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Research Review

The Genus *Elaeagnus* as a Potential Source of Antioxidant Lycopene, an Anti-Cancer Agent: A Review

Bristy Borgohain*[1], Bijoy Neog[2] and Pranit Saikia[3]

[1-2] Department of Life Sciences, Dibrugarh University, Dibrugarh - 786 004, Assam, India
[3] Centre for Biotechnology and Bioinformatics, Dibrugarh University, Dibrugarh - 786 004, Assam, India

Abstract

Lycopene is a lipid soluble carotenoid compound synthesized naturally by plants and microorganisms. It is one of the dominant antioxidants among dietary carotenoids and is principally responsible for imparting red colour in fruits and vegetables. Emerging research suggests, lycopene as an important micronutrient with many health benefits and it is a potent anticancer agent against several types of cancers including prostrate, epithelial, oral, hepatocarcinoma etc. Fruits of *Elaeagnus* species are an abundant source of lycopene and its derivatives. However, this genus remains underutilized due to lack of proper knowledge and scientific study. Here, in this review we have summarized the chemical nature of lycopene, its availability in different species of the genus *Elaeagnus* and its role in prevention of cancer. The obtainable data is promising, however more detailed information on the bioavailability, biochemistry and anticancerous activity of lycopene are needed to utilize fruits of this genus as functional food and in pharmacological industries in near future. We hope that this review will prompt future researches and shade light on the value of lycopene in the fruits of the genus *Elaeagnus*.

***Key words*:** Anticancerous, Antioxidant, Carotenoids, *Elaeagnus*, Lycopene, Underutilized

The genus *Elaeagnus* belongs to the family Elaeagnaceae and order Rosales, consists of about 100 wild and cultivated species that are distributed worldwide [1]. The members of this genus are mostly deciduous or evergreen shrubs, small trees or some are climbers [2]. Leaves are alternate, green in colour with silvery-white scale at beneath. Fruits of *Elaeagnus sp*. are known as oleaster, silverberry, autumn olive, goumi berry, thorn olive, Russian olive, Persian olive, wild olive etc. They are fleshy drupes with a single large seed. When these berries ripe, they become attractive red in colour with gold and silver-coloured speckles and taste sweet with a hint of sourness [3]. Species of this genus are mostly found in wild and their fruits lacks market demand, however some species such as *E. angustifolia*, *E. multiflora* and *E. umbellate* are cultivated for their fruit [4]. Fruits of *Elaeagnus* species were found to be rich in various bioactive compounds such as phenols, flavonoids, ascorbic acid, carotenoids etc. The major carotenoids present in these fruits are lycopene, phytoene, and lutein [5]. At fully ripen stage, lycopene predominates over other carotenoids [6]. Lycopene is a bright red non-pro-vitamin A carotenoid pigment principally responsible for the yellow, orange, and red colors of fruits and vegetables. They also function as excellent antioxidants due to their ability to quench singlet-oxygen [7]. Among the pro-vitamin A carotenoids**,** β carotene is known for its antioxidant property, however it sometimes accounts for adverse effects and can lead to cancer. In such a case, lycopene is a much safer antioxidant than β carotene, as it does not lead to adverse effects [8]. From many recent studies lycopene has gained notable attention due to its significant role in reduction of tumorgenesis and other non-communicable diseases [9]. Levy *et al*. [10] reported that Lycopene is a much potent inhibitor than α and β carotene, in inhibiting several types of cancer cells, including those of prostate, mammary, lung and endometrium. According to Livny *et al*. [11], Lycopene can be used as a chemopreventive agent for precancerous oral lesions and as an adjuvant in the treatment of oral cavity cancer. Due to such health-promising activities of lycopene, demand for lycopene-rich food and nutraceutical products is increasing now-a-days.

