REVIEW

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Coumarins as potential supportive medication for the treatment of epilepsy

Jarosław Bryda[1,2], Mirosław Zagaja[2], Aleksandra Szewczyk[2] and Marta Andres-Mach[2]*

[1] Department of Veterinary Hygiene, Voivodship Veterinary Inspectorate, Lublin, Poland,
[2] Isobolographic Analysis Laboratory, Institute of Rural Health, Lublin, Poland,
** E-mail: mandres@wp.pl*

Epilepsy, one of the most common neurological disorders, is a chronic disease of the brain manifested by seizures due to sudden, spontaneous bioelectrical discharges in nerve cells. An estimated 50 million people worldwide suffer from epilepsy. Antiepileptic drugs are the mainstream treatment for epilepsy; however, the drug resistance occurring in 20-30% of patients and side effects of available medications have resulted in a search for natural remedies that can support disease therapy. Coumarins may be a promising option. They are a group of natural plant-derived substances of great interest due to their broad spectrum of biological activities, including potent pharmacological properties. Recent data from experimental models demonstrates the possibility for coumarin use as a supporting treatment of epileptic seizures. This article focuses on the most recent research reports available in the literature relating to the use of several selected coumarins in different experimental models of epilepsy.

Key words: coumarins, antiepileptic drugs, epilepsy

INTRODUCTION

Coumarins are organic, biologically active compounds belonging to the benzopyrone family (1,2-benzopyrones or 2H-1-benzopyran-2-ones). They are divided into four subtypes based on their chemical structure. Simple coumarins are formed by benzene rings fused with α-pirons which are hydroxylated, alkoxylated or alkylated at the C7, C6 and C3 positions of benzopyrone. Isocoumarin derivatives are formed by two rings: benzene and α-isopirone with substituents in positions C3, C6, C7 and C8. Furanocoumarins, consisting of a five-membered furan ring fused with coumarin, are divided into two types – psoralen, at the C6-C7 positions, or angelicin, at the C7-C8 position. Pyranocoumarins, with substituents, condense a six-membered pyran ring with a coumarin ring at the C6-C7 position (Mead et al., 1958; Jain et al., 2012; Medina et al., 2015). Variable chemical structures and a diversity of substitutions in the skeleton affect the diverse pharmacological activities of coumarins (Kumar et al., 2015; Kubrak et al., 2017). Coumarins are mainly found in secondary plant metabolites, acting as growth regulators, controlling biochemical transformations and demonstrating defensive properties against infection (Chattha et al., 2018). They are also found in some bacteria, fungi or sponges and can be synthesized chemically (Matos et al., 2015).

Coumarins and coumarin-related compounds possess a wide range of pharmacological profiles. Their properties and their impact on the cardiovascular system (Najmanova et al., 2015), nervous system (Skalicka-Woźniak et al., 2016), body immunity (Rohini et al., 2014) and digestive system (Popp et al., 2017) are currently being researched. New derivatives are still being discovered and synthesized due to their potential uses.

Recent studies have revealed the effective use of coumarins in cancer therapy as medicaments and for

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mitigating the effects of radiotherapy (Rohini et al., 2014). One of the most common coumarins, warfarin (4-hydroxycoumarin), is used in medicine as an oral anticoagulant (Kumar et al., 2015). Antitumor activity has been demonstrated for osthole in the suppression of the spread of breast cancer cells. Tests with bioluminescence have shown that osthole inhibits the promoter of matrix metalloproteinase-2 (MMP-2) and indirectly inhibits the activity of this enzyme, which may lead to inhibition of tumor migration (Yang et al., 2010). Anticancer properties were also exhibited by imperatorin, esculetin, chartreusin and fraxetin with various mechanisms of action (Luo et al., 2011). Interestingly, coumarins have been shown to possess strong anti-inflammatory properties. This is due to their antioxidant activity and effect on reactive oxygen species. Esculetin exhibited protective effects on rat intestines in colitis (Witaicenis et al., 2010). In other studies, extracts used externally have been shown to reduce skin inflammation and edema (Kwon et al., 2011). Derivatives such as esculetin, fraxetin and daphnetin exhibit antioxidant activity, acting as inhibitors of the lipoxygenase and cyclooxygenase enzyme pathways (Kirsch et al., 2016). *In vitro* studies on coumarin compounds have served to demonstrate their antimicrobial and antifungal activity. Tests carried out on *Staphylococcus aureus*, *Bacillus subtilis* and *Escherichia coli* strains revealed a much stronger antibacterial effect of synthetic coumarin compounds compared to several conventional antibiotics (Vyas et al., 2012). Much research has been devoted to the effect of coumarins on the central nervous system (CNS). Therefore, numerous experimental studies focus on disorders such as epilepsy, schizophrenia, depressive and anxiety disorders or Alzheimer's disease (Skalicka-Woźniak et al., 2016).

