Results showed the potential to delay onset and/or progression of cataract, at least during in vitro conditions. Results indicate the possibilities of evaluating this extract for its use as ant cataract agent during in vivo conditions. (Dubey et al., 2015)

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