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A Comprehensive Study of Possible Crosstalk between Angiogenic and Metabolic Signaling Pathways in Cancer

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Abstract

Sea buckthorn or Elaeagnus rhamnoides is thorny tree with the height of 1 to 3m growing in Europe, western and central Asia to the west of china and northwest of Himalaya and in Iran it is found in Alborz mountain to Azerbayijan and Taleghan and Karaj valley. It has long and narrow leaves, sharped with the length of 5-6and one cm width. Its fruit is sphere, yellow and orange with sour taste. Different parts of plant particularly its fruits have phenolic compounds, vitamins (especially vitamin C), unsaturated fatty acids, and phytosterols such as beta-sitosterol beign investigated by some researchers. These fruits have useful antioxidant, anti-inflammatory and anticancer effects. It has also anti-proliferation properties and can induce apoptosis and stimulate the immune system; sea buckthorn oil counteracts many side effects of chemotherapy by restoring kidney and liver function, increasing appetite, and keeping general good health. Although the anticancer activity of sea buckthorn has been confirmed by many in vitro and in vivo animal studies, measurements should be taken for the development of well-controlled clinical experiments to determine the therapy and preventive does in this area. The present study discusses briefly about whether sea buckthorn is used as an anti-inflammatory and anticancer drug or not.

Keywords:

Sea buckthorn,

Antioxidant,

Anticancer,

Herbal treatment.

Introduction

Sea buckthorn (Elaeagnus rhamnoides (L.) A. or Hippophae rhamnoides) is a member of the Elaeagnaceae family. It is a forest species extending to Europe, western and central Asia to the west of china and North West of Himalaya and in Iran, it is extended from Alborz Mountain to Azerbaijan, Taleghan and Karaj valley. The results of a study showed that the collected samples from Alborz, Mazandaran, Eastern Azerbayijan and Ghazvin provinces belong to E.rhamnoides subsp. Caucasica but the samples collected from western Azerbaijan province are introduced with two noucleotide differences as a new sub-species as E. rhamnoides subsp. Azerbaijanica (Ahani, Jalilvand and Vaezi, 2016). Sometimes, this species is mistaken for Melia azederach L due to the Persian name similarity (Sadeghipour Rudsari et al., 1956).

Its local names are Kam, Keham (Karaj valley), Kah (in Taleghan), Chali (in Gharetape and Ishlegh in Mianeh)(Kokord (western Azerbayijan) around Tehran, it is called willow thorn and in Arabic, it is called "Shokolghesar " as its root is used as a latherwort to wash clothes. Some Arabs call it also Roman Ghasul (Ghasul means latherwort) and in old medicine books, it is called as "Aboghanes". All the organs of this plant such as its leaves, roots, seeds, and berries (known as seaberry) have a wide range of anti-inflammatory, anticancer, antioxidant, and anti-atherosclerotic activities (Zeb, 2006; Basu et al., 2007; Kumar et al., 2011; Suryakumar and Gupta, 2011; Xu et al., 2011; Christaki, 2012; Teleszko et al., 2015; Olas, 2016; Ulanowska et al., in press).

Vitamins (especially A, C, and E), lipids, carotenoids, amino acids, unsaturated fatty acids, and phenolic compounds that are found in the berries (Olas, 2016; Gradt et al., 2017; Ulanowska et al., in press) are presented in Table. The amount of minerals and vitamins in the fruits depends on the climate conditions, size, growth of the plant, and the method used to process and stores the plant material (Fatima et al., 2012; Malinowska and Olas, 2016). Gao et al. (2000) report changes

in antioxidant properties, besides other types of biological activity, in sea buckthorn berries during maturation stage, which were strongly correlated with the content of total phenolic compounds and ascorbic acid. Moreover, the antioxidant activity increased significantly and is related to the increase in total carotenoid content.

Figure 1- Sea buckthorn shrub

Table 1- The chemical composition of isolated parts of the sea buckthorn (44; modified).

