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# Effect of baicalin on gestational hypertension-induced vascular endothelial cell damage

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## Abstract

**Objective:** Baicalin is a compound extracted from the dried root of *Scutellaria baicalensis* Georgi. Studies have shown that baicalin has a protective effect on vascular endothelial cells, but whether baicalin could alleviate ascular endothelial cell damage in pregnancy-induced hypertensive patients remains unknown.

**Materials and methods:** We established a hypertensive pregnant rat model to study vascular endothelial injury during pregnancy-induced hypertension. Plasma epoprostenol (PGI-2), thromboxane A2 (Txa-2), β-human chorionic gonadotropin (β-HCG), and estrogen levels in rats were detected using ELISA. Vascular endothelial growth factor (VEGF), endothelial nitric oxide synthase (eNOS), and C-reactive protein (CRP) expression were detected using western blotting and quantitative PCR (q-PCR).

**Results:** Results showed that baicalin alleviated symptoms of pregnancy-induced hypertension. CRP, Txa-2, and β-HCG expression were significantly upregulated, while VEGF, eNOS, PGI-2, and estrogen expression was decreased in plasma and placental tissues of hypertensive rats. However, the levels of these injury indicators were significantly decreased after baicalin therapy, while the expression of protective indicators was significantly increased.

**Conclusion:** Baicalin reversed vascular endothelial cell injury in pregnant hypertensive rats by promoting VEGF, eNOS, PGI-2, and estrogen expression.

## Keywords

Pregnancy induced hypertension, baicalin, vascular endothelial cell injury, VEGF, eNOS, PGI-2, estrogen

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## Introduction

Pregnancy-induced hypertension is a common disease in pregnant women. The main symptoms of this disease are a persistent increase in blood pressure, proteinuria, and edema after 20 weeks gestation. These symptoms will affect normal fetal development.[1] Pregnancy-induced hypertension is also harmful for the pregnant woman. When gestational-induced hypertension occurs, the permeability of the glomerular filtration barrier is increased and a large amount of albumin is filtered by the glomerulus, which in turn causes edema and severe complications such as metabolic disorders.[2] The liver is the main organ of metabolism. Higher levels of estrogen and progesterone in the serum of pregnant women markedly affect the metabolic process of the liver, which increases synthesis and secretion of enzymes and accelerates metabolism of harmful substances. In patients with pregnancy-induced hypertension, because of hepatic arteriolar vasoconstriction and hepatic ischemic injury, liver metabolism is suppressed, which affects the health of the pregnant woman.[2] Studies have shown that the hypertension will lead to the damage of the vascular endothelium.[3] Vascular endothelial injury accompanied by decreasing nitric oxide (NO) bioavailability could ultimately lead to the development and occurrence of multiple vascular diseases.[4] Elevated blood pressure levels can be treated with many different drugs, but complications such as vascular endothelial damage that is associated with hypertension is difficult to treat and resolve.[5,6] Therefore, it is critical to develop a new medicine to treat various types of hypertension including pregnancy-induced hypertension and complications such as vascular endothelial injury.

The *Scutellaria baicalensis* Georgi is a traditional Chinese medicine. Many studies have revealed that *S. baicalensis* Georgi could exert antioxidant, anti-inflammatory, antibacterial, and immune-enhancing functions.[7–11] Baicalin is a flavonoid that was extracted from the dried roots of *S. baicalensis* Georgi. Baicalin has been widely studied as an extract from traditional Chinese medicine, and some studies indicated that baicalin could exert anti-inflammatory effects through various routes.[12,13] Baicalin has also shown anti-tumor efficacy, and it could suppress the occurrence and development of tumors by inducing cell cycle arrest.[14,15] Studies have revealed that baicalin could inhibit the development of breast cancer and induce apoptosis in gallbladder carcinoma.[16,17] Moreover, another study showed that baicalin could enhance the viability and decrease the apoptosis rates of arterial endothelial cells.[18] Baicalin could also protect endothelial cells from the angiotensin II-induced endothelial dysfunction.[19] Thus, baicalin has a therapeutic effect on many diseases including vascular endothelial injury and dysfunction. However, whether baicalin can be used to treat vascular endothelial injury, which is a complication of pregnancy-induced hypertension, remains unknown.

