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REVIEW PAPER

In vitro and *in vivo* activities of flavonoids – apigenin, baicalin, chrysin, scutellarin – in regulation of hypertension – a review for their possible effects in pregnancy-induced hypertension

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Summary

Flavonoids and their conjugates are the most important group of natural chemical compounds in drug discovery and development. The search for pharmacological activity and new mechanisms of activity of these chemical compounds, which may inhibit mediators of inflammation and influence the structure and function of endothelial cells, can be an interesting pharmacological strategy for the prevention and adjunctive treatments of hypertension, especially induced by pregnancy. Because cardiovascular diseases have multifactorial pathogenesis these natural chemical compounds with wide spectrum of biological activities are the most interesting source of new drugs. Extracts from one of the most popular plant used in Traditional Chinese Medicine, *Scutellaria baicalensis* Georgi could be a very interesting source of flavonoids because of its exact content in quercetin, apigenin, chrysin and scutellarin as well as in baicalin. These flavonoids exert vasoprotective properties and many activities such as: anti-oxidative *via* several pathways, anti-inflammatory, anti-ischaemic, cardioprotective and anti-hypertensive. However, there is lack of summaries of results of studies in context of potential and future application of flavonoids with determined composition and activity. Our review aims to provide a literature survey of *in vitro*, *in vivo* and *ex vivo* pharmacological studies of selected flavonoids (apigenin, chrysin and scutellarin, baicalin) in various models of hypertension carried out in 2008–2018.

Key words: ***flavonoids, pharmacological activity, in vitro models, animal models, hypertension, pregnancy-induced hypertension***

Słowa kluczowe: ***flawonoidy, aktywność farmakologiczna, modele in vitro, modele zwierzęce, nadciśnienie, nadciśnienie indukowane ciążą***

INTRODUCTION

Flavonoids and their conjugates are a very large group of natural chemical compounds. The analysis of these metabolites is one of the most important areas in the field of drug discovery and development. These natural chemical compounds show a wide spectrum of biological activities and among others they can play in prevention and treatment of multifactorial cardiovascular diseases. The activity of certain flavonoids on vascular dysfunction has been the subject of many studies and reviews, since 1959 [1]. Recently, attention has been paid to natural chemical compounds in order to the discovery of new antihypertensive therapeutics especially as drug candidates in prevention and treatment of hypertension [2]. Among the active plant phenolics the most interesting are quercetin, apigenin, chrysin and scutellarin, baicalin occurring in the various extracts from *Scutellaria* sp. [3-7].

One of important medical and therapeutic problems is hypertension induced by pregnancy (PIH) [2]. According to review by Ożarowski *et al.* [2], hypertensive disorders diagnosed during pregnancy were classified as: (1) chronic hypertension, (2) preeclampsia-eclampsia, (3) preeclampsia superimposed on chronic hypertension, (4) gestational hypertension (transient hypertension of pregnancy or chronic hypertension identified in the latter half of pregnancy). PIH may lead to functional and structural complications, i.e. placental abruption, elevated levels of liver enzymes, hemolysis, renal failure, cerebral vascular accidents [8]. As it was described previously [2, 9, 10] "preeclampsia is was defined as high blood pressure (≥140 mmHg systolic or ≥90 mmHg diastolic, or increases of 30 mmHg systolic or 15 mmHg diastolic from the baseline on at least two occasions, six or more hours apart) that develops from the 20th gestational week in a previously normotensive woman, with proteinuria (one 24-hour urine collection with a total protein excretion of at

least 300 mg/l)". The main pathological basis is damage of endothelial cells, followed by dysfunction of vasoactive, inflammatory and clotting factors. Furthermore, an oxygenation plays a key role in the course of pathogenesis in preeclampsia.

Hence, there is a possibility of intervention with the use of flavonoids as dietary components or herbal medicinal drugs. Presented review is a summary of recent results on activity of selected flavonoids in pharmacological models in vascular disorders, especially in hypertension, taking into account pregnancy-induced hypertension.

APIGENIN

Natural source and pharmacological profile

A 4',5,7-trihydroxyflavone (fig. 1), called apigenin, is a flavonoid common in vegetables, fruits or plants with medical properties, i.e. in *Petroselinum crispum* Mill.) Fuss. (parsley, *Apiaceae*) and *Matricaria chamomilla* L. (chamomile, *Asteraceae*) [11, 12] or celery seeds (*Apium graveolens* L. (*Apiaceae*)) [13, 14]. Biological properties of the compound with its influence of cardiovascular system were summarized by Wang *et al.* [15], Zhou *et al.* [14] and Ali *et al.* [16].

