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REGULATING MECHANISM OF BLOOD PRESSURE BY THE HAWTHORN AND OLIVE PHYTO- AND GEMMO-THERAPIC EXTRACTS

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Abstract: The Hawthorn and Olive are known from ancient time as phytotherapics with beneficial effect on heart and circulatory system, decreasing or regulating the blood pressure. By HPLC analysis were identified polyphenols with proved effect on angiotensin converting enzyme (ACE), the key compound of blood pressure regulation through renin-angiotensin-aldosterone system. The chlorogenic acid, caffeic acid, luteolin, quercitrin and even hyperosid, have the structural elements to block the active center of ACE. Due by the fact that these compounds are in significant quantities, we can conclude that these phyto- and gemmotherapic extracts's normo- or hypotensive effect is done also by the mechanism of ACE inhibition.

Keywords: hawthorn and olive gemmotherapic extracts, hawthorn phytotherapic extracts, HPLC, ACE inhibition, renin-angiotensin-aldosterone system.

INTRODUCTION

Hawthorn is represented in our region mainly by the species *Crataegus monogyna* Jacq. and/or *Crataegus oxyacantha* L., being a medicinal plant known since ancient times for its beneficial properties on the heart. In classical phytotherapy, it has been used for centuries to treat various cardiovascular diseases, which are now the main cause of morbidity and mortality, especially early mortality, in the developed world (Drăgulescu *et al.*, 2020).

Studies show that after the year 2000, the use of plant-based food supplements became widespread and that today there is a growing trend towards their use in the elderly, noting that at least 30 to 35% of people with cardiovascular disease use a Hawthorn-based supplement (Tassel *et al.*, 2010).

Phytochemical analyses have revealed that Hawthorn contains polyphenols of the flavonoid and proanthocyanidin classes, bioactive compounds that have specific effects on the cardiovascular system. From Hawthorn species usually there are used the leaves and inflorescences (when flowering), or the fruit, respectively, and these phytoconstituents are present in all these parts. Phytochemical studies indicate a higher concentration of flavonoids, particularly hyperoside, in the fruit and leaves; the flowers contain more of another flavonoid, vitexin-2-ramnoside (Kingston, 2007). Flowers have a higher flavonoid content, while leaves contain mainly oligomeric procyanidins (Mills *et al.*, 2000; Vanhelen *et al.*, 1989).

Hawthorn's polyphenols give it strong antioxidant activity. Hawthorn has been shown to improve the activity of enzymes such as superoxide dismutase and catalase, protect *alpha*-tocopherol and inhibit the activity of tyrosinase, lipooxygenase and superoxide and hydroxyl radicals, respectively (Guo, 2003; Yoo, 2007; Ljubuncic *et al.*, 2005).

Hawthorn's hypotensive effect is partly due to its antioxidant activity, but also to its spasmolytic effect, which relaxes the endothelium by stimulating nitric oxide (NO) synthesis, an effect due mainly to procyanidine oligomers. The relaxing effect on the vessels is also explained by a reduction in the level of circulating catecholamines and a decrease in peripheral vascular resistance (Wojdyto *et al.*, 2006; Brixius *et al.*, 2006; Tsuyaki, 2000; Orhan, 2007; Vierling *et al.*, 2003). Another mechanism involved in this effect is the moderate inhibition of angiotensin-converting enzyme (ACE) (Cui *et al.*, 2006).

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Another biological effect of hawthorn, linked to the cardiovascular system, is its anti-atherosclerotic effect, which is due to the antioxidant effect of polyphenols (Wojdyto *et al.*, 2006), inhibition of capase-3 gene expression (Ling, 2007), regulation of lipoprotein lipase expression (Fan *et al.*, 2005) and inhibition of thromboxane A2 synthesis. A decrease in the activity of intestinal acyl-coenzyme A-cholesterol-acyltransferase has also been observed, leading to a reduction in the absorption of dietary cholesterol (Zhang, 2002).

