



# Russian olive (*Elaeagnus angustifolia*) as a herbal healer

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## Abstract

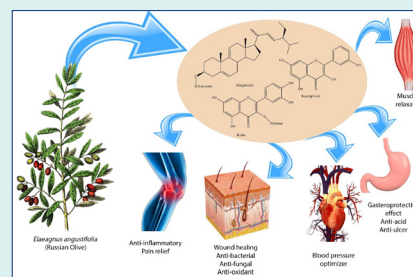
**Introduction:** *Elaeagnus* spp. is one in the family of riparian trees growing near the rivers or water corridors. In this family, *Elaeagnus angustifolia* (Russian olive) is famous because of its medical applications.

**Methods:** A comprehensive review was performed to extract the related data from published literature.

**Results:** Traditionally, it has been used as an analgesic, antipyretic and diuretic herbal medicine.

A large number of compounds have been derived from Russian olive and made this plant a source of flavonoids, alkaloids, minerals and vitamins. Although the purpose of most studies is to use this plant for preparation of herbal medicines and as an ingredient for drug formulation, there is no available drug dosage form commercially.

**Conclusion:** This review aimed to provide the most important documentary information on the active components of *Elaeagnus* spp. and their relation to the pharmacological properties and compare them with reported medicinal effects.



## Introduction

*Elaeagnus* spp. (Plantae>Rosales>Elaeagnaceae>Elaeagnus) is in the family of riparian trees growing near rivers or water corridors.<sup>1</sup> It is mostly found in central Asia<sup>2</sup> including Iran,<sup>3</sup> Uzbekistan,<sup>2</sup> Syria<sup>4</sup> and north-west of China<sup>5</sup> and exotically in river banks of central Spain,<sup>6</sup> Canada<sup>7</sup> and west of United-states.<sup>1</sup> The family Elaeagnaceae, consists of three genera and 50 species. *Elaeagnus angustifolia* (Russian olive) (Fig. 1) and *E. pungens* are partially adapted to the center of Asia. *Shepherdia canadensis* belongs to the Unites-states and Canada. *Hippophae rhamnoides* is endemic in Europe.<sup>8</sup> In this family; *E. angustifolia* is famous for its medical benefits. Traditionally, it has been used as an analgesic, antipyretic and diuretic herbal medicine. A large number of compounds have been derived from Russian olive and made this plant a source of flavonoids, alkaloids, minerals and vitamins. Several experimental studies have been done and some advances in drug formulation and herbal medicine have been achieved. This review tries to gather the most important documentary information

on its active components and their relation to the Russian olive pharmacological properties and compare them with reported medicinal effects. Another review on this plant has been published recently, but we tried to check more articles with conflicting reports for writing better and more comprehensive systematic review.<sup>9</sup>

## Active ingredients

The aqueous and non-aqueous extracts of *E. angustifolia* are full of medically significant active ingredients. The extracts contain a variety of compounds such as flavonoids and alkaloids, simple sugars and complicated sterols (Fig. 2).

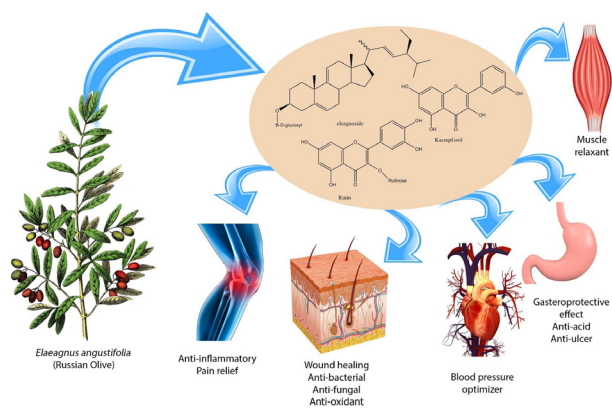
## Flavonoids

Flavonoids (which are commonly referred to vitamin P) are a large set of polyphenolic compounds with a benzo- $\gamma$ -pyrone structure and are found exclusively in plants. They can be categorized in different classes like: flavones, flavonols, flavanones, flavanonols, isoflavones and flavan-3-ols.<sup>10</sup>

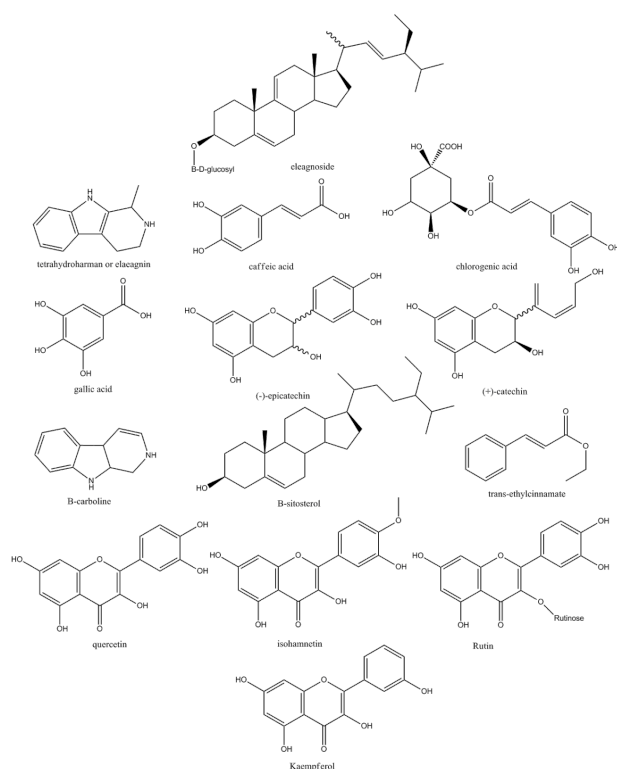
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**Fig. 1.** A brief review of *E. angustifolia*.