Currently, there is an increasing interest in pro-health and healing properties of apigenin due to its proved relatively low toxicity on non-affected cells and its effectiveness on cells with altered biochemistry, which is particularly evident in the case of cancer cells [17]. Results of growing number of studies underlines apigenin's strong therapeutic potential against a number of diseases [14, 16]. Particularly noteworthy is the increasing number of data indicating the properties of apigenin, which may be helpful in the prevention or inhibition of symptoms manifested as a hypertension developed during pregnancy.

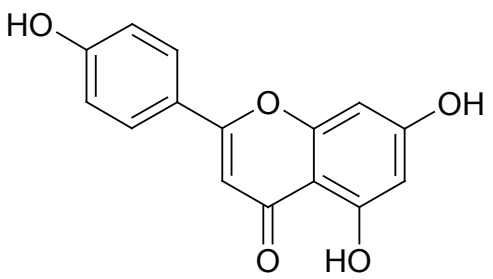

Figure 1
Chemical structure of apigenin (ISIS Draw).

In vitro and *ex vivo* results of apigenin's influence on the causes of hypertension

Vasodilatation

In early 90's [18], the *in vitro* vasodilatory effect of apigenin on rat thoracic aorta rings isolated from the extract from *A. graveolens* (celery) seeds was observed, which, as it has been postulated, could act *via* inhibition of the Ca^{2+} influx *via* ligand and/or voltage-gated calcium channels. In this study, this compound inhibited the contraction of aortic rings caused by cumulative concentrations of calcium (0.03-3 mM) (IC_{50} = ca 48 μM) [18]. Promising results were also obtained in rats aorta rings *ex-vivo* (*via* influence on the Ca^{2+} influx into cells or the extrication of Ca^{2+} from smooth muscles sarcoplasma) in the case of hexane extract, however, the observed properties were attributed primarily to its another active component n-butylphthalide (NBP) [13]. In another, similar study in dissected endothelium-stripped thoracic aortic rings from male Sprague–Dawley rats pretreated with phenylephrine, apigenin (0.5–72 μM) caused vasorelaxation (the E_{max} = 28.7%±7.3%) and attenuated decreased endothelium-dependent vasorelaxation triggered by pyrogallol (with relaxation at maximum level from 55.8%±6.6% to 69.5%±6.4%, respectively) [19]. It has resulted in quantitative indications of oxidative stress and nitric oxide turnover, mainly it elevated the superoxide anion suppression process (from 94.6% to 74.5%), the nitric oxide level, and the constitutive nitric oxide synthase activity [19]. Another one comparative analysis of vasodilatory effect of the subfractions isolated from the *Ziziphora clinopodioides* Lam. (*Lamiaceae*) hydroalcoholic extract (in Uighur's medicine commonly used against hypertension symptoms) containing apigenin and other phenolic compounds (acetovanillone, thymonin, chrysin, acacetin, 4-hydroxyacetophenone, ethyl 4-coumarate) was carried out in isolated rat thoracic aortic rings, as a result of which the highest potential of the isolated apigenin and other two flavones (ethyl 4-coumarate, chrysin) was observed [20].

In vivo studies related to the various models of hypertension

In comparative study by Tashakori-Sabzevar *et al.* [13], in which especially the hexanic extract of *A. graveolens* seed strongly decreased four heart pressure parameters, such as: the diastolic (DBP), systolic (SBP), mean arterial blood pressure (MABP), and