Hawthorn also acts on the myocardial cell by increasing coronary flow and relaxation velocity, as well as having a moderate inotropic effect and moderately increasing heart rate. Due to its inhibition of 3',5'-cAMP phosphodiesterase, it has a negative chronotropic and antiarrhythmic effect (Schüssler *et al.*, 1995; Long *et al.*, 2006).

Clinical studies have confirmed the beneficial effect of hawthorn-based products in various cardiovascular diseases, and the hypotensive effect is mainly due to antioxidant mechanisms, an ACE inhibitor and, to a lesser extent, beta-adrenergic receptor blockade. Interaction studies with digoxin and other drugs indicated for heart failure have demonstrated the safety of co-administration with hawthorn products (Tassel *et al.*, 2010).

The olive tree, *Olea europaea* L., is another species widely used in the treatment of cardiovascular diseases. As well as tasty drupes, olive leaves have been shown to be an important source of polyphenols - flavonoids such as luteolin, kaempferol, apigenin and their derivatives; phenolic acids such as caffeic acid, ferulic acid; coumarins such as esculin, scopoletin (PDR, 2007). In addition to these components, olive leaves contain chalcone and tannins also, hydroxytyrosol, oleuropein and triterpenes such as oleanolic acid (Filtonic *et al.*, 2012).

Polyphenols from various species have been shown to have a number of biological effects at vascular level. Firstly, they relax the endothelium by competitively inhibiting e-NO synthetase and guanylate cyclase respectively (Fitzpatrick *et al.*, 1993; Schini-Kerth *et al.*, 2010). They also inhibit the synthesis of angiotensin II by inhibiting NADPH oxidases, which are associated with oxidative stress and hypertension (Sarr *et al.*, 2006).

Olive's antihypertensive effect is due in part to its polyphenols, but also to oleuropein. Polyphenols relax vascular smooth muscle by blocking calcium channels or through a calcium antagonist effect (Somova *et al.*, 2003; Scheffler *et al.*, 2008). They also have an anti-platelet effect and inhibit the synthesis of thromboxane A2 (Petroni *et al.*, 1995). Polyphenols and oleuropein have antihypertensive and ACE inhibitory effects (Hansen *et al.*, 1996), and oleuropein and oleanolic acid also have cardioprotective activity (Andreadou *et al.*, 2006; Andreadou *et al.*, 2007).

After the 1940s, a new branch of phytotherapy appeared on the scene, which is now part of the current trends in this field in terms of obtaining extracts using fresh plant material: phytoembryotherapy or, better known, gemmotherapy or, under the more correct name - meristemotherapy. This new form of phytotherapy uses undifferentiated meristematic tissues to obtain stronger, more valuable therapeutic effects than with extracts used specifically in traditional phytotherapy. Hawthorn and olive extracts are also used in gemmotherapy, obtained from the meristems found in young shoots. Observations have also revealed beneficial effects on the cardiovascular system in the case of these gemmotherapeutic extracts (Pitera *et al.*, 2018).

The aim of this article is to compare the phytochemical profile of phytotherapeutic extracts of Hawthorn, and gemmotherapeutic extracts of Hawthorn and Olive, in order to establish from these profiles the mechanism of action in regulating blood pressure.

MATERIALS AND METHODS

Plant material and extracts

Commercial products manufactured by SC PlantExtrakt SRL, Rădaia (Cluj County, Romania) were used.

The gemmotherapic extracts of the young shoots of Hawthorn (EGP) and Olive (EGM) were manufactured according to the standard method of the French Pharmacopoeia and the European Pharmacopoeia (the editions in force), processing fresh plant material from the spontaneous flora of the Cluj region, for Hawthorn, respectively from crops, from the south of Italy, for Olive.

The phytotherapic extracts were obtained from hawthorn flowers and leaves (EFFP) and hawthorn fruits (EFP) respectively, in the form of hydroalcoholic solutions from fresh plant material, in accordance with the European, French and German homeopathic pharmacopoeias.