Lycopene has been found to be present in red fruits and vegetables viz. tomato, watermelon, pink guava, carrot, red bell pepper etc. [12]. Among all other dietary carotenoids, lycopene in tomato exhibits highest singlet oxygen quenching ability and antioxidant activity [13-14]. Recent studies on the genus *Elaeagnus* reveals that, ripe *Elaeagnus* fruits contain high lycopene content which is found to be 10-12 times higher than

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Correspondence to: Bristy Borgohain, Department of Life Sciences, Dibrugarh University, Dibrugarh - 786 004, Assam, India, Tel: +91 7002331971; E-mail: rs_bristyborgohain@dibru.ac.in

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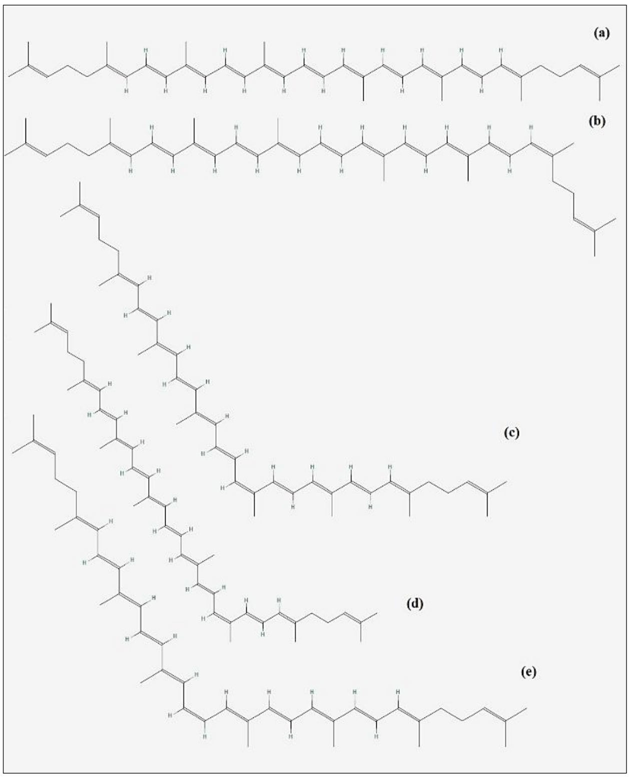
in ordinary tomato fruits [6], [15]. This review summarizes lycopene content and its anticancer activity in different species of the genus *Elaeagnus* along with their comparison with other lycopene-rich fruits.

Chemistry of lycopene

Lycopene with the molecular formula $C_{40}H_{56}$ and molecular weight of 536.85 daltons, is the predominant carotenoid hydrocarbon present in the genus *Elaeagnus* [16]. It is lypophilic and do not show provitamin A activity as it lacks the β-ionone ring structure, which is present in pro-vitamin A carotenoids such as α and β-carotene [17]. Lycopene is an acylic compound comprising of 13 double bonds in its backbone, out of which two are non-conjugated and 11 are conjugated linearly arranged double bonds. This distinguishing conjugated polyene structure is responsible for the red colour and antioxidant activities of lycopene [18]. The conjugated double bonds present in lycopene molecules efficiently quench the energy from singlet oxygen and thereby scavenge a large spectrum of free radicals [19]. Lycopene exists in numerous isomeric forms. Generally, all biologically occurring lycopene are trans isomers, which is thermodynamically the most stable form, however when it is exposed to light, heat and other chemical reactions, the double bonds present in lycopene undergo isomerization from trans to mono or poly-cis isomers [20-21].