heart rate (HR) after intravenous injection. They found that hexanic extract and nifedipine (a positive control) similarly lowered diastolic and systolic heart pressure, and mean arterial value in rats with normal and hypertension, while taking into account the HR parameter - in the case of hexanic extract an induction of bradycardia was observed. They postulated that the presence of this nonpolar flavonoid, as well as another two compounds – sedanenolide and sedanolide – could contribute to these effects. Exactly which one of these compounds the kind of effect caused – this type of analysis was not carried out in abovementioned experiment. Tang *et al.* investigated the vasodilatory mechanism of fresh juice from *A. graveolens* and the results obtained prompted the research team to suggest that it might act as inhibitor of the receptor-operated channel (ROC) in the smooth muscles [21]. It is in relation with another study in which it was shown that a peripheral vascular resistance may significantly influence on the DBP; therefore, *A. graveolens* extract from seeds gave vasorelaxant effects, which could be due to NBP, observable concentrations of apigenin, d-limonene, linalool and/or other similar substances. In a study on the N-nitro-L-arginine methyl ester hydrochloride (L-NAME) (nitric oxide-deficient) hypertensive rats [22] it was found that apigenin, among other compounds, significantly reduced their elevated blood pressure that is related with the chronic deficiency of NO. Other study by Paredes *et al.* [23] also revealed vasorelaxative properties of apigenin in different strain of rats - SHR (spontaneously hypertensive rats) animals, in which after administration with this flavone for 6 (SHR6 group) or 12 weeks (SHR12 group) a correction of relaxation of the aortic blood vessels and elevated plasma and urinary nitrites excretion was detected as well as the reduction of excretion of the urinary thiobarbituric acid reactive substances (TBARS) and proteinuria. In the SHR6 group administration with apigenin led to moderate improvement of pathologically changed vascular lumen/wall ratio in heart arteries and thoracic aorta [23]. Other study performed on 12 weeks aged SHR showed that apigenin (0.007, 0.026, 0.104 and 0.417 g/kg) lowered systolic blood pressure related to up-regulation the expression of mRNA ACE2 in kidney [24]. The improvement of hypertensive cardiac hypertrophy and glycolipid metabolism in abnormal heart muscle due to apgenin's treatment seemed, as authors concluded, to take place according to influence on expression of genes regulating glycolytic and glycerol-lipid biosynthesis, shifting of cardiac metabolism mediated by hypoxia-inducible factor 1α (HIF-1α), peroxisome proliferator-activated receptor α, γ (PPARα, γ) [25]. It decreased of myocardial HIF-1α transcription, up-regulated the expressions of myocardial PPARα and its target genes: carnitine palmitoyltransferase (CPT-1), pyruvate dehydrogenase kinase (PDK-4), down-regulated of myocardial PPARγ and its target genes: glycerol-3-phosphate acyltransferase (GPAT), GLUT-4 (on mRNA and protein level) expression [26]. Furthermore, this flavone applied as a diet, revealed also a preventive property on hypertension-induced renal fibrosis in male hypertensive Sprague-Dawley rats induced by deoxycorticosterone acetate (DOCA) – salt agonized the activity of transient receptor potential vanilloid 4 (TRPV4) in both, the kidney and renal cells, strongly weaken the DOCA-salt-induced damage of kidneys structure and function, with simultaneous down-regulation of transforming growth factor-β1 (TGF-β1)/Smad2/3 signal transduction route, AMP-activated protein kinase (AMPK)/sirtuin 1 (SIRT1) cascade and extracellular matrix proteins expression [27].

Results by Zhang *et al.* provided evidences for regulatory activity of apigenin on cholesterol metabolism *in vivo* (administered *p.o.* in hypercholesterolemic ICR mice once per day through 28 consecutive days) causing the significant, dose-dependent lowering concentrations of low-density lipoprotein cholesterol (LDL-C), triglycerides (TG) and total content of cholesterol (TC) in their serum, consequently reducing their total body mass. Authors attempted to evaluate the molecular mechanism of action of apigenin's ability to decrease the concentration of fat in blood of studied animals. For this purpose, liver's transcription levels changes of three genes encoding enzymes limiting the cholesterol metabolism, such as: cytochrome P450 type 7 (CYP7A1 – catalyzing cholesterol transformation into bile acid [29]), LDL-R (receptor crucial for mediating of LDL-C uptake in liver) [30], and 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase (HMG-CoAR: crucial in cholesterol synthesis rate) were quantified, all of which were substantially down-regulated in a high-fat diet animals. Above mentioned flavonoid significantly stimulated the expression of mRNAs for CYP7A1 in animals administered with its higher dose, while in both groups of mice (high and low-dosage ones) the number LDL-R transcripts were also elevated in a significant manner [28]. Furthemore, in EA.hy926 (macrophage-derived foam) cells it also dose-dependently stimulated the superoxide dismutase (SOD) and decreased the degree of proliferation of vascular smooth muscle cells as well [28].