In our research, we established pregnancy-induced hypertension animal models and these rats were treated with baicalin. Blood pressure and urinary protein content were then measured. Plasma and placental vascular endothelial growth factor (VEGF), endothelial nitric oxide synthase (eNOS), and C-reactive protein (CRP) levels in these rats were measured to clarify the efficacy of baicalin on the damage to the vascular endothelium,

which is a complication of pregnancy-induced hypertension.

## Materials and methods

The experiments in this study were approved by the ethics committee at Shanghai Sixth People's Hospital.

### *Establishment of the hypertensive rat model*

In this study, we established the hypertensive rat model by intraperitoneal injection of the nitric oxide synthase (NOS) inhibitor N(ω)-nitro-L-arginine methyl ester (L-NAME). Rats were treated using the L-NAME dose that was determined in a previous study.[20] These pregnant rats were intraperitoneally injected with L-NAME from day 11 to day 18 (50 mg/kg, once a day) to establish the hypertension model. The specific pathogen free (SPF) levels in Sprague–Dawley rats (13–14 weeks) were obtained from the Laboratory Animal Center, Shanghai Academy of Chinese Science (Shanghai, China). All rats were divided into six groups (control group, positive group-magnesium sulfate 100 mg/kg, model group, baicalin 50 mg/kg, baicalin 100 mg/kg, and baicalin 150 mg/kg). The pregnant rats in the control group were intraperitoneally injected with normal saline from day 11 to day 18. The model group was injected with the L-NAME once a day (50 mg/kg). The positive group was injected with magnesium sulfate (100 mg/kg), which is an effective drug to induce hypertension in pregnancy.[21,22] The baicalin groups were injected with different doses of the baicalin. The blood pressure (systolic blood pressure) in the caudal artery of these pregnant rats was detected on days 8 and 18, respectively. A 24-hour urine sample was collected from these rats to detect changes in the urine protein content. All the pregnant rats were sacrificed after 3 weeks. The placental tissue was then collected and stained using hematoxylin and eosin (HE). HE staining was performed based on the standard procedure (fixation, dehydration, embedding, section, and staining).

### *Blood pressure and urine protein measurement*

A rat sphygmomanometer was used to detect blood pressure in the caudal artery on days 8 and 18 to confirm establishment of the hypertension models. The rats' tails were initially warmed, and then a fixator was used to limit the rats' movement. Blood pressure (systolic blood pressure), using the same position on the rats' tail, was detected using the rat sphygmomanometer (Yuyan Co., Shanghai, China). Urine output from these pregnant rats was collected on days 9 and 19. The urine protein content was examined using the bicinchoninic acid (BCA) (Beyotime, Jiangsu, China) method.

### *ELISA assay*

Plasma epoprostenol (PGI-2; Cayman Chemical Co., Ann Arbor, MI, USA), thromboxane A2 (Txa-2; Cayman Chemical Co.), β-human chorionic gonadotropin (β-HCG; ab53087, Abcam, Cambridge, MA, USA), and estrogen levels were determined using ELISA assays, in accordance with the manufacturer's protocol. Plasma was collected when the rats were sacrificed. A reagent tube (BD Biosciences, San Jose, CA, USA), which contained an anticoagulant, was used to collect and extract the plasma.