Possible anticonvulsant properties of natural coumarins

Epileptic seizures are the result of excessive abnormal neuronal activity in the brain. The primary treatment for epilepsy is the administration of antiepileptic drugs (AEDs). These drugs reduce the frequency of seizures and help patients control seizure occurrence. Unfortunately, a significant proportion of patients exhibit little or no improvement with current drug therapies. Moreover, the issue of chronic side effects due to the drugs is also significant (Sharma et al., 2013).

Experimental epileptic models are used to assess the activity of potential anticonvulsant drugs and enable an estimation of the clinical profile of a substance's action on the CNS. One of the basic *in vivo* animal models for assessing potential anticonvulsant properties of drugs is the maximal electroshock seizure (MES) test in rodents (Castel-Branco et al., 2009). It allows for the modeling of specific pharmacodynamic effects required to protect against seizures. Additionally, it is possible to assess the bioavailability of a given substance based on the analysis of its concentration in specific brain structures in post-mortem tissue preparations (Rogawski et al., 2006).

Anticonvulsant effects of coumarins are likely related to their influence on the ionotropic receptor for γ-aminobutyric acid (GABA). This was demonstrated by studies in which furanocoumarins were found to be partial benzodiazepine receptor antagonists, inhibiting the binding [^{3}H] of diazepam to these receptors (Singhuber et al., 2011). In this study, which examined the effects of eighteen furanocoumarins on GABA-induced chloride currents (I_{GABA}), seven compounds showed a greater than 20% enhancement of I_{GABA}. Similar results were obtained in studies of coumarins isolated from *Angelica pubescens (L.)* that described their $GABA_A$ receptor-modulating activity (Zaugg et al., 2011). *In vivo* analysis of the anticonvulsive activity of coumarins suggests they may indirectly act to increase GABA concentration in the CNS by affecting the activity of glutamic acid decarboxylase (Luszczki et al., 2007a; Singhuber et al., 2011; Zaugg et al., 2011).

Recent research provides evidence of positive supporting effects for coumarin compounds on the conventional AEDs (Table I, Table II). The promising pharmacological activity was demonstrated by the simple coumarins osthole and umbelliferone and also by several furanocoumarins – xanthotoxin and imperatorin (Luszczki et al., 2007a; 2009; 2010; 2011).

Osthole

Osthole (7-methoxy-8-(3-methyl-2-butenyl)-2H-1--benzopyran-2-one) is a simple natural origin coumarin, which occurs in several medicinal plants such as *Cnidium monnieri (L.)* or *Angelica pubescens (L.)*. Both *in vitro* and *in vivo* studies have revealed that osthole demonstrates neuroprotective (Liu et al., 2010), osteogenic (Ming et al., 2011), immunomodulatory (Liao et al., 2010), anticancer (Yang et al., 2010; Kao et al., 2012), hepatoprotective (Zhang et al., 2011), anticoagulant and antimicrobial properties (Rosselli et al., 2007).

The neuroprotective effects of osthole are related to an increase in neuronal conduction in the hippocampus. Osthole affects the membrane receptors by increasing the release of glutamate from rat hippocampal nerve terminals. It facilitated 4-aminopyridine (4-AP-)-evoked glutamate release by activating N- and

Table I. Effect of coumarins on the anticonvulsant activity of conventional antiepileptic drugs against maximal electroshock-induced seizures in mice.

	CBZ ED_{50} (mg/kg)	PB ED_{50} (mg/kg)	PHT ED_{50} (mg/kg)	VPA ED_{50} (mg/kg)	References
Imperatorin + AEDs	10.3 / 6.0	19.6 / 12.2	12.8 / 8.5	247.9 / 213.4	Luszczki et al., 2007
Osthole + AEDs	8.87 / 6.89	18.17 / 12.35	9.2 / 7.48	212.5 / 173.8	Luszczki et al., 2010; 2011
Umbelliferon + AEDs	13.97 / 11.76	35.39 / 21.78	13.26 / 10.84	281.4 / 215.5	Zagaja et al., 2015a
Xanthotoxin + AEDs	13.97 / 5.01	35.39 / 27.87	13.26 / 12.21	281.4 / 195.5	Zagaja et al., 2015b

Results are presented as median effective doses (ED_{50} in mg/kg; with 95% confidence limits in parentheses) required to protect 50% of animals tested against maximal electroshock-induced seizures. Bolded ED_{50} values corresponds to the significantly reduced effective dose of combination in comparison to the AED itself. AEDs – antiepileptic drugs, CBZ – carbamazepine, PB – phenobarbital, PHT – phenytoin, VPA – valproate.