Influence in pregnancy

One of interesting studies is the research by Lim *et al.* [31], prone to penetration of apigenin through placenta cells, suggesting that this polyphenol, as well as two other ones studied (curcumin, naringenin) were able to reduce infection, mediators promoting labour-induced experimental inflammation state (LPS-treatment) in human placenta tissue extracts such as human amnion epithelial cells (extracted from foetal membranes) and human uterine smooth muscle cells (derived from human pregnant myometrium) and influenced on oxidative stress markers (being considered as a promoting of several pregnancy-related disorders promoting process, i.e. pre-eclampsia, or preterm labour [32, 33]). Obtained results defined their actions to the modulation of NF-κB signaling pathway playing an important role in human labour and delivery [31]. Apigenin (5 and 20 μM) significantly slowed down the IL-6 secretion, previously stimulated by the lipopolysaccharide (LPS) treatment. Its 20 μM concentration significantly down-regulated the level of LPS-induced IL-6 and IL-8 transcripts in human placenta, foetal membranes and myometrium cells, thus strongly inhibited LPS-stimulated these cytokines secretion, with no effect on the IL-1β-induced encoding gene transcription and release. Furthermore, it strongly lowered the level of LPS-induced COX-2 transcripts and attenuated its secretion. For the PGF2a release results of apigenin action were similar. In placenta, apigenin did not influence the MMP-9 mRNA, previously induced by LPS, moreover it attenuated increased by LPS pro-MMP-9 activity, and down-regulated the IL-1β-stimulated MMP-9 encoding gene transcription. However, in IL-1β stimulated myometrial cells the level MMP-9 transcripts was lowered after the treatment with apigenin with no influence on this IL-1β-induced active metalloproteinase activity [31]. Bearing in mind the fact that oxidative stress may play important, causative role in the processes related with preterm, premature rupture of the membranes (PPROM) [34, 35] prompted authors for the further in-depth examination of this issue. For this purpose the study aiming the influence of this polyphenol on an example of lipid peroxidation marker, such as 8-isoprostane, was conducted, which showed an attenuation of LPS-induced 8-isoprostane secretion in placenta tissue (no potential changes could be detected using the technique in myometrial cells) [36]. Authors concluded that this flavonoid can act as a potent antioxidant leading to the lowering of pro-labour mediators. The effect of this flavone on pro-inflammatory cytokines, prostaglandins and above mentioned metalloproteinase in human gestational tissues suggests its involvement in modulating of events promoting rupture of membranes and PPROM and myometrial contractions. Even more, in placenta in foetal membranes apigenin reduced also LPS-stimulated NF-κB p65 DNA-binding activity. The abovementioned results, along with the results of study by Nicholas *et al.* [37], proving that apigenin is capable to inhibit NF-κB, clearly indicate its properties against inflammation in human gestational tissues via the NF-κB pathway. According to Lim *et al.* [31] besides the obvious beneficial antioxidant and anti-inflammatory actions of apigenin (and two other polyphenols), there is a growing number of information about their toxicity [38], which, according to the authors, together with their multidirectional mechanism of action speaks for a significant extent for the possibility of using their potential application in pregnancy-induced hypertension.

BAICALIN

Natural source and pharmacological profile

Baicalin (5,6-dihydroxy-7-O-glucuronide flavone) (fig. 2a, 2b) is a predominant flavone glycoside occurring in roots of *Scutellaria baicalensis* Georgi (Huang Qin) [3, 39], and also naturally occurring flavonoid in other plants of *Scutellaria* such as *S. lateriflora* L. [40], *S. barbata* D. Don [41], *S. galericulata* L. [4], *S. amoena*, *S. viscidula* [7]. Baicalin has been widely studied in several *in vitro* and *in vivo* models and showed many activities such as: anti-viral [42], anti-oxidative *via* several pathways [43], neuroprotective and enhancin cognitive functions [44, 45], anti-inflammatory [46], anti-cancer [47, 48], and hepatoprotection [49]. In recent years, many studies showed anti-hypertensive properties of baicalin [46, 50-60], and also cardioprotective [50], antiplatelet, anticoagulant, and profibrinolytic activities [61].

In vitro and *ex vivo* studies related to the causes of hypertension
Vasodilatation

Lin *et al.* [59] showed that baicalin at 30 and 100 μM alleviated KCl-induced contraction in a dose dependent manner in isolated rat mesenteric artery.

The mechanism of induced relaxation after administration of baicalin may involve activation of large-conductance Ca^{2+}-activated K^+ (BKCa) channels and inhibition of VDCC channels *via* up-regulating two pathways such as cGMP/PKG and cAMP/PKA.