### Western blotting

Placental VEGF (ab32152, Abcam), eNOS (ab76198, Abcam), and CRP (ab211631, Abcam) levels were detected using Western blotting. RIPA (Beyotime) was used to extract the proteins from the tissues. The sample concentration was then determined using the BCA method. Loading buffer (Beyotime) was added to the samples and they were incubated at 99°C for 10 minutes. These samples were separated using 10% sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE; Beyotime). Then these proteins were transferred to a polyvinylidene fluoride (PVDF) membrane (Millipore, Billerica, MA, USA), and the membrane was blocked with 5% skimmed milk powder and incubated with the primary antibody at 4°C overnight. The next day, the membrane was washed with the phosphate buffered saline Tween-20 (PBST) three times. The membrane was then incubated with the second antibody at the room temperature for 2 hours, and the membrane was washed with the PBST three times and exposed using a Tanon 4600 (Tanon Co., Shanghai, China).

### RT-PCR

Total RNA was extracted from the rat placenta using Trizol (Thermo Fisher Scientific, Rockford, IL, USA) method. The mRNA was then reverse transcribed using a Reverse Transcriptase kit (Takara, Shiga, Japan). PCR was performed using the Applied Biosystems$^{TM}$ 7500 (Thermo Fisher Scientific). The target gene levels were calculated using the $2^{-\Delta\Delta CT}$ method. Glyceraldehyde 3-phosphate dehydrogenase (GAPDH) was used as a reference gene. The primers used in this research are listed in Table 1.

**Table 1.** Primer sequences.

| Gene | Primer sequence |
|---|---|
| VEGF | Forward primer: 5′-AATCGAGACCCT GGTGGACA-3′ |
| | Reverse primer: 5′-TTAACTCAAGCT GCCTCGCC-3′ |
| eNOS | Forward primer: 5′-GACCAGAAACTG TCTCACCTG-3′ |
| | Reverse primer: 5′-CGAACATCGAAC GTCTCACA-3′ |
| CRP | Forward primer: 5′-ATTTCCCAGTCT GTAAATAAGCAAA-3′ |
| | Reverse primer: 5′-AATGGGAAATGG TAACATATTAATC-3′ |
| GAPDH | Forward primer: 5′-GAGTCAACGGAT TTGGTCGT-3′ |
| | Reverse primer: 5′-GACAAGCTTCCC GTTCTCAG-3′ |

VEGF, vascular endothelial growth factor; eNOS, endothelial nitric oxide synthase; CRP, C-reactive protein; GAPDH, glyceraldehyde 3-phosphate dehydrogenase.

### Statistical analysis

Data analysis was performed using GraphPad Prism7 (GraphPad Software Inc., La Jolla, CA, USA). A Student's *t*-test was used to determine the differences between groups. The data are presented as the mean ± standard deviation (SD). P values $< 0.05$ was considered to represent a significant difference. All the experiments were repeated three times.

## Results

### Baicalin reduced the symptoms of pregnancy-induced hypertension

Hypertension during pregnancy is a normal gynecological disease. Previous research has established a rat model of hypertension in pregnancy by adding the L-NAME into the drinking water of pregnant rats to induce the higher blood pressure (systolic blood pressure $\geq$140 mmHg).[23] We constructed a rat model to study hypertension during

pregnancy in this study. Blood pressure was measured to confirm the establishment of the hypertension models and the effect of the baicalin. As shown in Figure 1a and Figure 1b, the blood pressure in the model group was significantly higher compared with the control group ($P < 0.05$). After 24 hours, the urinary protein content was also increased compared with the control group ($P < 0.05$). However, after baicalin treatment, the blood pressure of these rats had significantly decreased ($P < 0.05$) and the urinary protein content was also significantly decreased after 24 hours ($P < 0.05$) compared with the model group. With an increase in the baicalin dose, the symptoms resolved. The blood pressure and urinary protein content in the positive control group rats, which received magnesium sulfate to induce high blood pressure, was similar compared with the baicalin treated groups.

## *Baicalin alleviated placental injury*

HE staining was performed to observe the pathological changes in the placenta. The main cells of placental villus in the control group were syncytiotrophoblasts, and there were fewer cytotrophoblasts in the placental villus compared with the control group (Figure 2). Compared with the control group, the number of placental villi decreased and the structure of the placental villi shrank, part of the villus showed fibrinoid necrosis, and the trophoblast cells showed compensatory proliferation in the model group. However, after baicalin treatment, the placental villous fibrosis and the syncytiotrophoblast nodules were reduced. The status of the HE staining in the positive group was similar to that of the control group. Therefore, baicalin treatment reduced the formation of nodules and lesions that were induced by hypertension during pregnancy in the placenta.