Part of sea buckthorn	**Chemical composition**
Fruits (berries)	Vitamins (C, E, B, K1, D, A, folic acid)
	Micro and rare elements (potassium, magnesium,
	calcium, iron, sodium, manganese, zinc, copper, nickel)
	Carotenoids
	Phenolic compounds
	Lipids
	Amino acids
	Organic acids
	Proteins
	Sugars
	Pectins
Leaves	Vitamins (E, folic acid)
	Calcium, magnesium, potassium
	Carotenoids
	Phenolic compounds
	Amino acids
	Chlorophyll
	Proteins
	Pectins
Seeds	Carotenoids
	Phenolic compounds
	Lipids
	Proteins
Roots	Carotenoids
	Phenolic compounds
	Lipids- Proteins
Bark	Phenolic compounds

The main sources of ingredients are found not only in the raw fruits, but also in preparation of its products such as jams, juices, marmalades, or tinctures. Sea buckthorn fruits can be also used to make cookies (Li and Hu, 2015). Hu (2005) reports that sea buckthorn seed can be used to make oil and the leaves can used to make tea. While teas made from the seeds have laxative properties and help weight loss, infusions of the leaves have antidiarrheal properties; in addition, fruit teas strengthen the immune system, and fights against skin diseases (Sarwa, 2001; Frohne, 2010). The positive and unique properties of sea buckthorn have been known since at least the 12th century BC.

Nowadays, its products are used in many industries, especially the pharmaceutical, cosmetic and food industries. According to historical records, sea buckthorn was first used as a drug in China, and in modern era, the plant was formally listed in the Chinese pharmacopoeia in 1977 (The Comitte of Medicine and Treatment of China, 1977). Modern studies have shown that the different parts of sea buckthorn can be applied as natural remedies for cardiovascular diseases, as well as diseases of the skin, liver, and stomach. The therapeutic potential of its bioactive compounds is shown in Table . This study reviews the current knowledge about the different organs of sea buckthorn, and discusses whether they may represent an option for the treatment of cancer or not. It is worth to mention that the source information for this paper is derived not only from in vitro models, but also in vivo models.

Anticancer activity of sea buckthorn

A number of medicinal herbs compounds, particularly phenolic compounds such as proanthocyanidins, curcumin, and resveratrol, have offered significant benefits in cancer chemotherapy (Barrett, 1993; Bagchi and Preuss, 2004; Bagchi et al., 2014; Shanmugam et al., 2015; Ko et al., 2017) and radiotherapy (Cetin et al., 2008).

It is well proved that higher dietary use of phenolic compounds, especially procyanidins and flavonoids are associated with a lower risk of cancer (Barrett, 1993; Bagchi and Preuss, 2004; Duthie et al., 2006; Zafra-Stone et al., 2007; Cetin et al., 2008; Seeram, 2008; Bagchi et al., 2014; Chen et al., 2014; Wang et al., 2014; Giampieri et al., 2016; Kristo et al., 2016).

Sea buckthorn has a wide range of biological and pharmacological activities, including anticancer properties. Although their molecular mechanisms remain unknown, these compounds are present in different organs and their products, especially in the extract and oil (Xu et al., 2011).

The antitumor activity of sea buckthorn can be attributed to antioxidant compounds, particularly phenolic compounds such as flavonoids, including kaempferol, quercetin, and isorhamnetin as these compounds protect cells from oxidative damage that can lead to genetic mutation and to cancer (Christaki, 2012).

In vitro studies

Various in vitro studies have shown that sea buckthorn has anticancer activity. For example, Zhang et al. (2005) investigated changes in the expression of apoptosis-related genes in the human breast carcinoma cell Bcap-37 induced by flavonoids from sea buckthorn seed. Their bioinformatics analysis showed that the expression of 32 analyzed genes, including CTNNB1, IGFBP4, GADD34, and caspase 3 with the apoptosis of Bcap-37 cells, was affected by flavonoid treatment.

Teng et al. (2006) revealed that isorhamnetin (3′-methoxy-3,4′5,7-tetra hydroxyl flavone; a flavonoid isolated from sea buckthorn) has cellular toxicity effects against hepatocellular carcinoma cells (BEL-7402), with an IC50 of about 75 cc/μg after 72h treatment. Li et al. (2015) also found isorhamnetin has anti-proliferation effects on lung cancer cells in vitro as its concentrations ranging from 10 to 320 cc/μg were administrated orally in C57BL/6 mice (50 mg/kg/day) for 7 days. The authors suggest that the mechanism of isorhamnetin action may involve the apoptosis of cells induced by the down-regulation of oncogenes and up-regulation of apoptotic genes. Other observations showed that isorhamnetin inhibits the proliferation of cells from the human colorectal cancer cell (HT-29, HCT 116, and SW480), and stops cell cycle at the G2/M phase, and suppresses cell proliferation by inhibiting the PI3K-Akt-mTOR path. In addition, isorhamnetin reduces the phosphorylation levels of Akt (Ser473), phosphat-p70S6 kinase, and phosph-4E-BP1 (t37/46) protein, and enhances the expression of cyclin B1 protein at concentrations of 20 and 40 μM (Li et al., 2014).