Analysis by high performance liquid chromatography (HPLC)

Apparatus: Shimadzu Nexera-I HPLC, Japan.

Column: Fortis C18, 150 x 2.1 mm x 3 m.

Mobile phase: gradient with mixture - purified water with 0.1% formic acid and acetonitrile. The aqueous phase decreased from 80% to 10%, and in the last few minutes increased again to 20% and then to 80%.

Elution rate: 0.8 ml/min.

Control solutions: chlorogenic acid (0.16 mg/ml), caffeic acid (0.10 mg/ml), hyperoside (0.17 mg/ml), quercitrin (0.11 mg/ml), luteolin (0.10 mg/ml), luteolin-7O-glucoside (0.16 mg/ml), all prepared in HPLC-grade methanol.

Test solutions: individual extracts were diluted every 1 ml to 50 ml with methanol.

Injection volume: 5 ul from control and test solutions.

Detection: DAD detector at 320 nm for phenolic acids and 360 nm for flavonoids (Criste *et al.*, 2020).

RESULTS AND DISCUSSION

Following HPLC analysis, we identified a series of polyphenols on the basis of retention times and absorption maxima in the UV-Vis spectra. The results are presented in Table 1 and Figure 1.

The results show a high degree of similarity between the parameters of the controls and the compounds separated from the extracts, so we can conclude that these polyphenols have been identified.

The results of the quantitative assessment are presented in Table 2. These results indicate a significant amount of chlorogenic acid in both extracts, most of it in the hawthorn gemmotherapic extract.

Table 1.

The results of qualitative HPLC analysis

Samples		Retention time, min	Maximum absorption wavelength(s), nm
Standards	Chlorogenic acid	6,53	242, 326
	Caffeic acid	7,43	242, 323
	Hyperoside	15,33	256, 355
	Luteolin	20,78	254, 350
	Luteolin -*7*-*O*-glucoside	14,44	255, 349
	Quercitrin	17,65	257, 350
EFFP	Chlorogenic caid	6,49	325
	Luteolin	20,62	256, 350
EFP	Chlorogenic caid	6,51	329
	Caffeic acid	7,31	325
EGP	Chlorogenic caid	6,51	242, 327
	Hyperoside	15,03	260, 353
	Quercitrin	17,52	260, 350
EGM	Chlorogenic caid	6,51	328
	Luteolin	20,63	260, 350
	Luteolin -*7*-*O*-glucoside	14,28	256, 350