## *Baicalin reduced vascular endothelial cell damage during the progression of pregnancy-induced hypertension*

To further explore the effect of the baicalin, we determined the PGI-2 and Txa-2 levels

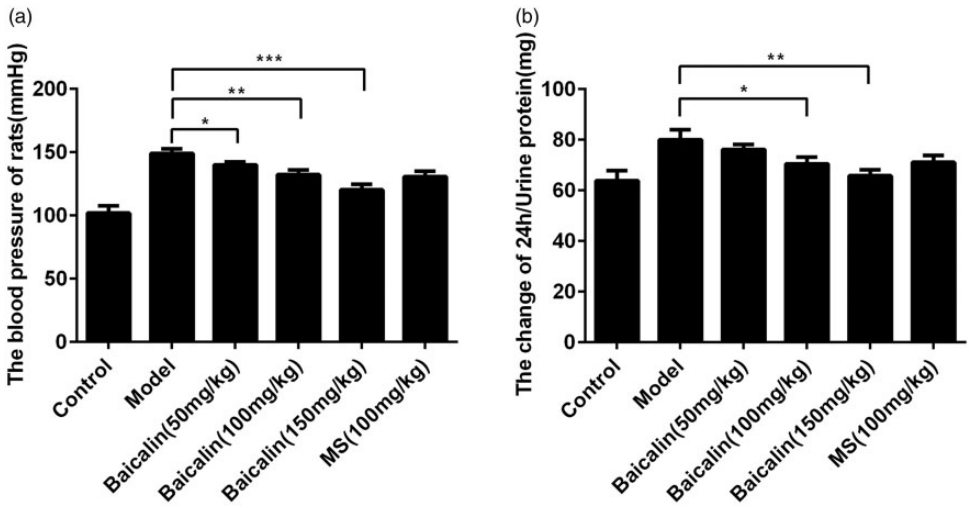


**Figure 1.** Hypertensive symptoms in rats were alleviated after baicalin therapy. (a) Rat blood pressure was measured using a rat blood pressure meter. (b) The urine protein content was detected using commercial kits. *p<0.05, **p<0.01, ***p<0.001.
MS, magnesium sulfate (used as a positive control).