**Fig. 2.** Major constituents of *E. angustifolia*.

In the pulp of Russian olive, 4 glycosylated flavonoids<sup>10</sup> identified: Quercetin 3,4'-O- $\beta$ -D-diglucoside, Isorhamnetin-3-O- $\beta$ -D-galactopyranoside, Quercetin 3-O- $\beta$ -D-Galactopyranoside-4'-O- $\beta$ -D-glucopyranoside and Isorhamnetin 3-O- $\beta$ -D-Galactopyranoside-4'-O- $\beta$ -D-glucopyranoside.<sup>11</sup>

Rutin glycosylated kampferols such as kaempferol 7-p-coumaroyl-3-D-glucoside, kaempferol-3-D-glucopyranoside (astragalin) and kaempferol 3-O-D-glucosido-41-p-coumaroyl-7-O-D- acyl galactoside are other available flavonols of the fruits.<sup>12</sup>

Rutin eleagnoside and kampferol are also available in the flavonoid fraction of the fruit. In acetone extract from the bark of Russian olive, (flavan-3-ol<sup>10</sup>) obtained two catechins as well: (+)-catechin and (-)-epicatechin.<sup>13</sup>

Glycosylated flavonoids have difficulty in absorption; af-

ter hydrolysis by lactase phlorizin hydrolase (LPH), they should transfer from Na<sup>+</sup>-dependent glucose cotransporter in small intestine. Mostly, the glycosylated flavonoids pass the colon and exit. For these reasons, *E. angustifolia* flavonoids may also exit the colon and have no benefits. So, it should be taken into account whether the amount of absorption is enough for medical benefits or not.<sup>10</sup>

However, they have different roles in plants; for example, they play a major role in oxidative stress response and are also used as growth regulators. But, talking about the exact amount of the flavonoids in each plant is something difficult. Recent studies showed that geographical location may influence the quantity and quality of flavonoids.<sup>10</sup>

#### Fatty acids

Fatty acids of this family first recognized by Obodovski and Devyatnin. Total lipid content of *E. angustifolia* varies between 0.8% in pericarp to 26% in seeds per mass.<sup>12</sup>

Fruit methanol extract from Russian olive contains different kinds of fatty acids. In an experiment by Kusova *et al.* oleic acid and linoleic acid made up 92.8% of the petroleum extract of the fruit accompanied by a low concentration of fat-soluble vitamins.<sup>14</sup>

In another study which published in the journal of the chemistry of natural compounds on the Russian olive seeds, six epoxy acids and five hydroxy acids were collected: C18:0, C18:1 and C18:2 diepoxy acids and C18-hydroxy acids with double bonds at the 9-C atoms.<sup>15</sup>

Palmitic acid (16:1) is also present in trace amount (3%-10%)<sup>16</sup> in both seeds and fruits,<sup>16,18</sup> but, it is not a chemotaxonomic compound for this tree.<sup>16</sup>

In general, flesh of the fruit is low in lipids but seeds and pericarps of Russian olive are saturated with these compounds. Triacylglycerol with linoleic acid is the main lipid of the seeds. Saturated free fatty acids (octadecanoic acid 1.63% and hexadecanoic acid 3.91%)<sup>17</sup> are eminent; however, the highest concentration among free fatty acids belongs to essential linoleic acid (49.12%).<sup>17</sup> These amounts are somehow identical to the pericarp, except for the amount of triacylglycerol which is lower (18%-30%) in the pericarp.<sup>16</sup>

The amount of fatty acids and their derivatives are different from tree to tree based on cultivation soil, tree age and planting area.<sup>16</sup> However, what is important is whether the amount of fatty acids is commercially efficient or not; far seeds with 26% fatty acid per total mass, it seems applicable but for the rest (pericarp, leaves and flowers), it needs cost-benefit experiments.

#### Sterols

The most significant sterol of Russian olive is  $\beta$ -sitosterol.<sup>16,18</sup> It is found mainly in seeds, leaves and tree branches. Eleagnoside with a sterol-like structure is derived from the name of this family and present in the fruits of Russian olive.<sup>12,19</sup>

#### Carbohydrates

Usually, free sugars are the first descriptors of the fruits. In Russian olive, fructose and glucose are the predominant monosaccharides. The percentage of weight of fructose and glucose to the total dried weight of the fruit is 32%-

34% and 23%-24% respectively.<sup>20</sup> In the ripened fruits there is no significant amount of sucrose; it is said that this might be due to the effects of invertase during ripening process<sup>20</sup>; In another study, it became clear that raw fruits have variable amount of sucrose but during the process of ripening, sucrose cleaves to fructose and glucose.<sup>21</sup> Sugars can also be seen in combination with flavonoids; derivatives of isoharmentin, like isoharmentin 3-β-D galactopyranoside that are present in the fruits.<sup>21</sup> Among reducing sugars, xylose, mannose and rhamnose are also present in fruit extracts.<sup>13</sup> To sum up, in every Russian olive trees, fructose and glucose seemed to be the major composition of the sugars but the amount of sugars does not depend on the origin or age of the trees.<sup>21</sup>

**Alkaloids**

Alkaloids were detected by TLC of different fractions of Russian olive. They are mainly condensed in the root, bark and aerial part of the plant. The most famous alkaloid of Russian olive is elaeagnin or calligonin which is structurally a tetrahydroharman. In the bark of this plant, N-methyl harmol, N-methyl tetrahydroharmol, Harman, dihydroharman, 2-methyl-1,2,3,4- tetrahydro-β-carboline, harmin and harmol are available as well.

There are some unlabeled medical usages of elaeagnin and β-carbolinesuch as the reduction of blood pressure and antimalarial effect, but none of them were investigated for the extracts of this plant.<sup>12,22-24</sup>

**Other ingredients**

Vitamins and minerals play a major role in the medical properties of *E. angustifolia*. Vitamin A and K are oleophilic vitamins available in the methanol extract of the flowers of the plant. B vitamins are also present in the flowers.<sup>25</sup>

The highest concentration of a mineral element in this plant belongs to potassium with a concentration of 8504 mg/kg. Second and third highest levels belong to sodium and phosphorus with 1731 and 635 mg/kg, respectively.<sup>26</sup> Calcium is also found with high levels in this plant and traditionally the flowers of Russian olive were considered a good source of Ca<sup>2+</sup> among people of Iran.<sup>25</sup>

Steroidal glycosides (saponins) can be detected in the fruits by Fontan-Candel method (foam-forming reaction). The saponins of Russian olive do not cause hemolysis of erythrocytes in isotonic saline. Aglycone part of

saponins can be either neutral or acidic. Total amount of saponins in the fruits of EA estimated to be 1.96 % of the net weight of the fruit.<sup>13</sup>

Free acids are also present in the fruits of this plant: benzoic acid, 4-hydroxy benzoic acid and vanilic acid are the benzoic derivatives. The derivatives of cinamic acid, like caffeic acid and ferulic acid are available as well. In this list,4-hydroxy benzoic acid and caffeic acid are found in highest concentration, respectively.<sup>20</sup>