Figu 1 Chemical structure of (a) (all-E)-lycopene, (b) (5Z)-Lycopene, (c) (13Z)-Lycopene, (d) (9Z)-Lycopene and (e) (15Z)-Lycopene

In the genus *Elaeagnus*, several geometrical isomers of lycopene were identified in the fruit pulp, skin and seeds viz. (all-E)-lycopene, (15Z)-lycopene, (13Z)-lycopene, di-Z lycopene, (9Z)-lycopene and (5Z)-lycopene (Fig 1). Among these isomers, (all-E)-lycopene predominated in *Elaeagnus* and accounted for about 90% of all identified lycopene isomers [5] (Lachowicz *et al*., 2020). Most works on (all-E)-lycopene reported to have strong antioxidant properties as it scavenges free radicals such as 2,2-diphenyl-1-picrylhydrazyl (DPPH), 2,2'-azobis(2-amidinopropane) dihydrochloride (AAPH) or tert-butyl hydroperoxide. Müller *et al*. [22] studied the antioxidant capacity of (Z)-isomers of lycopene and compared it with (all-E) isomers of lycopene using 4 *invitro* assays viz. FRAP assay, αTEAC assay, LPSC assay and $MbFe^{III}$-LP assay. Their results reported that, all assessed lycopene isomers showed strong antioxidant activity than α-tocopherol and β-carotene and also the peroxyl radical scavenging activity of lycopene enhances when isomerization of (all-E)-lycopene to its (Z)-isomers takes place. These strong antioxidant activities of lycopene help in regulating cholesterol metabolism, minimizing the effects of cholesterol on the heart and muscle disease [23]. It has also been found that the consumption of lycopene offers protection against cataracts on the eye lens of people [24].

Availability of lycopene along with other bioactive compounds in fruits of different Elaeagnus species

The genus *Elaeagnus* contain a matrix of important bioactive compounds including vitamin C (ascorbic acid), vitamin E, carotenoids, anthocyanins, tannins, saponins, flavonoids and many essential fatty acids such as palmitic, oleic, eicosanoic, palmitoleic, stearic, linoleic etc. [25]. The synergistic interactions of these compounds, when used in combination, may be responsible for many advantageous biological activities of *Elaeagnus* fruits [26] (Table 1).

Elaeagnus fruits are a rich source of carotenoids and its content changes at various stages of growth. During ripening period of these fruits, among all the carotenoids (such as β-carotene, α-cryptoxanthin, β-cryptoxanthin, phytoene, lutein and phytofluene), lycopene is the dominant one [27]. In fully ripe berries, it accounts for about 72-82% of the overall carotenoids [28].

Fordham *et al*. [28] reported carotenoids such as lycopene, β-carotene, phytoene, α-cryptoxanthin, β-cryptoxanthin, lutein and phytofluenelycopene in fresh *E. umbellata* fruits from both wild and cultivated species. In wild *E. umbellate* fruits, lycopene content was found to be 15-54mg and in red-pigmented cultivated species 18-48mg per 100g. They also estimated lycopene in a yellow cultivar, which was found to be very low (0.47 mg/100) as compared to the red-pigmented cultivated species. In 2005, another study was carried out by Perkins-Veazie *et al*. [29] in six selections and varieties of *E. umbellate* where, the lycopene content was estimated to be 30 to 55 mg/100g. Wang and Fordham [30], reported the lycopene content to be ranging from 30.58-46.23mg FW/100g in six genotypes of *E. umbellate*, representing 75.41-81.57% of the overall carotenoids. Guo *et al*. [6] also evaluated the lycopene content to be 1.822 mg/g of dry weight or 0.341 mg/g of fresh weight, which is 12 times higher than in ordinary tomato fruit (2.573 mg/100 g). In a more recent study, the lycopene from *E. umbellate* fruits were extracted by a mixture of BHT in acetone, ethanol and hexane (1: 1: 2) and it was found to be 133.520mg/100g [30].

Phytochemical evaluation of *E. angustifolia* fruits extract indicates the presence of polysaccharides, vitamins, amino acids, carotenoids, flavonoids, terpenoids, saponins, sitosteroles, coumarines, cardiac glycosides, phenol carboxylic acids and tannins [31-32]. In ripe *E. angustifolia* fruits, the carotenoid content was found to be 3.2 ± 0.6 µg/g of dry weight, which is 3:1 ratio higher than chlorophyll-b and 70% higher than chlorophyll-a [33].