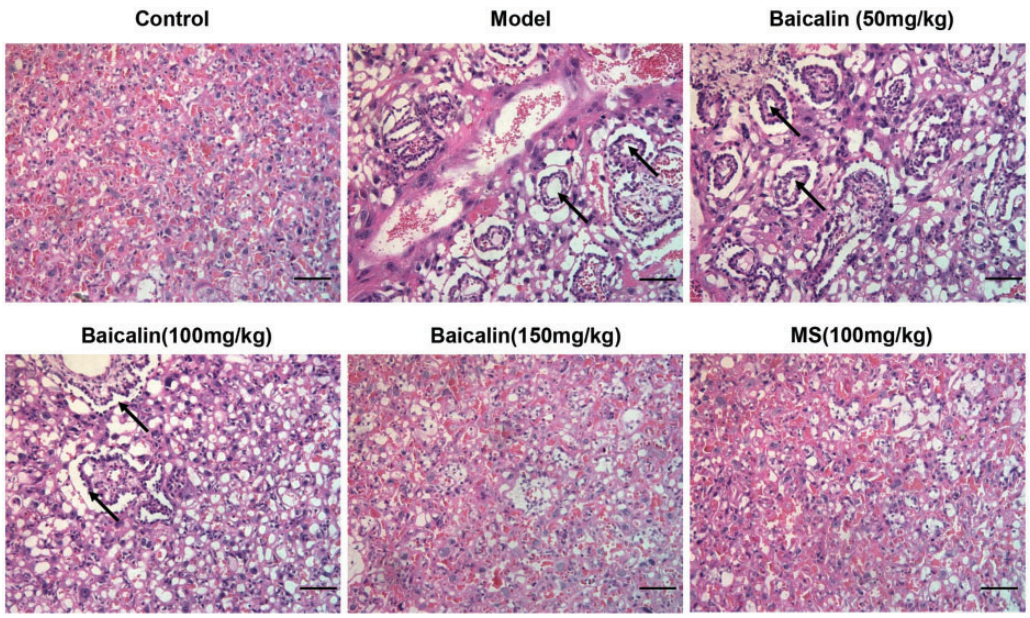


**Figure 2.** Treatment with baicalin reversed placental damage. Representative photographs of HE stained placenta. These images showed that baicalin therapy reversed the formation of nodules and lesions. Scale bar, 100 μm.
HE, hematoxylin and eosin.

in the plasma (Figure 3a). The PGI-2 levels in the model group were decreased ($P < 0.05$), while Txa-2 levels were increased ($P < 0.05$) compared with the control group. After treatment with baicalin, Txa-2 levels remained decreased and PGI-2 levels remained increased. The Txa-2 levels decreased and PGI-2 levels increased with an increasing of dose of baicalin. Additionally, β-HCG and estrogen levels in the plasma were detected. The results (Figure 3a) showed that compared with the control group, β-HCG levels were increased ($P < 0.05$), but estrogen levels were decreased ($P < 0.05$) in the model group. In the baicalin-treated group, β-HCG expression was suppressed ($P < 0.001$) and the estrogen level was gradually increased ($P < 0.01$) compared with the model group. Similarly, the degree of the change in these proteins increased with an increasing dose of baicalin.

VEGF plays a crucial role in the health of endothelial blood vessels, and eNOS is also critical for the health of the vascular endothelium. Therefore, VEGF and eNOS expression in placental tissues of these rats were detected using the qPCR and western blotting. The results show that the VEGF and eNOS expression was suppressed after the construction of the model compared with the control group ($P < 0.05$ for both). However, with the increase in the baicalin dose, eNOS and VEGF levels gradually increased ($P < 0.01$ for all) (Figure 3b and Figure 3c). In addition, the CRP is a widely studied marker of inflammation, and it has often been used to predict the risk of cardiovascular disease.[24,25] In our research, we showed that the CRP levels in the placental tissues of these rats were increased in the model group compared with the control group ($P < 0.05$), and the CRP levels were decreased after treatment with baicalin