Amino acids such as aspartic acid, threonine, serine, glutamine, proline, glycine, alanine, valine and some others were observed as well (Table 1).<sup>13</sup>

**Traditional remedies**

Traditionally, Russian olive was used as an anti-ulcer remedy for wound healing or sometimes gastric disorders.<sup>27</sup> *E. angustifolia* fruits were also famous in Turkish folklore as tonic, antipyretic, kidney disorder healing (anti-inflammatory and/or kidney stone treatment) and anti-diarrhea (astringent).<sup>16,28</sup>

In ancient Iran, the fruit decoction of Russian olive was taught to be used a good remedy for fever, jaundice, asthma, tetanus and rheumatoid arthritis by Iranian apothecaries. In general, it was used as a substitute of any anti-inflammatory and analgesic agent, in the first line.<sup>29</sup>

The leaves and fruits of the plant were also famous as diuretics and antipyretic agents. In Turkey, it was common to eat the fruits an hour before the meal as an appetizer.<sup>21</sup> In Table 2 the traditional uses of this plant summarized. In the next sections, we will discuss some parts in detail.

**Experimental and clinical studies**

**Anti-inflammatory and analgesic effects**

Animal studies have shown the effectiveness of the aqueous and ethanol extract of Russian olive in pain and inflammation treatment. Flavonoids play the main role in this matter,<sup>37</sup> although anthocyanins, saponins<sup>38</sup> and terpenoids may take part as well.<sup>39</sup> There is a controversy on the success of the extract of this plant on acute or chronic pain. Formalin test is one of the reliable tests in both acute and chronic pain. In the first phase of formalin test, 5 minutes after injection, the direct influence of the compound on the pain fibers is tested and mostly called as an acute phase. 20 to 30 minutes after injection, the chronic phase or the inflammatory pain starts. For some medicines such

**Table 1.** Percentages of the active ingredients of dried ripe fruits of *Elaeagnus angustifolia*<sup>13</sup>

<i>Elaeagnus</i> spp. is in the family riparian trees growing near the rivers or water corridors	Percentage in dried ripe fruits of <i>E. angustifolia</i>
Reducing sugars	50.67-55.75%
Total sugar	60 ± 5%
Pectic polysaccharides	3.58 ± 0.3%
Total flavonoids and polycarboxilic acids	1.35 ± 0.15%
Total saponins	1.96 ± 0.52%
Ascorbic acid	5.6 mg%
B-carotene	17.5 mg%
Tannin	5.03 ± 0.05%

**Table 2.** Traditional remedies of *Elaeagnus angustifolia*

Extract/Country	Application	Rout of administration
Iran		
Infusion of the dried flowers	Anti-pyretic	oral <sup>30</sup>
Infusion of the dried leaves	Astringent	oral <sup>30</sup>
Turkey		
Fresh branch in hot water	To remove wart	External <sup>31</sup>
Decoction of barks	Gall bladder problems and kidney stones	Drink one teacup twice a day for 20 days <sup>32</sup>
Extract of leaves with the ash of <i>Salix</i> sp. bark	To treat abscess	external <sup>33</sup>
Fruits	Kidney stones	oral <sup>34</sup>
Tea or decoction of root barks	Dysuria	Oral <sup>35</sup>
Extract of leaves with <i>Juglansregia</i> and <i>Menthalongifolia</i>	Sun block	External <sup>36</sup>
Azerbaijan		
Infusion of the aerobic parts	Treatment of alimentary canal	Oral (NAPALERT)

as morphine and codeine with a central effect both phases can be suppressed but for some others like non steroid anti-inflammatory drugs (NSAIDs) and steroids only the chronic phase can be effected.<sup>40,41</sup>

While Farahbakhsh *et al.*<sup>39</sup> believe in ineffectiveness of the aqueous extract of the Russian olive in the acute phase; Hosseinzadeh *et al.*<sup>18</sup> and Ahmadiani *et al.*<sup>29</sup> proved ( $p < 0.001$ ) the comparable effect of the fruit extract with both NSAIDs and narcotics. Altogether, it can be inferred that the fruit extract of Russian olive with low doses (20-40 mg/kg) only suppresses the chronic pain<sup>29</sup> and high doses (130-450 mg/kg) can be successfully used against both chronic and acute pain.<sup>37,38</sup>

On the other hand, the mechanism of its analgesic effects was also tested in hot-plate and writhing test. In comparison to indomethacin with a proven peripheral mechanism of pain relief in writhing test, the flavonoid extract of the Russian olive (134-402 mg/kg) showed both peripheral and central effects in hot-plate and writhing tests.<sup>38</sup>

Quercetin is one of the most famous flavonoids with an analgesic effect available in Russian olive. It can block the activity of cyclooxygenase (COX) and lipooxygenase. *In vitro*, it has an inhibitory effect on the secretion of the immunoglobulins.<sup>10</sup> Bioflavonoids with an ability to block the release of the bradykinin and arachidonic acid play an important role in the mechanism of controlling the chronic pain. Sometimes, muscle relaxant ability of the plant is known as an axillary mechanism for pain relief. Available alkaloids, such as harman and harmaline, inhibit mono amino oxidase (MAO) and increase serotonin and nor-adrenaline (like tricyclic antidepressants) at the synaptic sites. This mechanism can also be a part of analgesic effect of the plant.<sup>37</sup> Based on pharmacological information, flavonoids can block N-Methyl-D-aspartate (NMDA) receptor and reduce the amount of intracellular calcium and lead to reduced enzymatic activity of nitric oxide and phospholipase A2-Calcium-dependant protein.<sup>42</sup> Flavonoids fill the ATP binding sites of kinases (serine/threonine or tyrosine kinase). These results obtained in less activation of phospholipase A2 and less production of COX. Some other flavonoids can block cAMP phosphodiesterase in the platelets. The reduction of cAMP chang-

es cytoskeletal rearrangements and deactivates special protein kinases. The substrates of the kinases like vasodilator-stimulated phosphoproteins remain inactive and finally platelet secretion, adhesion and aggregation stops. This is one of the important mechanisms in controlling inflammation.<sup>43</sup>

Linoleic acid can also suppress the gene expression inflammatory cytokines. The inflammation is mediated by inhibition of NF- $\kappa$ B (a protein complex that controls cytokine production) activation through PPAR-gamma pathway.<sup>44</sup>