Renin and ACE inhibitory activities

It is well known that the renin-angiotensin system is a key regulator in the pathogenesis of hypertension. Deng *et al.* [58] revealed *in vitro* that baicalin showed the inhibition of renin activity with an IC_{50} value of 120.36 μM and revealed a low level of inhibition of *angiotensin-converting-enzyme (*ACE) activity with an IC_{50} value of 2.24 mM. Study of interaction showed that a complex of baicalin – renin was more stable in comparison with complex of baicalin – ACE. These results explain stronger inhibition of renin by baicalin compared to ACE inhibition.

Anti-inflammatory activity

Dong *et al.* [62] also studied the anti-inflammatory activity of baicalin (10, 50, 100 μg/ml) on inflammation caused by lipopolysaccharide (LPS) in HBE16 airway epithelial cells. They observed that this flavonoid in a dose-independent manner inhibited expression of mediators such as IL-6, IL-8, and TNF-α *via* preventing signaling NF-κB pathway in cell culture. The anti-inflammatory activity of baicalin was also found in other cell cultures i.e. human arterial endothelial cells (HAECs) exposed to ischemia reperfusion injury [63], human chondrocyte cell line CHON-001 treated with IL-1β [64], human hepatocyte cell lβe [66], human cervical cancer cell lines HeLa and SiHa [67].

In vivo studies related to the various models of hypertension

Baicalin is intensively studied in various animal models of hypertension, atherosclerosis and myocardial ischaemic injury, but most studies were carried out only in model of pulmonary hypertension (PH). Chen and Wang [53] showed in an infant rodent model of PH that baicalin exerted anti-inflammation activity. It was observed that after oral administration in the doses from 10 mg/kg/day to 30 mg/kg/day baicalin significantly attenuated pulmonary arterial pressure, and right ventricular hypertrophy in infant rats. Few biomarkers such as advanced glycation end products, IL 6, TGFβ1 in bronchoalveolar lavage fluid (BALF) were also reduced after baicalin treatment [53]. Furthermore, in this study it was shown that HMGB1/RAGE signaling can be taken into account as a molecular point of action for baicalin. Therefore, baicalin is mentioned as anti-inflammatory flavonoid which can play beneficial role in prevention and treatment of infant PH [53]. Luan *et al.* [46] observed the protective effects of intragastric administration of baicalin (100 mg/kg) in rat model of monocrotaline (MCT)-induced PH. After two weeks it was observed the inhibition of vascular endothelial inflammatory response mainly by decreasing of levels of mRNA for several factors such as TNF-α, IL-1β, IL-6, ET-1, TGF-β1, ICAM-1, NF-κB. Moreover, baicalin caused reducing right ventricular hypertrophy, and attenuating pulmonary vascular remodelling. In other study [54], carried out in the same model of PH, showed that 2% baicalin solution downregulated the p38 mitogen-activated protein kinase MAPK/MMP-9 pathway and expression levels of MMP-9. Huang *et al.* [51] observed additionally that baicalin (60 mg/kg *i.p.*) attenuated chronic hypoxia-induced PH *via* adenosine A2A receptor-induced SDF-1/CXCR4/PI3K/AKT signaling. Liu *et al.* [55] investigated the effects of baicalin

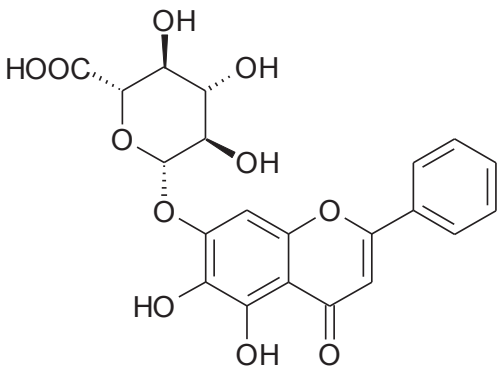

Figure 2a

Chemical structure of baicalin (ISIS Draw)