The carotenoid profile of *E. multiflora* shows lycopene (about 39.16–169.00mg/100g) as the dominant carotenoid over phytoene and lutein [5]. Nowak *et al*. [34] extracted lycopene and β-carotene by ultrasound treatment with three power levels such as 200W, 400W, 600W and found out the lycopene content to be 1.071μg/g, 0.681 μg/g and 0.463μg/g respectively, whereas the β-carotene content as 3.069 μg/g, 1.744 μg/g and 1.052 μg/g respectively.

Nath *et al*. [35], studied the physical and biochemical properties of *E. latifolia,* where the lycopene content was estimated as 0.115-0.215mg/100g. In a more recent study, the bioactive compounds in *E. latifolia* were identified and quantified and it is found as a rich source of ascorbic acid, carotenoids (such as lycopene, β-carotene) minerals, organic acids and phenolics. The lycopene content was estimated to be 2.06±0.38 mg/100g [36].

Table 1 Bioactive compounds and their biological activities in some *Elaeagnus* species

Species	Common name	Phytoconstituents	Biological activity	References
E. angustifolia	Russian olive, Oleaster	flavonoids, terperiolds, cardiac glycosides, polysaccharides, anthocyanins, coumarins (p-coumaric acid), phenolcarboxylic acids, amino acids, saponins, carotenoids, vitamins (C,A,E,K), tannins (catechins)	Antinociceptive, Anti-inflammatory	[37-39]
E. latifolia	Bastard oleaster	carbohydrates, ascorbic acid, tannins (tannic acid), phenolics, flavonoids (quercetin, catechin, rutin), carotenoids (lycopene, β-carotene)	Antioxidant, DNA protector, Anti-microbial,	[40], [36]
E. multiflora	Cherry silverberry, goumi	Tocopherols, ascorbic acid, phenolic (caffeic, chlorogenic, and p-formic acids), flavonoid (quercetin and rutin), polyphenols, carotenoid (phytoene, lycopene, lutein), tannin, alkaloid, saponin	Antioxidant, Antidiabetic, Anticancer	[41-42]
E. umbellata	Autumn olive, Japanese silverberry	Phenolic (4-hydroxybenzoic acid), Flavonoids (quercetin, rutin), Benzoic acids, Carotenoids (phytoene, lycopene, α-carotene, lutein, β-carotene), Tannins, Alkaloids, Saponins, Vitamin C, anthocyanins	Antidiabetic, Neuroprotective, Antiamnesic effects	[4], [43]
E. kologa	Oleaster, silverberry	Vitamin C, Tannins, Saponins, Flavonoids	Antibacterial, Anthelmintic	[44]
E. pungens	Thorny olive, spiny oleaster, silverthorn	Vitamins (especially in vitamins A, C and E), Minerals, flavonoids (quercetin and kaempferol)	Anti-inflammation	[45-46]
Elaeagnus × *ebbingei*	Ebbing's silverberry	Vitamins (A, C and E), minerals, flavonoids, essential fatty acids	Anticancerous	[45]

Comparison of lycopene content in Elaeagnus species and other lycopene rich fruits

The lycopene content in different varieties of fruits and vegetables can vary significantly at the time of ripening. Its content varies depending on several factors such as degree of maturity, the temperature and the soil quality [47] (Gujral, 2018). Tomato and tomato-based products are considered as the major dietary source of lycopene and in western countries, they account for about 80% of the total lycopene consumed [48] (Clinton, 1998). Besides these, there are many other fruits such as watermelon, pink guava, apricot, papaya etc. which also provides sufficient amount of lycopene. Recent works suggest *Elaeagnus* fruits as an excellent source of lycopene and depending on the variety, its content is 10-12 times higher than in ordinary tomatoes [6], [15] (Guo *et al*., 2009; Wang *et al*., 2020). (Table 2) gives a comparative account of the lycopene content in *Elaeagnus* fruits and other lycopene rich fruits and fruit products.