Recently in a clinical study, Russian olive extract (medulla powder and whole fruit, 15 g/kg, 8 weeks) showed a significant improvement in pain and inflammation management of knee osteoarthritis in women. It can reduce serum levels of inflammatory cytokines (TNF- $\alpha$ , MMP-1, etc) and also enhance patients' presentation of the disease; but the study was only carried out in obese women (according to reported body mass index) having chronic arthritis pain. It may need another comprehensive study containing at least pregnant women or athletes bearing acute pain and a range of dosages corresponding to previous laboratory studies.<sup>45</sup>

Two separated randomized, double blind clinical studies, effectiveness of aqueous extract of Russian olive (300-600 mg/kg) which contained at least 0.21% kaempferol, was compared with ibuprofen (800 mg/kg) in women with knee osteoarthritis. *E. angustifolia* extract was very safe and tolerable in 2 doses and was so beneficial in reducing symptoms of osteoarthritis.<sup>46,47</sup> In Table 3 most of the available studies are summarized. What we can infer is that analgesic effects of *E. angustifolia* are the most important medical applications of this plant. It is concentrated mainly in fruits and specially seeds of the trees. The mechanism does not relate to the opioid receptors, but the polyphenolic extracts can attenuates pains as good as the opioids.

#### **Gastroprotective effect**

From ancient remedies, Russian olive is famous for its antiulcer effect. *In vivo* studies in rats proved that the alcoholic extracts of this plant in low doses (400-800 mg/



**Table 3.** Anti-inflammatory and analgesic effects of *E. angustifolia*

Extract and doses	Compared medicine and doses	Experiment	Results and considerations	References
Seed (aqueous, ethanol and polyphenolic fraction) 100-1000 mg/kg	Indomethacin (1 mg/kg) Morphine (5 mg/kg)	Hotplate test Writhing test	Aqueous and ethanolic extracts were effective in concentration above 500 mg/kg Polyphenolic extract was effective in 300 mg/kg The role of polyphenolic groups in pain relief were proved	38
Total fruit (aqueous fraction) 1000 mg/kg	Sodium salicylate (100-300 mg/kg)	Formalin test Tail-flick test Anti-inflammatory test	Acute phase of pain: peritoneal injection was effective Chronic phase of pain: like NSAIDs have pain relief effects even orally In both phases, naloxone could not reverse the effects Central mechanism was proved	29
Total fruit (aqueous fraction) 50 mg/kg	Morphine (10 mg/kg) Indomethacin (10 mg/kg) Dexamethasone (10 mg/kg)	Formalin test	No suppression in acute phase (because of low doses of extract) Pain relief in chronic phase with an inhibition of COX enzymes naloxone couldn't reverse the effects	39
Fruit (aqueous fraction) 20 mg/kg	Diclofenac (10 mg/kg)	Xylene-induced ear edema	Seeds have the most anti-inflammatory effect in chronic phase	18
Fruit (aqueous fraction) 250-500-700 mg/kg	Indomethacin (5 mg/kg)	Writhing test	Comparable visceral pain relief with NSAIDs	37
Fruit (aqueous fraction) 1-1.5 g/kg	Imipramine (40 mg/kg)	Hot-plate test	Comparable pain relief in chronic phase with imipramine	37

kg) and high doses (3150 mg/kg) can improve lesions of NSAIDs and ethanol, respectively. These properties are as effective as misoprostol and less operative than omeprazole. In histopathological examinations, no protective effect on stomach mucosa has been observed. In another study, aqueous extract of Russian olive imposed positive effects on pregnant mice. With doses as low as 640 mg/kg, fetal stomach cells became hypertrophic by gene regulation. In other words, *E. angustifolia* extract could reinforce fetus digestive system. There are also some evidences that Russian olive fruit extract can reduce gastric acid secretion simulated by cholinergic system in a dose and time dependent manner. Russian olive was shown to relax the muscle contraction of lumen and with its antioxidant effects; it works as a barrier on the surface of stomach against gastric mucosa.<sup>28,48-50</sup>

We can infer from this section that Russian olive ethanol extract is comparable with misoprostol on gastric ulcer lesions; it can reduce mucosal damage formed by aspirin, NSAIDs and alcohol like H<sub>2</sub> receptor blockers, but not as powerful as proton-pump inhibitors. With less side effects (especially no oxytocic property), Russian olive dosage forms or extracts can be administered before NSAIDs-intake or for pregnant women in controlled quantities.<sup>51</sup>

**Wound treatment**

In folk remedies, the extracts of Russian olive are known as a wound healing accelerator. If treatment of inflammation and proliferation is considered as the main steps of wound treatment, Russian olive fruit extracts can help in wound closure. It can increase the hydroxyproline content, improve the histological scores (epidermis regener-

ation, collagen deposition and proliferation), control the pain and inflammation and inhibit the cyclooxygenases I and II. Moreover, *E. Angustifolia* has a potent antibacterial property comparable with mupirocin 2% with added antioxidant activity. Phenolic compounds, mostly flavonoids are responsible for these effects. Vitamin A also plays important roles; the acceleration of cell replication, more collagen precipitation and induction of hyaluronate synthesis are the main effects of this vitamin in wound healing.<sup>39,52-55</sup>

**Antibacterial and antifungal effect**

In general, this plant shows lower overall antimicrobial effects in comparison to other similar species.<sup>56</sup> However, in some cases, extraordinary effects have been reported. Reported antifungal and antibacterial effects vary based on the dose used and the extraction method recruited. In an in vitro study, its leaf extract was used to treat mastitis pathogens.<sup>57</sup> These pathogens cause severe illnesses in domestic animals and by triggering steep decline in milk production result in vast economical loss.<sup>58</sup> Such illnesses are also classified as threatening to public human health.<sup>59</sup> They are caused by a group of bacteria such as *Staphylococcus aureus* and Coagulase Negative *Staphylococci* (CNS) which are susceptible to this plant's extracts.<sup>60</sup> In another study, four hospital germs were collected and tested in a disc diffusion method, and two soft extracts of leaves and flowers of Russian olive proved to have an intense antibacterial activity against wound germs (*S. aureus*), pharynx exudates (*Streptococcus pyogenes*), saliva (*Klebsiella pneumoniae*) and urine (*Escherichia coli*).<sup>61</sup> A brief review of antibacterial and antifungal activity of Russian olive is gathered in Table 4. In accordance with the