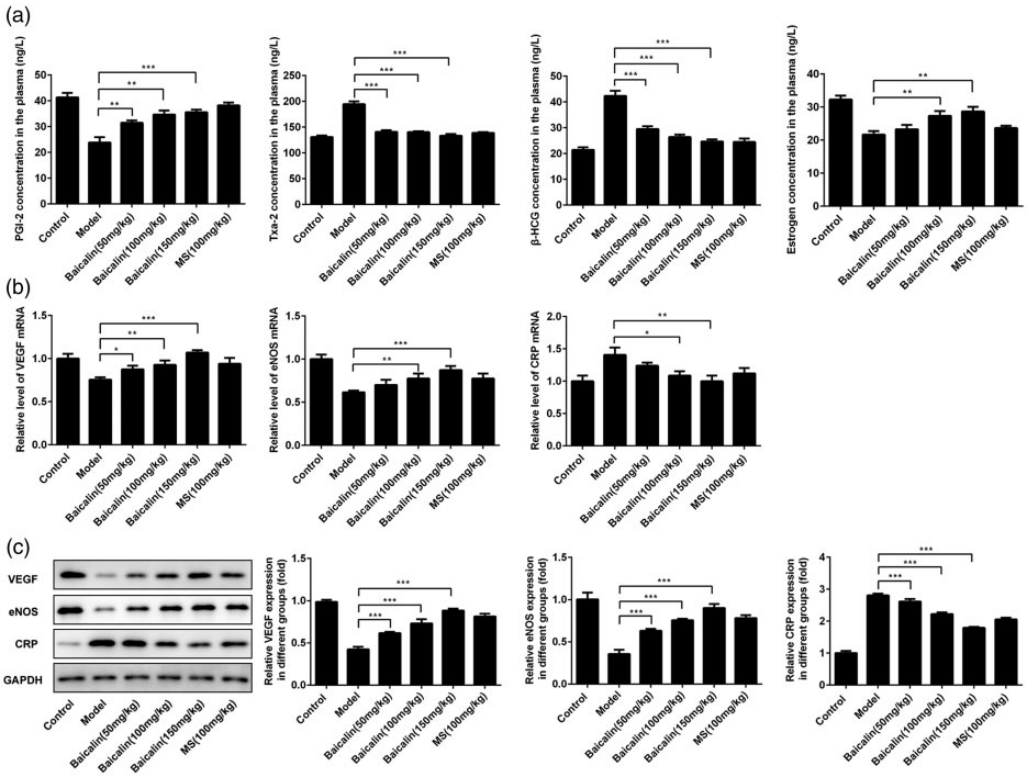


**Figure 3.** Treatment with baicalin reduced vascular endothelial cell damage. (a) PGI-2, Txa-2, $\beta$-HCG, and estrogen levels in plasma were determined using ELISA. (b) VEGF, eNOS, and CRP mRNA levels were detected using q-PCR. (c) VEGF, eNOS, and CRP protein levels were determined using western blotting. Quantitative protein expression data were also displayed in this figure.
*p<0.05, **p<0.01, ***p<0.001.
PGI-2, prostacyclin-2; Txa-2, thromboxane-2; $\beta$-HCG, $\beta$-human chorionic gonadotropin; ELISA, enzyme-linked immunosorbent assay; VEGF, vascular endothelial growth factor; eNOS, endothelial nitric oxide synthase; CRP, C-reactive protein; q-PCR, quantitative polymerase chain reaction; MS, magnesium sulfate (used as a positive control).

compared with the model group ($P < 0.05$ for all) (Figure 3b and Figure 3c).

## Discussion

Pregnancy-induced hypertension is a common disease during the gestational period. It includes preeclampsia, eclampsia, and gestational hypertension, and it is also an important cause of maternal death worldwide.[26] The development of pregnancy-induced hypertension is also accompanied by proteinuria, edema, and vascular endothelial injury. Vascular endothelial injury and dysfunction are primary complications in multiple types of hypertension including the pregnancy-induced hypertension.[3] Research has indicated that pregnancy-induced hypertension patients often have a decrease in circulating endothelial cells and circulating endothelial progenitor cells.[27]

VEGF is a protein that causes angiogenesis and maintains vascular endothelial cell

health.[28] Upregulation of VEGF could protect the HUVECs from apoptosis.[29] CRP is an indicator of inflammation and damage to the vascular endothelium.[30] Higher CRP levels increase the risk of hypertension and cerebrovascular disease.[31] In this study, we found that VEGF and eNOS expression in plasma and placental tissues from pregnancy-induced hypertension rats were lower, but CRP levels were higher compared with the control group. Therefore, our results indicated that pregnancy-induced hypertension is associated with vascular endothelial injury. Additionally, Txa-2 and PGI-2 play an important role in the blood. PGI-2 is a powerful anticoagulant that could inhibit the development of atherosclerosis.[32,33] A study also showed that Txa-2 could prevent blood vessel formation.[34] We observed that PGI-2 expression decreased while Txa-2 levels increased in the model group compared with the control group. These experimental results further demonstrated that pregnancy-induced hypertension could lead to vascular endothelial injury and dysfunction.