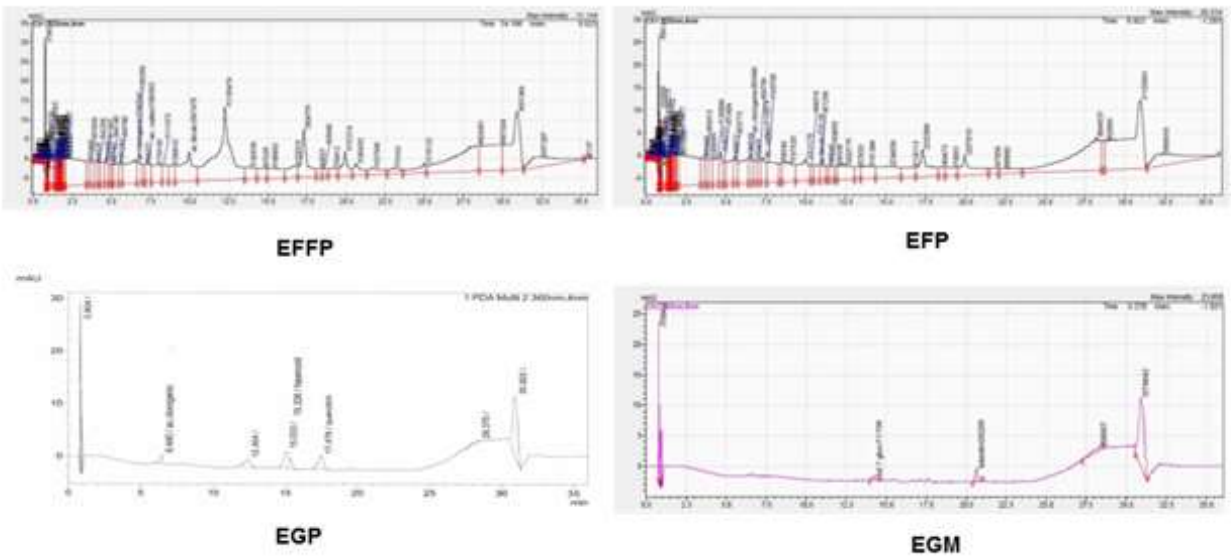

Fig.1. The HPLC chromatograms of the studied extracts.

Table 2.

The quantitative results of HPLC analysis

Samples	Content in individual polyphenols, mg/ml			
	Chlorogenic acid	Hyperoside	Luteolin	Luteolin -*7*-*O*-glucoside
EFFP	0,310 ± 0,0078			
EFP	0,089 ± 0,0004			
EGP	0,670 ± 0,0087	0,070 ± 0,0005	0,040 ± 0,0009	0,180 ± 0,0042
EGM	0,380 ± 0,0085			

Results are expressed in mean ± RSD.

The literature data indicate the primordial role of polyphenols in the biological effect of hawthorn and olive extracts (Tassel *et al.*, 2010; Scheffler *et al.*, 2008; Hansen *et al.*, 1996). The antihypertensive or blood pressure regulating effect is due to the effect on the endothelium, but also to the inhibition of ACE and calcium channels respectively. Binding simulations of polyphenols have shown that they can block the

catalytic center of the enzyme (ACE) due to phenolic groups.

ACE has a zinc ion in the catalytic center (Sturrock *et al.*, 2004), which can be coordinated by the non-participating electron pairs of the neightbouring phenolic oxygen on the benzene ring not condensed with other rings. The zinc ion is bound to the protein structure of the enzyme by histidine residues, which in turn bind to other amino acid residues. The peptide chain of the enzyme has tyrosine residues in the loop of the catalytic center that can interact with the phenolic groups present on the rest of the polyphenol molecule. By blocking the loop with the catalytic center of ACE, the polyphenols inhibit its activity and therefore the entire biochemical process in which this enzyme is involved. Figure 2 shows the formula of the polyphenols identified, and Figure 3 the possibilities of binding to ACE.