**Table 4.** Different extracts of *Elaeagnus angustifolia* and their effects on pathogens

	Aqueous	Ethanollic	Chloroform	Crude	n-Hexane	Methanolic
<i>Mastitis pathogen</i> <sup>60</sup>						√
<i>Staphylococcus aureus</i> <sup>62</sup>		√				
<i>Escherichia coli</i> <sup>62</sup>	√					
<i>Salmonella thyphimurium</i> <sup>57</sup>	√	√			√ (The most effective extract)	√
<i>Bascillusthurgiensis</i> <sup>56</sup>		√				
<i>Pseudomonas aeruginosa</i> <sup>62</sup>		√				
<i>Pseudomonas extorquous</i> <sup>56</sup>		√				
<i>Yersinia enterocolitica</i> <sup>63</sup>						√
<i>Candida albicans</i> <sup>57</sup>	√	√			√ (The most effective extract)	
<i>Aspergillus fumagatus</i> <sup>62</sup>				√	√ (The most effective extract)	
<i>Aspergillus favis</i> <sup>62</sup>	√	√			√ (The most effective extract)	
<i>Aspergillus niger</i> <sup>62</sup>		√			√ (The most effective extract)	
<i>Alternariasolan</i> <sup>64</sup>						√
<i>Bacillus subtilis</i> <sup>65</sup>	√	√			√	
<i>Shigelladysentriae</i> <sup>65</sup>	√	√			√	
<i>Vibrio cholerae</i> <sup>65</sup>	√	√			√	

importance of this plant in the traditional remedies, we considered some of its applications were related to its fungicidal and bactericidal properties. In ancient apothecary, it was said that *E. angustifolia* was administered to control the gull bladder problems and diarrheas. Gull bladder problems may be *E.coli* related or the table-listed gram negative bacteria could be responsible for the mentioned diarrhea and so on.

The exact mechanism of these properties is not clear, but most scientists believe in phenolic compounds,<sup>52,62</sup> alkaloids<sup>62</sup> and essential oils<sup>60</sup> as predominant reasons of being germicide in medical plants. Amongst its flavonoids, flavones like kaempferol, quercetin and isohamentin are deemed to provide such pharmacologic effects.<sup>52</sup> Flavonoids especially the ones with more lipophilic structures can penetrate into the cell wall of the bacteria easily and spoil its condensed structure. The intracellular components permeate and the bacteria are being killed. Another proposed mechanism is related to the complex of the flavonoids with active proteins of the bacteria with specific (covalent) or nonspecific (hydrogen or van der Waals) bonds and make critical changes in bacteria's function that may finally lead to the death of the microorganism.<sup>43</sup>

### Antioxidant effect

Most studies on *E. angustifolia* is related to its antioxidant capacity of phenolic compounds and antocyanosides. The highest content of total phenolic compounds can be extracted on the first 10 days of October, therefor the best time for harvesting Russian olive is exactly at this time in cases highest antioxidant properties are desired.<sup>66,67</sup> Apart from the seasonal changes, genotype is also important in the amount of antioxidant capacity. For *E. angustifolia* we know at least 7 genotypes (IEa1 to 7) in Iran.<sup>68</sup>

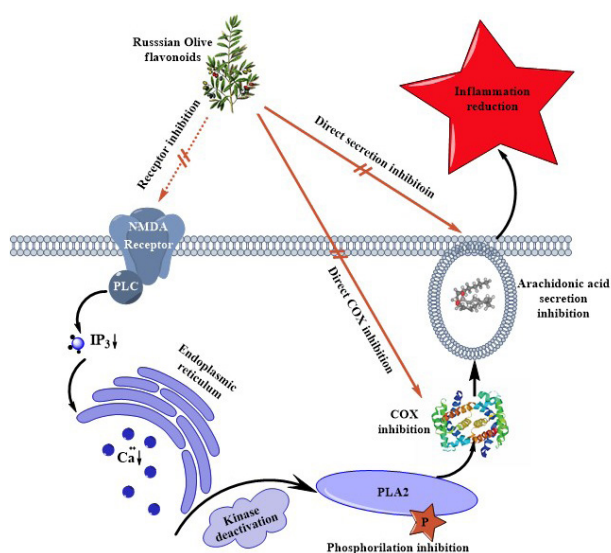
Polyphenols can suppress the oxidative stress produced by reactive oxygen species (ROS) with their hydroxyl groups. They can also chelate metals.<sup>69</sup> Antioxidant activity of raw

materials can be mainly evaluated in two methods: antioxidant capacity against of free radical species comprising of hydrogen atoms transfer reactions model (HAT), single electron transfer reactions model (SET) and a hydrogen-electron transfer models which is a mixture of HAT and SET methods; and antioxidant capacity against biological markers and characterized substrates.<sup>70</sup>

Oxygen radical absorbance capacity assay (ORAC), a HAT mechanism, is a core method in antioxidant studies. The senior method refers to the usage of  $\beta$ -phycoerythrin, a fluorescent hydrophilic probe, which was photo sensitive and caused false positive results. Fluorescein, eosin and 6-carboxyfluorescein with higher stabilities and more specific interactions with antioxidants are the probes of ORAC method.<sup>71</sup> Phenolic compounds and even vitamins of Russian olive can hydrogenate peroxy radicals of AAPH and increases the fluorescent emission strength. Among the extracts, water/ethanol (1:1) extracts of the leaves has the most potent antioxidant property. All in all, this method has exclusively been characterized to evaluate the antioxidant capacity of water-soluble phytochemicals and may not cover all aspects of this plant.<sup>72,73</sup>

Furthermore, 2, 2-Diphenyl-1-picrylhydrazyl (DPPH) radical assay based on Benvenuti *et al.* method is an available and cheap antioxidant analysis experiment. The stable and commercially accessible DPPH is a free radical that can accept hydrogens and electrons from polyphenols and also is one of the comparable methods of antioxidant measurement (Fig. 3).<sup>70,74</sup>

With an increase in the concentration and polarity of ethyl acetate extracts of Russian olive, its polyphenolic contents can clear DPPH radicals out up to 94%. It has been estimated and shown that its antioxidant ability is comparable with  $\alpha$ -tocopherol and BHT in terms of IC<sub>50</sub>. Polysaccharide contents of Russian olive comprising of monomers such as rhamnase, xylose, mannose, glucose and galactose can reduce DPPH free radicals up to 88.1%. From the con-