Table 2 Approximate lycopene content in *Elaeagnus* species and other lycopene rich fruits and food products

Fruits	Lycopene content (mg/100g)	References
Elaeagnus umbellata	30 – 55	[29]
Elaeagnus multiflora	39.16 – 169.00	[5]
Elaeagnus latifolia	2.06 ± 0.38	[36]
Watermelon	14.427 ± 0.001	[12]
Papaya	0.23 – 0.42	[49]
Pink Guava	0.34 – 0.92	[50]
Fresh tomatoes	0.72 – 20	
Tomato juice	5 – 11.60	
Tomato puree	16.67 – 34.7	[51]
Tomato paste	5.40 – 150.00	
Tomato Ketchup	9.90 – 17.00	
Canned cherry tomatoes	11.42 – 11.78	[52]

Anticancerous property of the genus Elaeagnus in relation to lycopene

Lycopene has been broadly used in the food processing and pharmaceutical industries due to their antioxidant, anticancererous and anti-inflammatory properties. The mechanism behind the inhibitory effects of lycopene could be due to free radical scavenging activity, up-regulation of detoxification systems, interference with cell proliferation, restoration of gap-junctions and suppression of cell-cycle progression [53].

The genus *Elaeagnus* is a potential natural source of lycopene and thus known to have anticancerous property [54-55]. *E. umbellate* shows antiproliferative activities against human leukemia cancer cells (HL-60) and human lung epithelial cancer cells (A549). The fruit extracts of *E. umbellate* can inhibit eukaryotic transcription factors AP-1 and NF-κB, which plays a crucial role in tumorgenesis and can induce apoptosis in cancer cells [56].

Different fractions of ethyl acetate fruit extracts of *E. angustifolia* showed strong anticancerous activity against human cervical cancer cells (HeLa). With the increase in concentration and polarity of the fractions, metabolic activities of HeLa cells decreased.The inhibition rate was found to be highest at 74.34% in the concentration of 2.5 mg/mL [57]. The whole fruit extract of *E. angustifolia* in ethanol also shows antiproliferative activity against glioblastoma cells C6 and U87 at the dose of 125-2000 µg/ml and 61.5-2000 µg/ml respectively. A recent study also reported that, the fruits extracts of *E. angustifolia* using different solvents such as methanol, ethanol, hydroalcoholic and aqueous can significantly reduce the viability of human breast cancer cells, MCF7 [58].

The aqueous fruit extract of *E. multiflora* when fermented by coculture of lactic acid bacteria viz. *Lactobacillus plantarum* and *Lactobacillus casei* (LPLC) showed strong anticancerous activity against colorectal cancer cells (SW480) at 25-50 µg/mL. The mechanism behind the antiproliferative activity of SW480 cells by LPLC extracts were due to induction of cell cycle arrest at the S and G2/M phases by downregulating the expression of cyclins, CDKs, and mitosis inducer cdc25c while upregulating the tumor suppressor protein such as p27, p53 [59]. *In-silico* molecular docking analysis of silver nanoparticles (AgNP) synthesized from fruit juice of *E. pyriformis* reveals cytotoxicity and anticancerous property against human renal adenocarcinoma cell line (ACHN). The mechanism behind this is the inhibition of anti-apoptotic protein Bcl-xL, which as a result activates Bak and bax and thereby induces apoptotic pathway [60].

CONCLUSION

For the last few centuries, lycopene has been a major carotenoid incorporated in human diet and its demand is increasing due to its emerging awareness of several health benefits among people. The genus *Elaeagnus* is plentiful in nutrients, particularly lycopene and thus have demonstrated notable biological and pharmacological activities such as antioxidant, anti-proliferative and cytotoxic activities. However, fruits of this genus are unable to attain commercial value like other lycopene rich fruits and remain underexploited due to lack of proper scientific exploration. Therefore, advanced studies are urgently needed to investigate and isolate lycopene from this genus in order to utilize its benefits in pharmaceutical industries.

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