P/Q-type Ca^{2+} channels through a signaling cascade involving protein kinase C (Wang et al., 2008).

In addition to the above-mentioned mechanism, and based on the intensification of glutamatergic transmission, the anticonvulsant activity of osthole has also been associated with modulation of membrane channel activity via blocking L-type Ca^{2+} channels and Na+ channels in mouse neuronal cells (Wu et al., 2002; Leung et al., 2010). Osthole was found to inhibit voltage-gated Na^{+} currents dependent upon its intracellular concentration and the current functional potential of the cell membrane in an N2A mouse neuroblastoma cell line (Leung et al., 2010). Moreover, osthole was identified as an activator of the $GABA_A$ receptor *in vitro* (Zaugg et al., 2011; Singhuber et al., 2011).

Research conducted by Luszczki et al. (2009) showed that osthole reduced seizures induced by the MES test in mice. The experiment was performed by a systematic administration of the compound 15, 30, 60 and 120 minutes before the test. The maximal anticonvulsant effect was obtained after intraperitoneal (i.p.) administration of osthole between 15 and 30 minutes. In addition, chimney test results showed no disturbances in motor coordination.

Subsequent studies conducted by Luszczki et al. (2010) for various combinations of osthole with classic AEDs showed that osthole at a dose of 200 mg/kg significantly increased the electroconvulsive threshold in mice. Osthole administered with carbamazepine (CBZ), phenobarbital (PB), phenytoin (PHT) and valproate (VPA) did not have a significant effect on the anticonvulsant activity of the studied drugs (at test doses for osthole 50, 100 and 150 mg/kg). Assessment of the motor performance of the mice treated with the combinations of osthole and the above-mentioned classical AEDs showed no side effects (Luszczki et al., 2010; 2011).

Umbelliferone

Umbelliferone (7-hydroxycoumarin) is a commonly occurring coumarin plant widely occurring in the *Apiaceae* (*Umbelliferae*) and *Rutaceae* families. Umbelliferone exhibits various pharmacological activities including antihyperglycemic (Ramesh et al., 2006), bronchodilating (Vasconcelos et al., 2009), antiedematogenic (Toyama et al., 2009), neuroprotective (Subramaniam et al., 2013), antinociceptive (Barros et al., 2010) and anticonvulsant (Zagaja, et al., 2015a) properties. Due to its simple structure, it is used as a parent compound in the synthesis of various coumarins and heterocyclic compounds (Mazimba et al., 2017).

Subramaniam and Ellis (2013) identified a neuroprotective effect for umbelliferone, where this couma-

Table II. Effect of imperatorin and xanthotoxin on the protective activity of various novel antiepileptic drugs against maximal electroshock-induced seizures in mice.

	LCM ED_{50} (mg/kg)	LTG ED_{50} (mg/kg)	OXC ED_{50} (mg/kg)	PGB ED_{50} (mg/kg)	TPM ED_{50} (mg/kg)	References
Imperatorin + AEDs	–	6.11 / 2.47	–	–	–	Luszczki et al., 2008
Xanthotoxin + AEDs	8.70 / 3.96	5.96 / 5.01	12.49 / 7.54	77.37 / 28.26	68.81 / 28.84	Zagaja et al., 2016

Results are presented as median effective doses (ED_{50} in mg/kg; with 95% confidence limits in parentheses) required to protect 50% of animals tested against maximal electroshock-induced seizures. Bolded ED_{50} values corresponds to the significantly reduced effective dose of combination in comparison to the AED itself. AEDs – antiepileptic drugs, LCM – lacosamide, LTG – lamotrigine, OXC – oxcarbazepine, PGB – pregabalin, TPM – topiramate.

rin significantly attenuated MPTP-induced neurotoxicity at the cellular level in mice by preventing the loss of dopaminergic neurons in the substantia nigra pars compacta.