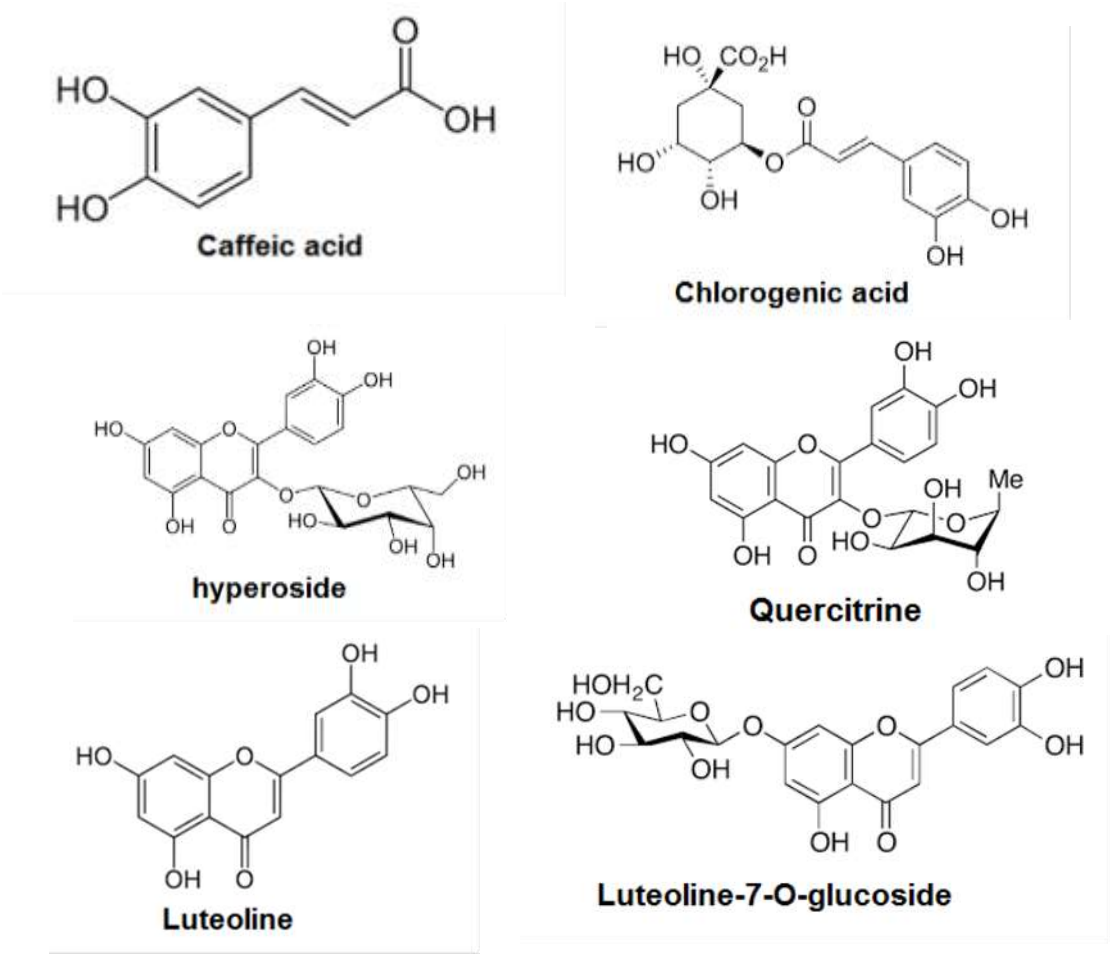

Fig. 2. The formula of identified polyphenols.

The images indicate the possibility of strong blocking of the ACE active site by coordination bonds from the phenolic oxygen to the zinc ion, but also by hydrogen bonds with the free phenolic hydroxyl of the tyrosine residues. The bonds are strong both for phenolic acids such as caffeic or chlorogenic acid and for flavonoids, in particular luteolin (aglycone) and the derivative -luteolin-*7-O*-glucoside (flavonoside).

The images indicate the possibility of strong blocking of the ACE active site by coordination bonds from the phenolic oxygen to the zinc ion, but also by hydrogen bonds with the free phenolic hydroxyl of the tyrosine residues. The bonds are strong both for phenolic acids such as caffeic or chlorogenic acid and for flavonoids, in particular luteolin (aglycone) and the derivative -luteolin-*7-O*-glucoside (flavonoside). Therefore, the blood pressure regulating effect by inhibiting ACE can be confirmed in hawthorn and olive tree gemmotherapic extracts, which has been confirmed by previous research on phytotherapeutic extracts of these species (Cui *et al.*, 2006; Hansen *et al.*, 1996; Guerro *et al.*, 2012).

Based on the results of this study, we can propose a mechanism of action for gemmotherapic extracts of Hawthorn and Olive.