**Fig. 3.** Anti-inflammatory mechanism of *E. angustifolia*: Flavonoids of *E. angustifolia* can directly block active sites of COX and the secretion of the arachidonic acid. Thus, arachidonic acid cannot change into prostaglandins and leukotrienes, the most important mediators of vasodilation, platelet activation and inflammation (filled arrows). Another proposed mechanism describes the importance of flavonoids in blocking NMDA receptors. NMDA receptor inactivation leads to a significant calcium secretion reduction from PLC pathway and finally no kinase, PLA2 and COX activation, respectively (dashed arrow). (N-methyl-D-aspartate: NMDA, phospholipase C: PLC, inositol trisphosphate: IP3, phospholipase A2: PLA2, cyclooxygenase: COX)

centration point of view, polyphenols radical scavenging activity is more than ten times stronger than polysaccharides.<sup>75-78</sup> As a suggestion, it is better to define antioxidant ability of the raw materials with a standard chemical like Trolox instead of IC<sub>50</sub> or percentage. Trolox which can be the positive control in research projects and the minimum inhibitory concentration, can become a measure of comparison in chains of studies.<sup>63</sup> However, what we are sure about is that the antioxidant capacity of this plant has a linear correlation with the amount of phenolic compounds.<sup>79</sup> Phenolic compounds can be extracted from the methanol or ethanol extracts. They can donate hydrogen or electron and remove the free radicals. They reduce the amount of ROS by controlling the free-radical-producer enzymes like NADH oxidase, glutathione s-transferase and micro-

somal monooxygenase or chelating trace elements. Some of active ingredients of *E. angustifolia* such as epicatechin, catechin, rutin, quercetin and kaempferol with a hydroxyl group in seventh position of the 4-chromanone ring of the base structure have the maximum efficacy against oxidative groups.<sup>80</sup>

**Anti-neoplastic effect**

With an increase in concentration and polarity of *E. angustifolia* extracts, its anti-tumor effects level up. In an *in vivo* study on mice, elevation in immunity with increase in spleen index and thymus index manifestation has been reported as the main anticancer mechanism of Russian olive extracts. It has been shown that the anti-cancer properties are the effects of essential oils (ethyl cinnamate, 2-phenyl-ethyl benzoate, 2-phenyl-ethyl isovalerate, nerolidole, squalene and acetaphenone), flavonoids and proanthocyanosides.<sup>75,81,82</sup>

Moreover, the efficacy of Russian olive in inhibition of angiogenesis in Human umbilical vein endothelial cells may result in control of diabetes, retinopathy, rheumatoid arthritis and skin diseases like psoriasis in addition to malignancies.<sup>83,84</sup> Documented studies on Russian olive extracts in anti-neoplastic effects have been summarized in Table 5.

Flavonoids can down regulate mutant p53 genes (p53 wild gene is a regulatory gene that codes special proteins which control cell cycles and known as a tumor suppressor gene) and arrest the cell cycle in G2 or M in malignant tumors. At the same time, flavonoids can suppress the expression of Ras protein and control the heat shock proteins especially in leukemia and colorectal cancers. Quercetin, one of the main flavonoid compositions of *E. angustifolia* is known as an anti-proliferative agent because it can block the cell surface tyrosine kinases and stops the transfer of growth messages to the nucleus.<sup>43</sup>

**Muscle relaxant**

In traditional medicine, muscle relaxant effects of EA has been noted upon in different literature.<sup>16</sup> An *in vivo* study on mice to investigate such effects showed that polar extracts of this plant can exhibit dose dependent effects comparable to diazepam (2 mg/kg). It was suggested that flavones available in such extracts possess a partial agonistic effect on benzodiazepine (BDZ) receptors.<sup>88</sup> Flavones

**Table 5.** Anti-neoplastic effects of *Eaeagnus angustifolia*

Type of extract	Cell line	Considerations	References
Hydroalcoholic of flowers	Human umbilical vein endothelial cells(HUVEC)	<i>In vitro</i> inhibition of angiogenesis	84
Phenolic extract	Human colorectal adenocarcinoma cells(HT29)	<i>In vitro</i> control of colorectal cancers in different stages	85, 86
Ethanollic of leaves	Breast adenocarcinoma cell(MCF7)	<i>In vitro</i> studies showed no significant difference with control group	87
Ethyl acetate of the whole plant	Human cervical carcinoma cells (Hela)	<i>In vitro</i> study	75
Edible parts of the plants	Human hepatoma cells(HepG2)	<i>In vitro</i> and <i>in vivo</i> studies on H22 cells-bearing mice	81
Tincture of flowers	Walker 256 carcinoma cells	<i>In vivo</i> study on Wistar rats	69

especially the 6-substitution compounds have strong affinity with GABA<sub>A</sub> receptors; however flavones which are naturally synthesized, have partial agonistic effect on BDZ receptors. This mechanism is mainly described for the sedative compounds; but in this filed, the extract shows a pharmacological effect comparing to diazepam for controlling muscle contractions. After the activation of GABA receptors, chloride channels open and hyperpolarize cell membrane which prevents further excitations.<sup>89</sup> On the other hand, the same muscle relaxant effect is produced in smooth muscles of the intestine, due to the acetylcholine antagonizing effects of the said extract. This provides a means to treat intestinal colic pains.<sup>90</sup>

### Cardiovascular effects

Elaeagnin, one of the alkaloids of *E. angustifolia*, was reported as a blood pressure optimizer. It has a tetrahydroharman structure resembling reserpine on the basis of overlay studies of bioinformatics (Fig. 4). It can bind reversibly or irreversibly to the human monoamine oxidase A (MAO-A) active site and lower the blood pressure. As elaeagnin can fit with X-ray structure of harmine in MAO-A active site, theoretically, it would be effective as a blood pressure controller like reserpine (harmine in white and elaeagnin in yellow). On the other hand, aqueous leaf extracts of *E. angustifolia* with antioxidant property, can improve oxidative stress state brought by ischemic/reperfusion (I/R) in rats. This extract (0.5 mg/mL and 1 mg/mL) can reduce cardio toxicity of I/R and increase myocardial biochemical parameters. Altogether, this plant with possible reduction of blood pressure and enhancing the recovery of I/R can be a good choice in cardiac diseases but more studies needed.<sup>37,91</sup> ROS production is one of the main mechanisms of myocardial dysfunction and necrosis after I/R. superoxide dismutase (SOD) enzymes can control the radical species or ROS in myocardium. But, the problem triggers when the amount of ROS exceed the threshold limit of SOD. The leaves extract of *E. angustifolia* with polyphenolic compositions can reduce the activity of ROS, serum level of carbonyl groups and malondialdehydes with the molecular mechanism described in Fig. 5 and increase the ability of SOD to control the oxidative stress.<sup>92</sup>