Zagaja et al. (2015a) examined the antiepileptic activity of umbelliferone alone and in combination therapy with classical AEDs in the MES model in mice. Umbelliferone was administered (i.p) at doses of 50, 100 and 150 mg/kg 30 minutes before electroshock. Umbelliferone alone at a dose of 150 mg/kg significantly increased the threshold for the maximal electroshock-induced seizure test CS_{50} in mice (about 37%). Interestingly, the same dose of umbelliferone enhanced the anticonvulsant effect of VPA and PB, reducing the ED_{50} from 281.4 to 215.5 mg/kg for VPA and 35.39 to 21.78 mg/kg for PB. Results from the total VPA and PB brain concentrations showed that the interaction between umbelliferone and AEDs was pharmacodynamic in nature. Moreover, no side effects such as impaired motor coordination, muscle strength or long-term memory were observed in the mice.

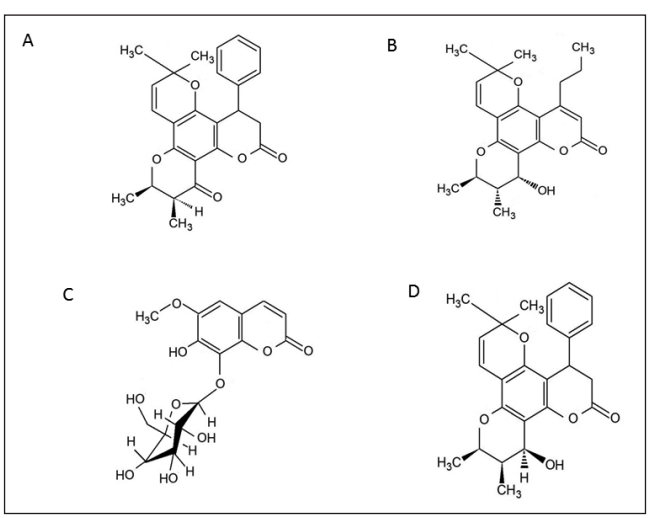

Fig. 1. Chemical structures of coumarins:
A. Osthole, B. Umbelliferone, C. Xanthotoxin, D. Imperatorin.

Xanthotoxin

Xanthotoxin, known as methoxsalen (8-methoxypsoralen), is furanocoumarin commonly occurring in plants. A high content was found in the *Apiaceae* family plant *Ammi majus (L.),* possessing numerous pharmacologically active properties, including photoreactivity used to treat skin autoimmune diseases (Selim et al., 2012).

It has been shown that xanthotoxin effectively penetrates the blood-brain barrier (BBB) (Tian et al., 2015). Skalicka-Wozniak and coworkers (2018) indicated that xanthotoxin improved the ability to remember in mice with scopolamine-induced memory deficits. Additionally, another study by Skalicka-Wozniak et al. (2014) showed an anticonvulsant effect for xanthotoxin in the mouse MES model. The compound had the most effective protective effect (ED_{50}=219.1 ± 4.7 mg/kg) when administered 60 minutes before the test.

Zagaja et al. (2015b) studied the effect of xanthotoxin on classic AEDs. The compound was administered in doses of 50, 100 and 150 mg/kg and protective activity was based on the evaluated threshold for MES. Xanthotoxin (100 mg/kg, i.p.) in combination with carbamazepine (CBZ) and VPA significantly increased their anticonvulsant activity (p<0.001): CBZ by 64% and VPA by 31%. Pharmacokinetics were assessed based on drug concentration in the post-mortem study of brain tissue. It was established that xanthotoxin increased the total concentration of CBZ and VPA in brain by 84% and 46%, respectively, compared to CBZ and VPA alone mice.

Similar research was carried out by the same team to assess the effect of xanthotoxin on the new-generation drugs lacosamide (LCM), pregabalin (PGB), topiramate (TP), oxcarbazepine (OXC) and lamotrigine (LTG) (Zagaja et al., 2016). As in the previous study, the protective activity of the drugs was determined based on the median effective doses (ED_{50} values in mg/kg) correlated to the maximum convulsions caused by electroconvulsion. Increased anticonvulsant effect was demonstrated for the combination of LCM, PGB, TP and OXC with xanthotoxin (100 mg/kg, i.p.). The assessment of long-term memory in the passive avoidance test showed no side effects in mice. The chimney test showed no significant changes in the motor coordination of mice. Only PGB caused a significant (75%) movement disturbance in comparison to the control group. Administration of xanthotoxin did not affect the total concentration of the drugs studied in the brain.

Imperatorin

Imperatorin (9-[(3-methyl-2-buten-1-yl)oxy]-7H-furo[3,2-g]chromen-7-one), a furanocoumarin, is produced as a secondary metabolite of plants from the *Apiaceae* and *Rutaceae* families. It possesses numerous pharmacological activities and, among other things, exerts a significant impact on the CNS (Kozioł et al., 2016).