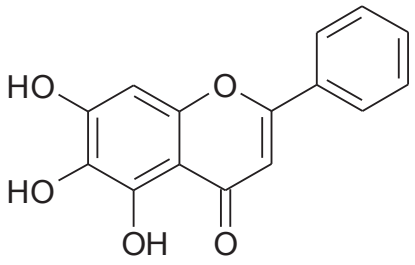

Figure 2b

Chemical structure of baicalein (aglycon of baicalin) (ISIS Draw)

at 30 mg/kg *i.p.* (daily dose) on the synthesis of collagen I in rats with PH caused by hypoxia. The found that baicalin significantly reduced: pulmonary artery pressure, the remodeling of the pulmonary artery under hypoxic conditions, the synthesis of collagen I in pulmonary arteries. Zhang *et al.* [57] showed that baicalin at dose 100 mg/kg *i.p.* (once daily for 14 days) reversed *in vivo* and *in vitro* the reduction of p27 caused by hypoxia and baicalin elevated AKT/protein kinase B phosphorylation p-AKT. In this study it was observed that baicalin could effectively attenuate right ventricular systolic pressures and hypoxia-induced PH. On the other hand, studies in rats with renovascular hypertension showed that baicalin (2 ml of 100 mg/kg baicalin *i.p.* for 4 weeks once a day) has no significant antihypertensive effect [52]. Baicalein (aglycon of baicalin) protected against hypertension associated with diabetes and showed decrease of vascular deleterious effects associated with both insulin deficiency (ID) and insulin resistance (IR) models. El-Bassossy *et al.* [56] carried out study of the potential protective effect of baicalein (100 mg/kg/day) against the hypertensive and harmful vascular effects of streptozotocin induced ID and IR caused by fructose in rats. In this study baicalein abrogated the elevation in blood pressure, and reduced the level of advanced glycation end products in both diabetic models, diminished the collagen deposition within aorta, caused a decrease in circulating serum level of TNF-α, and prevented the activation of the NF-κB in aorta.

Influence in pregnancy

So far, only one study on the effect of baicalin in preeclampsia (PE) has been carried out. Wang *et al.* [67] pointed to the protective role of baicalin during injury of liver and kidney caused by PE in rat model. Baicalin were treated pregnant rats with PE in tree following doses: 50, 100, and 150 mg/kg/day, which were given by the intraperitoneal injection for 20 days. Results showed that apoptosis of liver or kidney cells were gradually down-regulated after application of baicalin at doses of 50 mg/kg and 100 mg/kg. Moreover, expression of protein caspase 9 (indicator for apoptosis) diminished in live after middle dosages of baicalin, and the expression of XIAP (X-linked inhibitor of apoptosis protein) and bcl-2 (B-cell lymphoma 2) were diminished by different doses of baicalin. Additionally, it was indicated that baicalin leads to reversing the apoptotic processes in trophoblast in the placenta tissue of rats and ameliorating the ultrastructure of mitochondria by its down regulation of caspase-9 expression. Other study showed that baicalin promoted embryo adhesion and implantation by upregulating of marker of the endometrial receptivity (fucosyltransferase IV) both in human endometrial cells and endometrium of mouse during the period of implantation [68]. Chen *et al.* [69] observed that baicalin (40 mg/kg, *p.o.*) decreased levels of the estradiol on 4-8 days of pregnancy and increased levels of the progesterone at 3-8 days of pregnancy. Analysis of results allowed to conclude that baicalin possessed tocolytic properties ameliorating the environment of the endometrial tissue for the implantation of the blastocyst. Previously, it was revealed that baicalin showed better anti-abortive effect in comparison with baicalein and wogonin [70]. This activity of baicalin was confirmed by Wang *et al.* [71] which showed protective effects of baicalin on decidua cells of pregnant mice abortion caused by LPS, and anti-abortive activity of baicalin was observed by Ma *et al.* [72] in bromocriptine-treated pregnant mice. On basis of these results it can be concluded that baicalin is safe and may exert beneficial effect on animals during gestation.

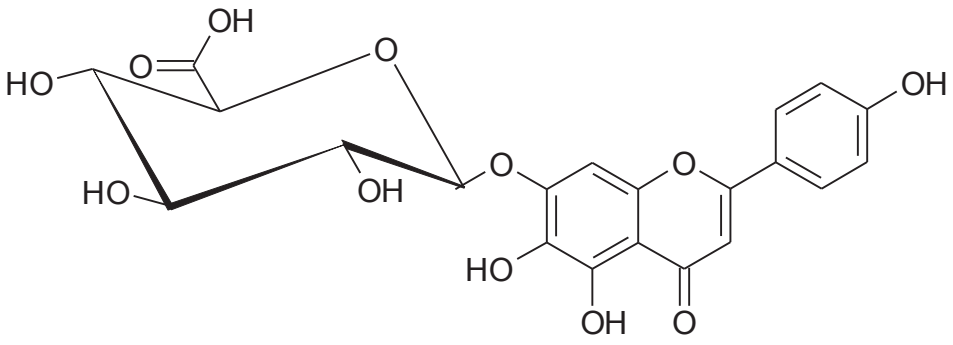

Figure 3

Chemical structure of scutellarin (ISIS Draw)