We know that the body regulates blood pressure in several ways:

- regulating diuresis, by retaining water or reducing the volume of liquid in the blood vessels;
- acting on specific receptors of the sympathetic nervous system, alpha- and beta-adrenergic receptors;
- by the renin-angiotensin-aldosterone system, by blocking the transformation of angiotensin into its

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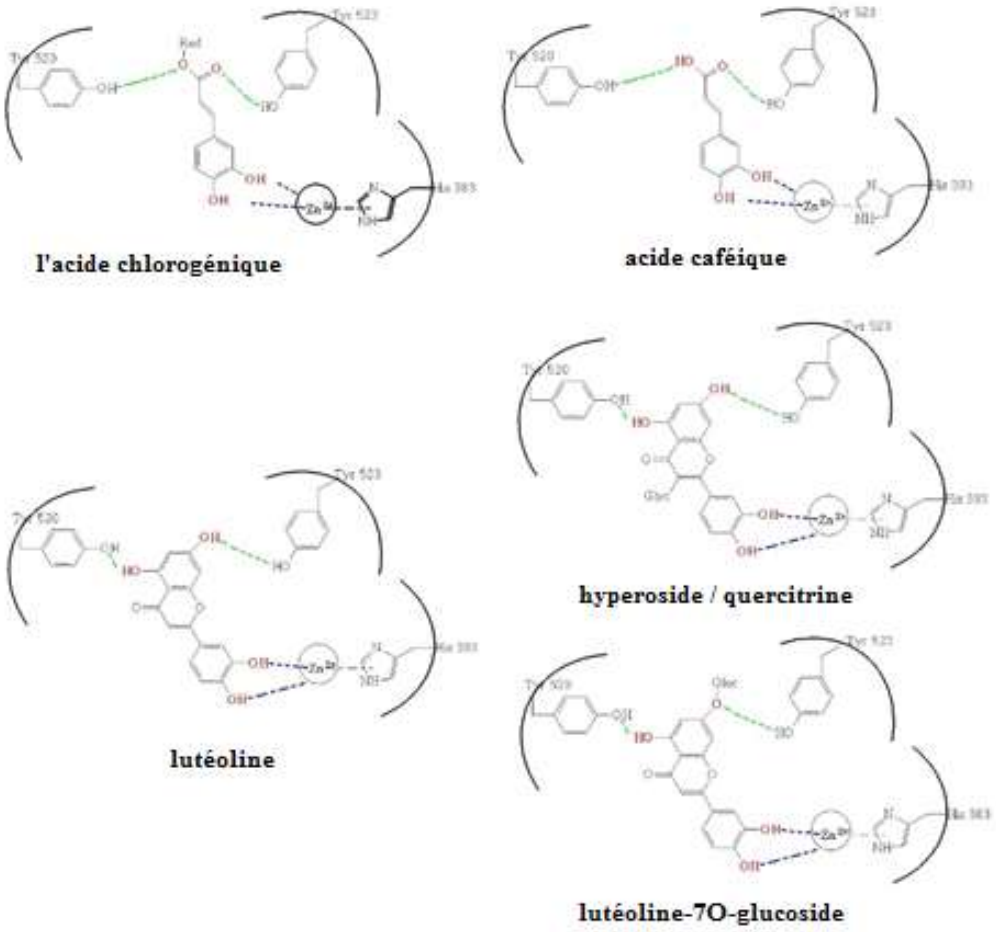

Fig. 3. The docking possibilities of identified polyphenols to the catalytic center of ACE. Coordinative bounds (pointed blue lines), hydrogen bounds (pointed green lines).