The baicalin is a component that is extracted from *S. baicalensis* Georgi. Some studies showed that baicalin could suppress the development of different cancers.[35–37] Other studies revealed that baicalin could scavenge free radicals, thereby showing an antioxidant effect.[38] Recently, some studies suggested that baicalin could alleviate hypoxia-induced endothelial injury and the angiotensin II-induced endothelial dysfunction.[19,39] Other studies showed that baicalin alleviated hypertension in rats and reduced pressure in pulmonary arteries.[40,41] In this research, we revealed that the symptoms of pregnancy-induced hypertension were decreased after the treatment with baicalin. Additionally, PGI-2, estrogen, VEGF, and eNOS levels were increased while CRP, Txa-2, and β-HCG levels were inhibited after baicalin treatment. These findings suggest that baicalin could alleviate vascular endothelial damage that is associated with progression of pregnancy-induced hypertension. Furthermore, placental health often affects normal growth of the embryo and fetus. A recent study showed that the infiltration of placental tissue cells is associated with the development of pregnancy-induced hypertension.[42] In our study, we found that the placental villi were significantly reduced in the model group, and this reduction was reversed after treatment with baicalin. This suggests that baicalin alleviates vascular endothelial injury and reduces damage to the placenta, which occurs during pregnancy-induced hypertension. Therefore, these experimental results showed that baicalin could maintain the health of blood vessels and the vascular endothelium, and it could also ensure the normal physiological function of the blood vessels.

Overall, these results demonstrated the protective efficacy of baicalin against vascular endothelial and placental injury. The results suggest the value of baicalin for treating vascular endothelial injury during pregnancy-induced hypertension. Our research also provides a traditional Chinese medicine-based approach for the clinical treatment of pregnancy-induced hypertension.

## Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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## References


1. Sun Z, Cade R, Zhang Z, et al. Angiotensinogen gene knockout delays and attenuates cold-induced hypertension. *Hypertension* 2003; 41: 322–327.
2. Kintiraki E, Papakatsika S, Kotronis G, et al. Pregnancy-induced hypertension. *Hormones (Athens)* 2015; 14: 211–223.
3. Li N, Luo W, Juhong Z, et al. Associations between genetic variations in the FURIN gene and hypertension. *BMC Med Genet* 2010; 11: 124.
4. Legeay S, Rodier M, Fillon L, et al. Epigallocatechin gallate: a review of its beneficial properties to prevent metabolic syndrome. *Nutrients* 2015; 7: 5443–5468.
5. Lou M, Zong XF and Wang LL. Curative treatment of hypertension by physical exercise. *Eur Rev Med Pharmacol Sci* 2017; 21: 3320–3326.
6. Lu J, Lu Y, Wang X, et al. Prevalence, awareness, treatment, and control of hypertension in China: data from 1.7 million adults in a population-based screening study (China PEACE Million Persons Project). *Lancet* 2017; 390: 2549–2558.
7. Huang WH, Lee AR and Yang CH. Antioxidative and anti-inflammatory activities of polyhydroxyflavonoids of Scutellaria baicalensis Georgi. *Biosci Biotechnol Biochem* 2006; 70: 2371–2380.
8. Jeong K, Shin YC, Park S, et al. Ethanol extract of Scutellaria baicalensis Georgi prevents oxidative damage and neuroinflammation and memorial impairments in artificial senescence mice. *J Biomed Sci* 2011; 18: 14.
9. Xu C and Ji GE. Bioconversion of flavones during fermentation in milk containing Scutellaria baicalensis extract by Lactobacillus brevis. *J Microbiol Biotechnol* 2013; 23: 1422–1427.
10. Yoon JJ, Jeong JW, Choi EO, et al. Protective effects of Scutellaria baicalensis Georgi against hydrogen peroxide-induced DNA damage and apoptosis in HaCaT human skin keratinocytes. *EXCLI J* 2017; 16: 426–438.
11. Zhou Y, Yang ZY and Tang RC. Bioactive and UV protective silk materials containing baicalin - The multifunctional plant extract from Scutellaria baicalensis Georgi. *Mater Sci Eng C Mater Biol Appl* 2016; 67: 336–344.
12. Huang Y, Sun M, Yang X, et al. Baicalin relieves inflammation stimulated by lipopolysaccharide via upregulating TUG1 in liver cells. *J Physiol Biochem* 2019; 75: 463–473.
13. Meng X, Hu L and Li W. Baicalin ameliorates lipopolysaccharide-induced acute lung injury in mice by suppressing oxidative stress and inflammation via the activation of the Nrf2-mediated HO-1 signaling pathway. *Naunyn Schmiedebergs Arch Pharmacol* 2019; 392: 1421–1433.
14. Pan TL, Wang PW, Leu YL, et al. Inhibitory effects of Scutellaria baicalensis extract on hepatic stellate cells through inducing G2/M cell cycle arrest and activating ERK-dependent apoptosis via Bax and caspase pathway. *J Ethnopharmacol* 2012; 139: 829–837.
15. Park JR, Lee MC, Moon SC, et al. Scutellaria baicalensis Georgi induces caspase-dependent apoptosis via mitogen activated protein kinase activation and the generation of reactive oxygen species signaling pathways in MCF-7 breast cancer cells. *Mol Med Rep* 2017; 16: 2302–2308.
16. Shu YJ, Bao RF, Wu XS, et al. Baicalin induces apoptosis of gallbladder carcinoma cells in vitro via a mitochondrial-mediated pathway and suppresses tumor growth in vivo. *Anticancer Agents Med Chem* 2014; 14: 1136–1145.
17. Zhou QM, Wang S, Zhang H, et al. The combination of baicalin and baicalein enhances apoptosis via the ERK/p38 MAPK pathway in human breast cancer cells. *Acta Pharmacol Sin* 2009; 30: 1648–1658.
18. Shou X, Wang B, Zhou R, et al. Baicalin suppresses hypoxia-reoxygenation-induced arterial endothelial cell apoptosis via suppressing PKCdelta/p53 signaling. *Med Sci Monit* 2017; 23: 6057–6063.
19. Wei X, Zhu X, Hu N, et al. Baicalin attenuates angiotensin II-induced endothelial dysfunction. *Biochem Biophys Res Commun* 2015; 465: 101–107.
20. Wang Y, Huang M, Yang X, et al. Supplementing punicalagin reduces oxidative stress markers and restores angiogenic