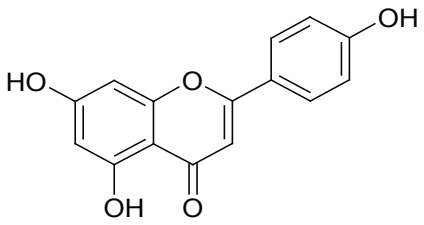

Figure 4

Chemical structure of chrysin (ISIS Draw)

SCUTELLARIN

Natural source and pharmacological profile

Scutellarin (4,5,6-trihydroxy flavonoid-7-glucuronide or scutellarein-7-O-glucuronide) occurs in aerial parts (leaves and flowers) of *Scutellaria baicalensis* Georgi [3], *Scutellaria galericulata* L. [4], and *Erigeron breviscapus* (Vant.) Hand.-Mazz [73, 35]. It was revealed that *Scutellaria* has many activities such as cardioprotective [74], vasoprotective [35, 75], anti-oxidative, anti-inflammatory, vascular relaxative, anti-platelet and anti-coagulative [76]. Many studies revealed neuroprotective effects of scutellarin in various *in vivo* models [76-80]. Moreover, scutellarin improved microcirculation, diminished blood viscosity, showed antihypertensive effect in cerebrovascular diseases [75, 81, 82] and has been successfully used in clinics for treatment of ischaemic diseases in China [83].

In vitro and *ex vivo* studies related to hypertension Vasodilatation, vasoprotection

Recently, Mo *et al.* [73] performed complex studies of scutellarin activity in various models *in vitro*. Their results showed that various concentrations of scutellarin used to estimation of antioxidative properties (total antioxidant capacity – TAC, 2,2-diphenyl-1-picrylhydrazyl - DPPH, superoxide anion, and hydroxyl radical) scavenged all types of radicals in a dose-dependent manner, value of EC_{50} in scavenging hydroxyl radical was 37.11 μM. Scutellarin normalized the changes in expression of mRNA SOD1 (superoxide dismutase 1), and mRNA Nox4 (NADPH oxidase 4) caused by H_2O_2 in a dose-dependent manner. Furthermore, study on influence of scutellarin on human umbilical vein endothelial cells showed that scutellarin at a concentration of 400 μM reduced the proliferation of these cells for 48 h. Moreover, it was observed that scutellarin alone did not induce relaxation in ring of aorta of rabbits. Previously, study [75] carried out in isolated rat coronary artery rings showed the vasoprotective properties of scutellarin (10–1,000 μmol/l) against endothelial dysfunction induced by hypertension. Moreover, scutellarin induced coronary artery vasodilation in an endothelium and protected impairment caused by hypertension by activation of protein kinase signaling pathway. In other study it was showed that scutellarin caused relaxation in endothelium-intact depending on the dose [84]. In cultured human cardiac microvascular endothelial cells, this flavonoid (1 and 10 μM) protected cell viability in dose dependent manner and increased expression of PKG-Iα [83].

ACE inhibitory activities

Wang *et al.* [35] showed the IC_{50} values of scutellarin against ACE *in vitro* is 48.13 μM, and it was concluded by authors that this flavonoid has a potent ACE inhibiting activity. Further studies were carried out by the same authors who applied AutoDock software and it was shown, using docking simulation, that ACE is the specific target of this flavonoid glycoside.

In vivo studies related to the various models of hypertension

Scutellarin (5 mg/kg and 20 mg/kg per day) significantly lowered systolic blood pressure in model of hypertensive rats (hypertension was induced using a 2-kidney, 2-clip method – 2K2C) [81]. It suppressed also the expression of Toll-like receptor 4 (TLR4) induced by hypertension and reduced hypertension-mediated induction of the inflammatory response by decrease the expression of proinflammatory mediators such as: NF-κB, TNF-α, IL-1β, and IL-18. On

the basis of results it was concluded that scutellarin may be use as a potential therapeutic agent in diseases associated with hypertension [81]. In other study [83], scutellarin (45 and 90 mg/kg, *i.v.*) significantly diminished ischemic size in myocardial ischemia reperfusion rat model. Other complex study [35] was performed in rats with permanent middle cerebral artery occlusion. Results showed that scutellarin dose-dependently (25, and 50, and 100 mg/kg *p.o.*) reduced of activity of angiotensin-converting enzyme (ACE) and the mRNA expression of receptor AT1 and ACE, and inflammatory mediators such as TNF-α, IL-6, and IL-1β. levels of these targets and angiotensin II were decreased.