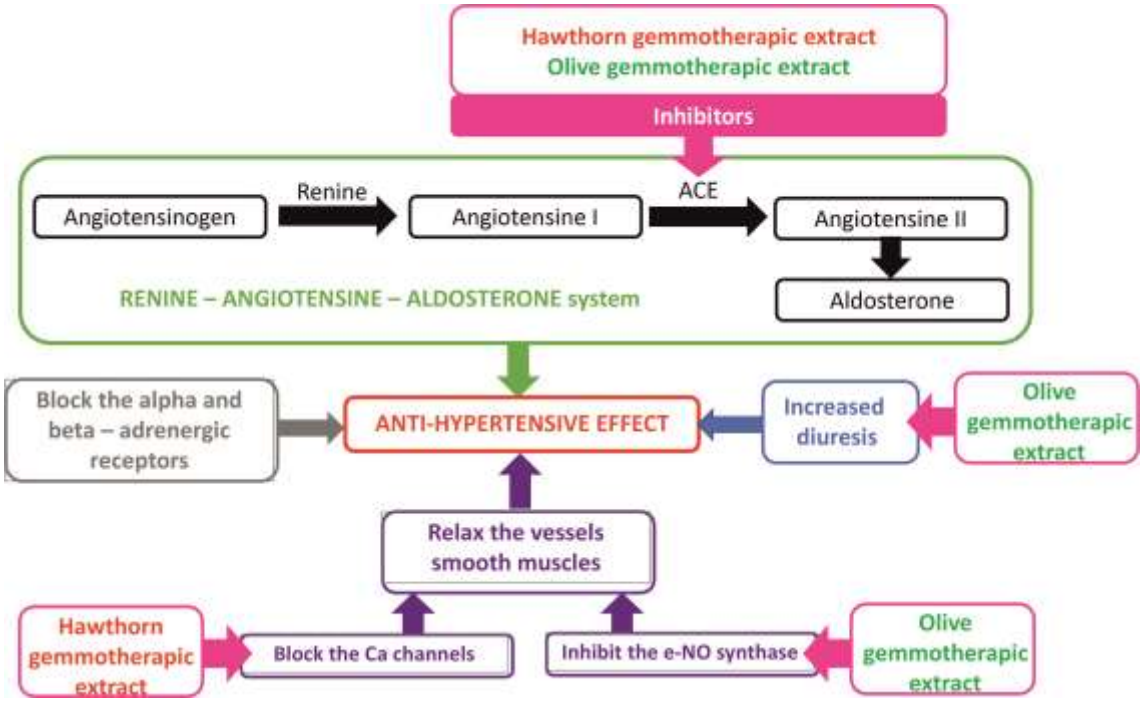

Fig. 4. Proposed involvement of Hawthorn and Olive gemmotherapic extracts in the regulation of elevated blood pressure.

active form or by acting on specific angiotensin II receptors (active form);

- acting on vascular smooth muscle, by relaxation or contraction, whether or not by blocking the calcium channels that regulate the balance of intra- and extracellular calcium concentrations, or by influencing the synthesis and release of NO.

On the basis of the results of this study and the data in the literature, we can conclude that (Fig. 4):

- hawthorn gemmotherapic extract will regulate blood pressure by inhibiting ACE, respectively endothelial relaxation by inhibiting e-NO-synthetase, an effect due to the polyphenols identified;

- olive gemmotherapic extract will regulate blood pressure by moderately increasing diuresis, relaxing blood vessel smooth muscle by blocking slow calcium channels, an effect due to the polyphenols, oleuropein and oleanolic acid, and ACE inhibition due to the phytocomplex as a whole.

CONCLUSIONS

Our study has elucidated part of the phytochemical profile of extracts of different vegetative parts of hawthorn and young shoots of olive; on the basis of this profile, data from the literature and simulation of the ACE binding of the compounds identified, we have succeeded in proposing a plausible mechanism of action for gemmotherapic extracts, which are less well known and studied.

Gemmotherapic extracts of Hawthorn and Olive regulate blood pressure by complex mechanisms involving several natural blood pressure regulation pathways in the human body. As a result, they may be of particular therapeutic value in patients suffering from complicated hypertension. It should be noted, however, that these extracts will be less effective in patients whose hypertension is due to excessive stimulation of adrenergic receptors.

AUTHORS CONTRIBUTIONS

*C*onceptualization: N.K.O, D.H., L.I., V.T. and E.M.; methodology, F.R.P.F., R.F.B., E.C. and V.B.B.; data collection A.A., I.M.H.C and O.U.; data validation, G.G.A, V.T. and E.M.; data processing N.K.O. and V.B.B..; writing—original draft preparation, A.A.; writing—review and editing, N.K.O., V.T. and E.M.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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