In a study on human breast cancer cells MDA-MB-231, Wang et al. (2014) found that sea buckthorn procyanidins isolated from the seeds to have inhibitory effects on fatty acid synthase (FAS): as a key enzyme for long-chain fatty acid biosynthesis and its high levels are found in cancer cells. This inhibition is dose-dependent at concentrations ranging from 0 to 0.14 μg/ml. A concentration of 0.087 μg/ml inhibited 50% of FAS activity. Moreover, cell growth was suppressed by treatment with sea buckthorn procyanidins at concentrations ranging 10 and 60 μg/ml. In addition, the tested procyanidins were found to induce cell apoptosis in a dose-dependent method. The authors suggest that these procyanidins can induce MDA-MB-231 cell apoptosis by inhibiting intracellular FAS activity.

Olsson et al. (2004) compared the effect of 10 different extracts of fruits and berries, including sea buckthorn fruit, on the proliferation of HT29 semi-colon cancer cells and MCF-7 breast cancer cells. They observed that sea buckthorn

had the highest inhibition effect for the proliferation of HT29 and MCF-7 cells at its two highest concentrations (0.25 and 0.5%). The authors suggest that the inhibition of cancer cell proliferation was associated with concentrations of carotenoids and vitamin C. Moreover, they proposed the presence of a synergistic action between carotenoids, vitamin C, and anthocyanins. In addition, McDougall et al. (2008) found that sea buckthorn fruit extract had antiproliferative effects against cervical and a semi-colon cancer cells growing in vitro.

Boivin et al. (2007) determined the antiproliferative activity of the extract of 13 types of berries, including sea buckthorn, at concentrations of 10–50 μg/ml against five cancer cells in vitro: AGS stomach adenocarcinoma, ACF-7—mammary gland adenocarcinoma, PC-3—prostatic adenocarcinoma, Caco-2—colorectal adenocarcinoma, and MDA-MB-231—mammary gland adenocarcinoma. It was shown that sea buckthorn fruit extract, like blackberry and black chokeberry had anti-proliferative properties. However, no significant association was found between the anti-proliferative properties of the berry extracts and their antioxidant capacity, and the inhibition of cancer cell proliferation by the extract did not involve caspase-dependent apoptosis. Despite this fact, suppression of tumor necrosis factor (TNF)-induced activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB) was observed.

Recently, Guo et al. (2017) studied the phytochemical compounds of the berries of four different subspecies of sea buckthornH. rhamnoides L. subsp. sinensis (Sinensis), H. rhamnoides L. subsp. yunnanensis (Yunnanensis), H. rhamnoides L. subsp. mongolica (Mongolica), and H. rhamnoides L. subsp. turkestanica (Turkestanica) , as well as their antioxidant and antiproliferative properties against HepG2 human liver cancer cells in vitro. Of these species, H. rhamnoides L. subsp. sinensis demonstrated the highest phenolic content (about 39 mg gallic acid (GA) equiv./g dry weight) and corresponding total antioxidant activity, while the greatest cellular antioxidant and antiproliferative properties were observed in H. rhamnoides L. subsp. yunnanensis. These properties were attributed to the action of phenolic acids and flavonoid aglycones.

Zhamanbaeva et al. (2014) studied the effects of ethanol extract from sea buckthorn leaves on the growth and differentiation of human acute myeloid leukemia cells (KG-1a, HL60, and U937). Although a plant extract was found to inhibit cell growth according to cell strain and extract dose, the study does not identify the chemical content of the tested extract. They used three concentrations of the extract: 25, 50, and 100 μg/ml. The findings of the study suggest that the antiproliferative effect of sea buckthorn extract on acute myeloid leukemia cells was determined by activation of the S phase checkpoint, which probably led to the decrease of the cell cycle and stimulation of apoptosis.

Table 2- Sea buckthorn bioactive compounds and their therapeutic effects (44; modified).