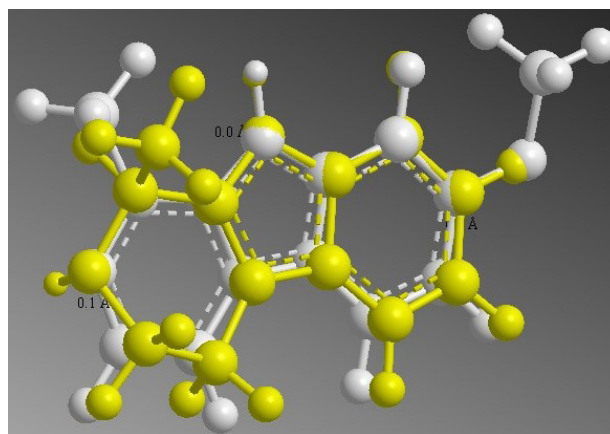


Fig. 4. Overlay of elaeagnin (the active component of *E. angustifolia*) and harmine

### Other medical applications

In animal models, aqueous extract of *E. angustifolia* can improve cognitive disorders. Tamtaji *et al.* treated the scopolamine-induced alzheimeric rats with increased doses (50-100-200-400 mg/kg) of Russian olive and resulted in significant improvements of special learning and memory.<sup>93</sup>

In a randomized clinical trial, females with orgasmic disorders received flower extract of *E. angustifolia* (4.5 g/D in 2 doses) and sildenafil citrate (50 mg, 1 h before intercourse), female sexual function and the levels of prolactin and TSH was measured after 4 weeks' treatment. Hormonal levels were found to remain even. Although Russian olive was less functional than sildenafil, it was effective in reduction of the frequencies of orgasmic disorders. The mechanism is not clear, but it may be the result of NO rise and subsequently cGMP increase in cells. It may cause vaginal smooth muscle relaxation, artery vasodilation and finally swelling of genital system.<sup>94</sup>

The effects of Russian olive in treatment of gastrointestinal problems have been proved. It may also be operative in ulcerative colitis and help to prevent cancers. Histopathological studies in rats with induced ulcerative colitis presented a significant improvement with edible extract (600 mg) and less improvement with the enema gel containing 20 percent extracts of Russian olive.<sup>95</sup>

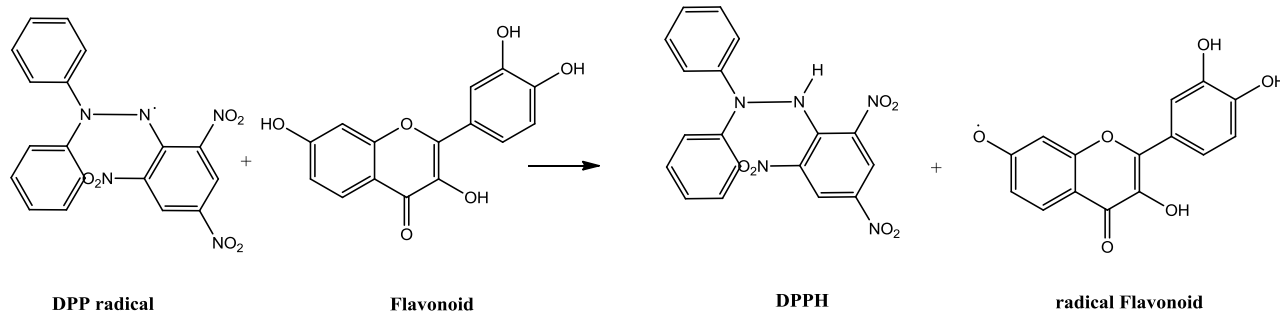


Fig. 5. Free radical scavenging mechanism of flavonoids.



### Drug formulation

Using herbal compounds as drug carriers due to their lower side effects is a good step forward.<sup>96</sup> In this category, several studies have been carried out using dried extract to transport calcium carbonate, naproxen and ibuprofen trying to increase drug wetting, prevent caking, increase particle surface and increase drug dissolution speed. These efforts are expected to result in increased blood concentration of medicines. Nanocapsules containing calcium carbonate and EA in addition to other formulation improvements in comparison to calcium carbonate nanocapsules and calcium carbonate tablets result in higher calcium blood levels. Solid dispersions containing naproxen and ibuprofen show higher analgesic and anti-inflammatory effects. Despite its lower efficacy, in comparison to chemicals such as cross povidone, extracts of this plant are still more favorable, in large part due to less documented side effects.<sup>97-99</sup>

Moreover, 6% soft extract of Russian olive can be useful in cream formulations. In addition to the antioxidant and anti-inflammatory effects for wound healing, it helps the spread capacity and thixotropic properties of cream or ointments bases. The best formulation for the extract insertion is an anionic base (oil/water emulsions).<sup>69,100,101</sup>

Russian olive extracts have also been inserted in topical gels for oral lesions. Clinical studies on 28 patients with oral lichen planus resulted in considerable decrease of lesion size and pain. Minerals and vitamins especially vitamin K with its efficacy in blood coagulation play main rolls in this matter.<sup>102</sup>

### Use in pregnancy controversies

Previously, in traditional benefits of Russian olive, it was described that its extract can be useful for the treatment of rheumatoid arthritis. Pregnant women were among the suggested groups by the alchemists to use this extract against pain, inflammation and all problems in their joints and bones. Recent studies have shown the disadvantages of the fruit extract on the embryo osteogenesis and chondrogenesis. Although this extract does not reduce the amount of calcium, it reduces the volume of bones and cartilages. In contrary, mouse embryos showed a significant increase in femur length. The exact mechanism is not clear, but we can say phytoestrogens like flavonoids and tannins may inhibit non-classic estrogen signaling pathway, G protein receptor 30 (GRP30), and exert these effects in a dose depending manner. To end up, Russian olive extract can improve osteogenesis and chondrogenesis, but may decrease bone mass in mouse embryos, although it makes no craniofacial malformation or limb abnormalities.<sup>48</sup> Therefore, in this case, pregnant mothers should avoid the traditional remedies for joint and bone disorders.<sup>103</sup>