Influence during pregnancy

In recent years studies on the impact of scutellarin during pregnancy in animals have not been published. Previously, acute and subacute toxicity studies in rodents showed that scutellarin has a sufficient margin of safety for therapeutic use [85].

CHRYSIN

Natural source and pharmacological profile

Chrysin (5,7-dihydroxyflavone) is a flavonoid occurring in many plants, honey, and propolis. According to review of Shang *et al.* [7], chrysin was identified in various plant of *Scutellaria* (*Lamiaceae*), such as: *S. amoena* C. H. Wright, *S. baicalensis* Georgi, *S. linearis* Benth., *S. viscidula* Bunge, *S. strigillosa* Hemsley, *S. discolor* Colebr. [5]. Moreover, chrysin was marked in herbs of *Scutellaria galericulata* L. [4], and *Passilora caerulea* L. [86, 87]. Chrysin showed various pharmacological effects, such as anti-inflammatory [88], antioxidant [89], and antihypertensive activity [86, 90, 91, 95], neuroprotective [86], anticancer properties [86], possessed protective effects against toxic agents [92], and many others [86].

In vitro and *ex vivo* studies related to the causes of hypertension

Vasodilatation, vasoprotection

In vitro study using primary human umbilical vein endothelial cells revealed that chrysin inhibited endothelial inflammation *via* the NF-κB signaling pathway because it can decrease level of pro-inflammatory factors [93]. Study performed in aortic rings showed that chrysin at concentration 10 μM stimulated release of nitric oxide from endothelial cells and lead to aortic relaxation *via* increasing of cGMP concentration in cells [94]. Additionally, chrysin (1, 10, and 100 μM) highly diminished proliferation in the cultured pulmonary artery smooth muscle cells. Furthermore, this dihydroxyflavone reduced the upregulated mRNA and expressions of collagen I and collagen III after hypoxia and chrysin could inhibit expression of mRNA NOX4. Next observation showed, that in this cell culture reduced generation of reactive oxygen species and content of malondialdehyde [91].

In vivo studies related to the various models of hypertension

Beneficial effect of chrysin was observed in pulmonary hypertensive rats after hypoxia [91]. In this study showed that treatment with chrysin at doses 50 or 100 mg/kg/day (s.c.) for 4 weeks significantly ameliorated homodynamic and cardiovascular remodeling, alleviated hypertrophy of the right ventricle and pulmonary arteries. Chrysin decreased also proliferation of smooth muscle cells in the vascular media of small pulmonary arteries [91]. Veerappan and Malarvili [90] observed that chrysin (25 mg/kg/day for 4 weeks, *p.o.*) administered to rats with hypertension caused by N-nitro-L-arginine methyl ester showed antihypertensive effect throughout the following mechanism of action such as: reduction in functions of left ventricular, oxidative stress in cardiac tissue and level of angiotensin II in plasma, and increasing of hexooxygenase in cardiac tissue, concentration of cGMP and a prevention of plasma nitric oxide loss. Other study was carried out to estimation of effects of chrysin supplementation on blood pressure of rats fed a high-fat and high-sucrose diet in comparison with quercetin [95]. Results showed that chrysin suppressed the elevation of blood pressure in normotensive rats and exerted an antihypertensive effect similar to quercetin.

Influence during pregnancy

There is a lack of scientific evidence on the use of chrysin during pregnancy. Chrysin did not showed activity using ovarian aromatase [96] or in endometrial cells [97].

CONCLUSION AND SUMMARY

In summary, the review of current studies shows that apigenin, baicalin, and also chrysin or scutellarin possess antihypertensive activities *via* various mechanisms of action. Apigenin and baicalin are the most investigated in this field and they showed mainly vasodilatative properties and protective activities for endothelial cells. So far, data on their effects in pregnancy-induced hypertension are generally (except baicalin) unavailable. Therefore, it would be interesting to conduct research on apigenin, baicalin, chrysin, scutellarin as a new potential complex plant-origin drugs in the treatment of hypertension induced by pregnancy in animal models.

Ethical approval: The conducted research is not related to either human or animal use.

Conflict of interest: Authors declare no conflict of interest.

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