Therapeutic effect	Bioactive compound
Antioxidant Analgesic Protection against destructive changes, thrombosis, and muscle cramps	Tocopherol
Antioxidant Involved in the synthesis of collagen Protection and restoration of the mucous membranes and epithelia Enhancing the immune system	Carotenoids
Anti-atherosclerotic action, anti-inflammatory and antibacterial properties The prophylaxis and treatment of hypercholesterolemia-induced cardiovascular disorders by lowering serum cholesterol concentrations Reducing the risk of stomach ulcers	Phytosterols
Protecting against cerebrovascular and cardiovascular disorders Stimulating the immune system Promoting cognitive function and bone health.	Unsaturated fatty acids

Positive effect on such neurological disorders as depression, schizophrenia, and Alzheimer's disease	
Fast wound healing Protecting against cerebrovascular and cardiovascular disorders	Organic acids
Antioxidant Involved in collagen synthesis Maintaining correct cell membrane integrity	Vitamin C
Prevention of bleeding Reducing the risk of stomach ulcers Helping the reconstruction of skin damage	Vitamin K
Antioxidant Reducing the risk of cardiovascular disease Involved in regulating heart rhythm Prevention of tumors Relieving the symptoms of aging	Phenolic compounds

The tested extracts considerably inhibit microsomal lipid peroxidation and protect normal erythrocytes against hypo-osmotic shock. A recent study by Kim et al. (2017) proposes that sea buckthorn extract containing about 70 mg/g phenolic compounds and about 460 μg/g catechin, may inhibit the rapid proliferation of rat C6 glioma cells when administered at 0.62, 6.2, and 62 μg/ml, probably by inducing the early events of apoptosis. The authors also suggest that the reduction of C6 glioma cell proliferation and viability following administration of the plant extract was associated with a drop in the production of reactive oxygen species as critical for the proliferation of tumor cells. Moreover, sea buckthorn not only strengthens the expression of the pro-apoptotic protein Bcl-2- X (Bax), but also promotes its localization in the nucleus. Various studies show that sea buckthorn oil also has anti-tumor properties. This oil can be placed in capsules, gelatin, and oral liquids (Yang and Kallio, 2002). Moreover, toxicity studies revealed no adverse effects in individuals administered with sea buckthorn oil (Upadhyay et al., 2009). Kumar et al. (2011) showed that sea buckthorn oil plays an important role in cancer therapy, including chemotherapy and radiotherapy complications, and using sea buckthorn oil may help fight against many side effects or treatment, restore kidney and liver function, increase appetite, and generally keep good health. Wang et al. (1989) observed that seed oil reduced tumor growth by 3–50%. Zhang et al. (Zhang, 1989) indicated that seed oil (1.59 g/kg body weight) significantly inhibited the growth rate of transplanted melanoma (B16) and sarcoma (S180) tumors in mice. Wu et al. (1989) attribute the protective effect of sea buckthorn seed oil against cervical cancer to the presence of vitamins A and E. Finally, Sun et al. (2003) found that flavonoids extracted from sea buckthorn seeds inhibit liver cancer cell BEL-7402 inducing apoptosis. The seeds and berry pulp of sea buckthorn contains various other bioactive compounds, including unsaturated fatty acids and phytosterols. Unsaturated fatty acids have a multidirectional influence on human health, for example, by stimulating the immune system. In addition, phytosterols have anticancer properties (Sajfratova et al., 2010; Dulf, 2012). More details about the composition and useful health aspects of sea buckthorn are presented by Olas (2018). The effect of sea buckthorn on cancer cells in different in vitro models is described in Table 3.

Table 3- The effect of sea buckthorn on cancer cells in in vitro models.