### Possible adverse effects

Russian olive is among the safest trees in the world and apart from possible allergies, there is no other hazard reports. Even though it is rich in heavy metals such as Cr,

Pb, Zn, Cu, Ni and Co, some researches proved that in any condition of harvesting, the amount of heavy metals in all parts of the tree will not exceed the WHO limits (based on WHO guideline: the permissible limit of Cr, Pb, Zn, Cu, Ni and Co in medicinal plants is 1.5, 10, 50, 10, 1.5 and 0.2 part per million, respectively).<sup>62,104</sup> Even in an investigation on pregnant mice, *E. angustifolia* extracts made no significant differences in weight and CRL of mice fetus; but, because of the effects of concentrated extracts on bones and cartridge volumes, especially in pregnant women, more consideration may be needed.<sup>48</sup>

### Allergenicity

Russian olive is common as a wind-cutting tree in American and European countries, so its pollens would spread widely in the cities especially in the pollination season, spring. In an investigation, Ole e 1 and Ole e 4-like allergens, major allergens in olive pollen,<sup>105,106</sup> were recognized in this plant. With a prick test, 30 % of patients with rhinitis and rhinoconjunctivitis were sensitive to Russian olive pollens and 44 percent of patients with sensitivity to pollens have positive Prick tests. With these findings and the fact that its pollen size is much greater than grass and olive pollens (40-50 µm), it can be concluded that *E. angustifolia* is one of the major causes of allergies in the cities.<sup>107</sup> The mechanism which triggers these reactions is an IgE-mediated type II allergic type.<sup>108</sup>

Moreover, dermatitis caused by contact with *Elaeagnus* sp. has already been reported; but, mostly among florists with repeated contact.<sup>109</sup>

### Concluding remarks

Utilizing the unlimited natural sources of medicines with the least restrictions of safety is one of the human beings goals. In this area, *E. angustifolia* can fulfill these objectives. This plant is a riparian tree considered as a N2-fixer herb, increases the nitrification of the soil (inorganic nitrogen).<sup>110</sup> It is rich in water and fat soluble vitamins, flavonoids, carbohydrates, alkaloids and biological active lipids. This review aimed to gather ethnopharmacological properties of *E. angustifolia* with focus on active constituents and medical benefits, and also make suggestions for future plans. For this purpose, almost all the medical articles from 1970 to 2016 were collected from various databases such as Embase, NCBI, Science Direct and Scopus. The most important and peer-reviewed information were analyzed and classified judiciously.

For years, *E. angustifolia* was used as an astringent, kidney stone removal, anti-inflammatory and pain relief agent. It was a well-known remedy for fever, jaundice, asthma, tetanus and rheumatoid arthritis. In turkey, *E. angustifolia* was an appetizer and a source of nutrition. It can be a food additive; as in an experiment by Cakmakc *et al.* addition of the flour and crust of the fruits as a flavor and formulation optimizer (viscosity enhancement) in an ice cream have showed perfect results. In food industry, natural plants with antioxidant properties can result in vast commercial advertisements.<sup>111</sup>

Effects of Russian olive on inflammation and pain have been studied the most. More than 4 clinical trials are available and all of them have reported a comparable efficacy as NSAIDs. Total fruit has muscle relaxant capacity in a dose-dependent manner comparable to that of diazepam, COX inhibition property like indomethacin and ibuprofen, and is full of kaempferol that can suppress inflammation mediators.

A number of experiments have evaluated its active constituents for their applications in malignancies, ulcers, gastric problems and osteoarthritis. Previous studies showed that even in injection forms in mice and rats, there is no significant immunological responses (as the corticosteroid levels were even),<sup>39</sup> this plant can even be applied in developed injection formulations for special applications like intra-articular vials.

In “experimental and clinical studies” section, the *E. angustifolia* extract was suggested as blood pressure optimizer, because of special structure similarity of elaeagnin to hamine and reserpine. Till now, no supported studies have proved it; perhaps due to the time-consuming mechanism of reserpine in controlling blood pressure. As known, reserpine blocks MAO irreversibly and then increases the amount of neurotransmitters in the synaptic cavity; this elevation of neurotransmitters lead to down regulation of the vascular receptors and decreases blood pressure subsequently. The aforementioned process is a long-lasting effect. None of the clinical studies of *E. angustifolia* extract consider time as a major factor in cardiovascular protective properties of the plant.<sup>112</sup>

Flavonoids of this plant are so hydrophobic. Lots of *E. angustifolia* medicinal benefits are related to this property of flavonoids. Anti-bacterial effects are one of them. Flavonoids can penetrate the cell membrane of the bacteria and exert their destructive effects. In most cases, aggregation of bacteria was seen. Some of its flavonoids like kaempferol and quercetin show slight  $\beta$ -lactamase inhibitory effects, as well. As presented in Table 4, the main antibacterial properties are related to the methanol or ethanol extracts.<sup>113</sup>

The lack of evidence on the relation of the medical applications and detailed structure of constituents, conceal its exclusive properties. There are no reports on experimental studies of pharmacologic/toxicologic effects of a few compounds like elaeagnine or elaeagnoside that are found in this plant. The gastroprotective effects of the plant appear to lead us towards development of medicines comparable with misoprostol. As for the anti-neoplastic effects or bactericidal effects, this plant can be a source of inspiration for rational drug design and medicinal chemistry. As a matter of fact, around 85 percent of chemotherapy agents have natural sources.<sup>114</sup> However, the lack of clinical studies on this plant has limited its availability in drug forms. It is certain that further studies would be necessary to fill such information paucity and gap.

#### Ethical approval

There is none to be declared.

## Review Highlights

### What is current knowledge?

✓ *E. angustifolia* can be a source of bioflavonoids that are so applicable in controlling pain and inflammation.

✓ Active ingredients of *E. angustifolia* can even be useful as anti-cancer, anti-bacterial and anti-fungal medicines.

✓ The protective properties of *E. angustifolia* extract in gastrointestinal system became clear.

### What is new here?

✓ The relationship between its active ingredients and medical properties are not mechanistically clear; but there are some evidences in participation of the flavonoids of Russian olive in controlling enzymes (COX) or blocking the receptors (NMDA-R or BDZ-R).

✓ One of the possible mechanisms in which active ingredients of Russian olive may decrease the blood pressure, have been discussed.

✓ No critical and significant side effects of this plant (even in high doses) have been reported.

#### Competing interests

There is none to be declared.

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