Imperatorin affects the CNS through various mechanisms. It has been shown to act by inhibiting GABA transaminase and increasing the concentration of synaptic GABA in neurons—suggesting a similar activity to vigabatrin (Choi et al., 2005). In studies by Zaugg et al. (2011), imperatorin, like osthole, is modulator of the $GABA_A$ receptor. Moreover, imperatorin inhibits volt-

age-gated Na^+ channel (VGSC) activity and suppresses action potential amplitude (Wu et al., 2013). In addition, imperatorin was shown to desensitize transient reversal potential (TRP) V1 channels, and such action may account for the anti-nociceptive effects of imperatorin on formalin- and capsaicin-induced pain in rats (Chen et al., 2014). Furthermore, Wang et al. (2015) suggest that imperatorin inhibited both K_v and K_{ATP} channels.

It has also been shown that imperatorin inhibits acetylcholinesterase activity in thin-layer chromatography (TLC) bioautography (Urbain et al., 2005). Interestingly, results presented by Cao and colleagues (2017) were indicative of antidepressant properties for imperatorin. Long-term oral administration of imperatorin at 15 and 30 mg/kg/day for 28 days increased the 5-HT concentration in rat hippocampus.

Imperatorin anticonvulsant activity was demonstrated in preclinical studies by Luszczki et al. (2007a) in the mouse MES threshold model. In this study, imperatorin increased the convulsive threshold in a dose-dependent manner. Statistically significant results were obtained for doses of 50 and 100 mg/kg administered (i.p.) at 30, 60 and 120 minutes prior to the test.

The influence of imperatorin on the antiepileptic action of the four classic AEDs was demonstrated in a study by Luszczki et al. (2007b). The anticonvulsant activity of CBZ, PB, PHT and VPA was studied in combination with several doses of imperatorin (20, 30, 40 mg/kg) in the MES test. A significant reduction of ED_{50} and an increase in the effect of the drugs were observed for PHT, PB and CBZ with 40 mg/kg of imperatorin (by 34, 38 and 42%, respectively). Statistically significant effects were also achieved for the combination of CBZ with imperatorin at a dose of 30 mg/kg (lowered ED_{50} by 32%). Combinations of imperatorin with the drugs did not disturb the muscular strength of animals in the grip-strength test or long-term memory in the passive avoidance test. Analysis of the total brain concentration of the AEDs showed no effect of imperatorin (at a dose of 40 mg/kg) on the total concentration of PHT and PB, which proves that the observed interactions were pharmacodynamic in nature. In turn, the concentration of CBZ, which was significantly increased in comparison to control, indicated a pharmacokinetic nature of the imperatorin and CBZ interaction. Similarly, imperatorin at a dose of 50 mg/kg was shown to reduce the median effective dose of LTG from 6.11 to 2.47 mg/kg in mouse MES model (Luszczki et al., 2008). Moreover, imperatorin had no impact on the acute adverse effects of lamotrigine in the chimney test and results from total brain LTG concentration analysis did not indicate any pharmacokinetic interaction between drugs (Table II).

CONCLUSIONS

Looking for new anti-epileptic drugs is a long-term process requiring thorough research. Phytochemicals, commonly found in plants, are characterized by interesting bioactive properties, including pharmacological ones. Among these substances, coumarins and their derivatives demonstrate beneficial, significant anticonvulsant activity. Coumarins have similarly been shown to act as anticonvulsants in various *in vitro* and *in vivo* assays, yielding promising results at the preclinical stage of experimental models of epilepsy. There are currently observable trends of supporting anti-epileptic treatment, especially drug-resistant epilepsy, with various "natural" diets. Therefore, patients treated with classic antiepileptic drugs may use "healthy" supplements prepared from medicinal plants and herbs, including coumarins, which may affect the anticonvulsant effect of antiepileptic drugs. In searching for novel medications, it is necessary to remember that the most important guideline is patient safety. Therefore, further evaluation of coumarins and approximations of the mechanism of their action is needed so that in the future they can support therapies for epileptic patients.

REFERENCES

Barros TA, de Freitas LA, Filho JM, Nunes XP, Giulietti AM, de Souza GE, dos Santos RR, Soares MB, Villarreal CF (2010) Antinociceptive and anti-inflammatory properties of 7-hydroxycoumarin in experimental animal models: potential therapeutic for the control of inflammatory chronic pain. J Pharm Pharmacol 62: 205–213.

Cao Y, Liu J, Wang Q, Liu M., Cheng Y, Zhang X Lin T, Zhu Z (2017) Antidepressive-like effect of imperatorin from *Angelica dahurica* in prenatally stressed offspring rats through 5-hydroxytryptamine system. Neuroreport 28: 426–433.