Reference	Effect	Concentration	Cancer cells	Extract/chemical compound or other form obtained from sea buckthorn
			Extract or other forms obtained from sea buckthorn	
Fruits extract	Cell of breast cancer,	10–50 µl/ml of medium	Inhibition of tumor cell	Boivin et al., 2007
Extracting from fruits in different solvents	prostate, stomach, and a semi-colon	<0.1–2% (v/v) of medium	proliferation of all tested line	Grey et al., 2010
Ethanol-water extract from berries	Cancer cells of a semi-colon and liver	0.025–0.5% the dry weight in medium	Inhibition of tumor cell proliferation of all tested	Olsson et al., 2004
Ethanol-water extract from berries	Cancer cells of the breast and a semi-colon	10–100 µg/ml	lines; extract with ethyl acetate also caused	Zhamanbayeva et al., 2016
Ethanol extract from berries	Acute myeloid leukemia cells	25, 50, and 100 µg/ml	apoptosis of these cells	Zhamanbaeva et al., 2014
Leaf extract	Acute myeloid leukemia cells	0.62, 6.2, and 62 µg/ml	Inhibition of tumor cell proliferation of all tested	Kim et al., 2017
Isorhamnetin isolated from berries of sea buckthorn	C6 glioma cells	25–300 µg/ml of medium (IC50 = 75 µg/ml)	lines	Teng et al., 2006
Isorhamnetin isolated from berries of sea buckthorn	Cancer cells of the liver	10–320 µg/ml	Anti-proliferative action	Li et al., 2015
Isorhamnetin isolated from berries of sea buckthorn	Lung cancer cells	20 and 40 µM	Anti-proliferative action	Li et al., 2014
Procyanidins isolated from seeds	Colorectal cancer cells	10–60 µg/ml	Anti-proliferative action	Wang et al., 2014
	Breast cancer cells		Cytotoxicity against cancer cells-a fall in their vitality, fragmentation and chromatin condensation	
			Anti-proliferative action	
			Anti-proliferative action Inducing apoptosis	

IN VIVO studies

Sea buckthorn had anticancer properties in both in vitro and in vivo studies on animal models. A study of the chemotherapy effect of sea buckthorn fruits by Padmavathi et al. (2005) showed that dimethylobenzenoantracen-induced skin papillomagenesis in mice is inhibited. The authors suggest that inhibition of carcinogenesis may be attributed to the concomitant induction of phase II enzymes, i.e., glutathione S-transferase, glutathione peroxidase, catalase, superoxide dismutase, and glutathione reductase in mouse liver. Moreover, the authors also suggest that the anticancer activity of sea buckthorn fruits may be based on its increase of the DNA-binding activity of interferon regulatory factor-1 (IRF-1), a known antioncogenic transcription factor causing growth suppression and apoptosis. Nersesyan and Muradyan (2004) report that sea buckthorn extract protects mice against the genotoxic action of cisplatin: a famous anticancer drug which also is very toxic to normal cells. Sea buckthorn extract (300 ml) was given to mice by gavage for 5 or 10 days. 3 hours after the last gavage, mice received cisplatin at concentrations of 1.2 or 2.4 mg/kg. Yasukawa et al. (2009) found that 70% ethanol extract of sea buckthorn branches (1 mg of plant extract/mouse) had antitumor properties in an in vivo two-stage carcinogenesis test with two groups of 15 mice; 7,12-dimethylbenzanthracene as an indicator, and 12-O-tetracecanoyl-phorbol-13-acetate as a promotor. Of the three phenolic compounds (catechin, gallocatechin, and epigallocatechin) and the triterpenoid ursolic acid isolated from the extract, epigallocatechin, and ursolic acid showed the most active ones. Wang et al. (2015) found that not only the phenolic compounds or phenolic extracts/some species sea buckthorn have anticancer properties: HRWP-A, a water-soluble homogenous polysaccharide with repeating units of (1 → 4)-β-D-galactopyranosyluronic residues, of which 85.2% are esterified with methyl groups,

also shows anticancer and immunostimulating activities in vivo. An antitumor activity test demonstrated that HRWP-A could significantly inhibit lung carcinoma growth in mice with tumur. In addition, this compound enhanced lymphocyte proliferation, strengthened macrophage activities, and promoted natural killer cell activity in mice with tumor. The authors used three different doses of polysaccharide (50, 100, and 200 mg/kg), which were administrated intragastrically each day for 14 days.

Conclusion

Although most of the studies have emphasized the anticancer activities of sea buckthorn, its suitable use in pharmaceutical and prevention applications is not clearly indicated and clinical tests except in vivo and in vitro are not performed. The studies have shown that sea buckthorn may play an important role in prevention and treatment of cancer and it is also important in healing the health of patients receiving chemotherapy by improving the immune system performance and reduction of blood cells damage. The effective substances in different parts of sea buckthorn have a wide range of useful properties including antioxidant, anti-inflammatory and anti-proliferation activities. They also strengthen the immune system of the body. However, before considering sea buckthorn a good option in cancer treatment, we need further studies regarding its effects and side-effects with the collaboration of cancer

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