Castel-Branco MM, Alves GL, Figueiredo IV, Falcão AC, Caramona MM (2009) The maximal electroshock seizure (MES) model in the preclinical assessment of potential new antiepileptic drugs. Methods Find Exp Clin Pharmacol 31: 101–106.

Chattha FA, Munawar MA, Kousar S (2018) Plant growth regulating activity of coumarin derivatives. Horticult Int J 2: 24–29.

Chen X, Sun W, Gianaris NG, Riley AM, Cummins TR, Fehrenbacher JC, Obukhov AG (2014) Furanocoumarins are a novel class of modulators for the transient receptor potential vanilloid type 1 (TRPV1) channel. J Biol Chem 289: 9600–9610.

Choi SY, Ahn EM, Song MC, Kim DW, Kang JH, Kwon OS, Kang TC, Baek NI (2005) *In vitro* GABA-transaminase inhibitory compounds from the root of *Angelica dahurica*. Phytother Res 19: 839–845.

Jain PK, Joshi H (2012) Coumarin: chemical and pharmacological profile. J App Pharm Sci 2: 236–240.

Kao SJ, Su JL, Chen CK, Yu MC, Bai KJ, Chang JH, Bien MY, Yang SF, Chien MH (2012) Osthole inhibits the invasive ability of human lung adenocarcinoma cells via suppression of NF-κB-mediated matrix metalloproteinase-9 expression. Toxicol Appl Pharmacol 261: 105–115.

Kirsch G, Abdelwahab AB, Chaimbault P (2016) Natural and synthetic coumarins with effects on inflammation. Molecules 21: 1322–1335.

Kozioł E, Skalicka-Woźniak K (2016) Imperatorin–pharmacological meaning and analytical clues: profound investigation. Phytochem Rev 15: 627–649.

Kubrak T, Podgórski R, Stompor M (2017) Natural and synthetic coumarins and their pharmacological activity. Eur J Clin Exp Med 15: 169–175.

Kumar AK, Renuka N, Pavithra G, Kumar GV (2015) Comprehensive review on coumarins: Molecules of potential chemical and pharmacological interest. J Chem Pharm Research 7: 67–81.

Kwon OS, Choi JS, Islam MN, Kim YS, Kim HP (2011) Inhibition of 5-lipoxygenase and skin inflammation by the aerial parts of *Artemisia capillaris* and its constituents. Arch Pharm Res 34: 1561–1569.

Leung YM, Kuo YH, Chao CC, Tsou YH, Chou CH, Lin CH, Wong KL (2010) Osthol is a use-dependent blocker of voltage-gated Na^+ channels in mouse neuroblastoma N2A cells. Planta Med 76: 34–40.

Liao PC, Chien SC, Ho CL, Wang EI, Lee SC, Kuo YH, Jeyashoke N, Chen J, Dong WC, Chao LK, Hua KF (2010) Osthole regulates inflammatory mediator expression through modulating NF-κB, mitogen-activated protein kinases, protein kinase C, and reactive oxygen species. J Agric Food Chem 58: 10445–10451.

Liu WB, Zhou J, Qu Y, Li X, Lu CT, Xie KL, Sun XL, Fei Z (2010) Neuroprotective effect of osthole on MPP+-induced cytotoxicity in PC12 cells via inhibition of mitochondrial dysfunction and ROS production. Neurochem Int 57: 206–215.

Luo KW, Sun JG, Chan JY Yang L, Wu SH, Fung KP, Liu FY (2011) Anticancer effects of imperatorin isolated from *Angelica dahurica*: induction of apoptosis in HepG2 cells through both death-receptor and mitochondria-mediated pathways. Chemotherapy 57: 449–459.

Luszczki J, Marczewski T, Mazurkiewicz L, Karwan S, Teresińska M, Florek-Łuszczki M, Gleńsk M (2011) Influence of osthole on the anticonvulsant activity of phenytoin and valproate in the maximal electroshock-induced seizures in mice. Annales UMCS 24: 33–44.

Luszczki JJ, Andres-Mach M, Cisowski W, Mazol I, Glowniak K, Czuczwar SJ (2009) Osthole suppresses seizures in the mouse maximal electroshock seizure model. Eur J Pharmacol 607: 107–109.

Luszczki JJ, Glowniak K, Czuczwar SJ (2007a) Time-course and dose-response relationships of imperatorin in the mouse maximal electroshock seizure threshold model. Neurosci Res 59: 18–22.

Luszczki JJ, Glowniak K, Czuczwar SJ (2007b) Imperatorin enhances the protective activity of conventional antiepileptic drugs against maximal electroshock-induced seizures in mice. Eur J Pharmacol 574: 133–139.

Luszczki JJ, Rękas A, Mazurkiewicz LP, Ossowska G (2010) Effect of osthole on the protective activity of carbamazepine and phenobarbital against maximal electroshock-induced seizures in mice. Annales UMCS 23: 145–156.

Luszczki JJ, Wojda E, Raszewski G, Głowniak K, Czuczwar SJ (2008) Influence of imperatorin on the anticonvulsant and acute adverse-effect potential of lamotrigine in maximal electroshock-induced seizures and chimney test in mice. Pharmacol Rep 60: 566–573.

Matos JM, Santana L, Uriarte E, Abreu OA, Molina E, Yordi EG (2015) Coumarins – an important class of phytochemicals. In: Phytochemicals – Isolation, Characterization and Role in Human (Rao V, Rao LG, Ed.). In Tech, Rijeka, Croatia p. 113–140.

Mazimba O (2017) Umbelliferone: sources, chemistry and bioactivities review. Bull Fac Pharm Cairo Univ 55: 223–232.

Mead JAR, Smith JN, Williams RT (1958) Studies in detoxication. 72. The metabolism of coumarin and of o-coumaric acid. Biochem J 68: 67–74.

Medina FG, Marrero JG Macías-Alonso M, González MC, Córdova-Guerrero I, Teissier García AG, Osegueda-Robles S (2015) Coumarin heterocyclic derivatives: chemical synthesis and biological activity. Nat Prod Rep 32: 1472–1507.

Ming LG, Zhou J, Cheng GZ, Ma HP, Chen KM (2011) Osthol, a coumarin isolated from common cnidium fruit, enhances the differentiation and maturation of osteoblasts *in vitro*. Pharmacology 88: 33–43.

Najmanova I, Dosedel M, Hrdina R, Anzenbacher P, Filipsky T, Riha M, Mladenka P (2015) Cardiovascular effects of coumarins besides their antioxidant activity. Curr Top Med Chem 15: 830–849.

Popp D, Plugge CM, Kleinsteuber S, Harms H, Sträubera H (2017) Inhibitory effect of coumarin on syntrophic fatty acid-oxidizing and methanogenic cultures and biogas reactor microbiomes. Appl Environ Microbiol 83: e00438–17.

Ramesh B, Pugalendi KV (2006) Antihyperglycemic effect of umbelliferone in streptozotocin-diabetic rats. J Med Food 9: 562–566.

Rogawski MA (2006) Molecular targets versus models for new antiepileptic drug discovery. Epilepsy Res 68: 22–28.

Rohini K, Srikumar PS (2014) Therapeutic role of coumarins and coumarin-related compounds. J Thermodyn Catal 5: 130–133.

Rosselli S, Maggio A, Bellone G, Formisano C, Basile A, Cicala C, Alfieri A, Mascolo N, Bruno M (2007) Antibacterial and anticoagulant activities of coumarins isolated from the flowers of *Magydaris tomentosa*. Planta Med 73: 116–120.

Selim YA, Ouf NH (2012) Anti-inflammatory new coumarin from the *Ammi majus L*. Org Med Chem Lett 2: 1–4.

Sharma S, Dixit V (2013) Epilepsy – a comprehensive review. IJPRR 2: 61–80.

Singhuber J, Baburin I, Ecker GF, Kopp B, Hering S (2011) Insights into-structure–activity relationship of receptor modulating coumarins and furanocoumarins. Eur J Pharmacol 668: 57–64.

Skalicka-Wozniak K, Budzynska B, Biala G, Boguszewska-Czubara A (2018) Scopolamine-induced memory impairment is alleviated by xanthotoxin: role of acetylcholinesterase and oxidative stress processes. ACS Chem Neurosci 9: 1184–1194.

Skalicka-Woźniak K, Orhan IE, Cordell GA, Nabavi SM, Budzyńska B (2016) Implication of coumarins towards central nervous system disorders. Pharmacol Res 103: 188–203.

Skalicka-Woźniak K, Zagaja M, Głowniak K, Łuszczki JJ (2014) Purification and anticonvulsant activity of xanthotoxin (8-methoxypsoralen). Cent Eur J Biol 9: 431–436.

Subramaniam SR. Ellis EM (2013) Neuroprotective effects of umbelliferone and esculetin in a mouse model of Parkinson's disease. J Neurosci Res 91: 453–461.

Tian W, Cai J, Xu Y, Luo X, Zhang J, Zhang Z, Zhang Q, Wang X, Hu L, Lin G (2015) Determination of xanthotoxin using a liquid chromatography-mass spectrometry and its application to pharmacokinetics and tissue distribution model in rat. Int J Clin Exp Med 8: 15164–15172.

Toyama DO, Marangoni S, Diz-Filho EBS, Oliveira SCB, Toyama MH (2009) Effect of umbelliferone (7-hydroxycoumarin, 7-HC) on the enzymatic, edematogenic and necrotic activities of secretory phospholipase A2 (sPLA2) isolated from *Crotalus durissus collilineatus* venom. Toxicon 53: 417–426.

Urbain A, Marston A, Hostettmann K (2005) Coumarins from *Peucedanum ostruthium* as inhibitors of acetylcholinesterase. Pharm Biology 43: 647–650.

Vasconcelos JF, Teixeira MM, Barbosa-Filho JM, Agra MF, Nunes XP, Giulietti AM, Ribeiro-dos-Santos R, Soares MB (2009) Effects of umbelliferone in a murine model of allergic airway inflammation. Eur J Pharmacol 609: 126–131.

Vyas KB, Nimavat KS, Joshi KM, Jani GR (2012) Synthesis of 3-[{(3-(2'--nitrophenyl)}-prop-2-enoyl]-4-hydroxy-6-methyl-2H-chromene-2-one and its metal complexes as antimicrobial agent. J Chem Pharm Research 4: 2720–2723.

Wang SJ, Lin TY, Lu CW, Huang WJ (2008) Osthole and imperatorin, the active constituents of *Cnidium monnieri* (L.) Cusson, facilitate glutamate release from rat hippocampal nerve terminals. Neurochem Int 53: 416–423.

Wang YW, Yang CT, Chen YH, Gong CL, Chen YF, Kuo YH, Leung YM (2015) Inhibitory effects of imperatorin on voltage-gated K(+) channels and ATP-sensitive K(+) channels. Pharmacol Rep 67: 134–139.

Witaicenis A, Seito LN, Di Stasi LC (2010) Intestinal anti-inflammatory activity of esculetin and 4-methylesculetin in the trinitrobenzenesulphonic acid model of rat colitis. Chem Biol Interact 186: 211–218.

Wu KC, Chen YH, Cheng KS, Kuo YH, Yang CT, Wong KL, Tu YK, Chan P, Leung YM (2013) Suppression of voltage-gated Na(+) channels and neuronal excitability by imperatorin. Eur J Pharmacol 721: 49–55.

Wu SN, Lo YK, Chen CC, Li HF, Chiang HT (2002) Inhibitory effect of the plant-extract osthole on L-type calcium current in NG108–15 neuronal cells. Biochem Pharmacol 63: 199–206.

Yang D, Gu T, Wang T, Tang Q, Ma C (2010) Effects of osthole on migration and invasion in breast cancer cells. Biosci Biotechnol Biochem 74: 1430–1434.

Zagaja M, Andres-Mach M, Skalicka-Woźniak K, Rękas AR, Kondrat-Wróbel MW, Gleńsk M, Łuszczki JJ (2015a) Assessment of the combined treatment with umbelliferone and four classical antiepileptic drugs against maximal electroshock-induced seizures in mice. Pharmacology 96: 175–180.

Zagaja M, Pyrka D, Skalicka-Woźniak K, Glowniak K, Florek-Luszczki M, Gleńsk M, Luszczki JJ (2015b) Effect of xanthotoxin (8-methoxypsoralen) on the anticonvulsant activity of classical antiepileptic drugs against maximal electroshock-induced seizures in mice. Fitoterapia 105: 1–6.

Zagaja MP, Andres-Mach MM, Patrzylas P, Pyrka D, Szpringer M, Florek-Łuszczki M, Żółkowska D, Skalicka-Woźniak K, Łuszczki JJ (2016) Influence of xanthotoxin (8-methoxypsoralen) on the anticonvulsant activity of various novel antiepileptic drugs against maximal electroshock-induced seizures in mice. Fitoterapia 115: 86–91.

Zaugg J, Eickmeier E, Rueda DC, Hering S, Hamburger M (2011) HPLC-based activity profiling of Angelica pubescens roots for new positive GABA(A) receptor modulators in Xenopus oocytes. Fitoterapia 82: 434–440.

Zhang J, Xue J, Wang H, Zhang Y, Xie M (2011) Osthole improves alcohol-induced fatty liver in mice by reduction of hepatic oxidative stress. Phytother Res 25: 638–643.