balance in a rat model of pregnancy-induced hypertension. *Korean J Physiol Pharmacol* 2018; 22: 409–417.
21. Ma L, Li L, Han P, et al. Effect of the drug combination of magnesium sulfate and phentolamine on homocysteine and C-reactive protein in the serum of patients with pregnancy-induced hypertension syndrome. *Exp Ther Med* 2019; 17: 3682–3688.
22. Magee LA and Von Dadelszen P. State-of-the-art diagnosis and treatment of hypertension in pregnancy. *Mayo Clin Proc* 2018; 93: 1664–1677.
23. Soobryan N, Murugesan S, Phoswa W, et al. The effects of sildenafil citrate on uterine angiogenic status and serum inflammatory markers in an L-NAME rat model of pre-eclampsia. *Eur J Pharmacol* 2017; 795: 101–107.
24. Pepys MB and Hirschfield GM. C-reactive protein: a critical update. *J Clin Invest* 2003; 111: 1805–1812.
25. Ridker PM. High-sensitivity C-reactive protein: potential adjunct for global risk assessment in the primary prevention of cardiovascular disease. *Circulation* 2001; 103: 1813–1818.
26. Say L, Chou D, Gemmill A, et al. Global causes of maternal death: a WHO systematic analysis. *Lancet Glob Health* 2014; 2: e323–e333.
27. Heimrath J, Paprocka M, Czekanski A, et al. Pregnancy-induced hypertension is accompanied by decreased number of circulating endothelial cells and circulating endothelial progenitor cells. *Arch Immunol Ther Exp (Warsz)* 2014; 62: 353–356.
28. Li XD, Hong MN, Chen J, et al. Adventitial fibroblast-derived VEGF promotes vasa vasorum-associated neointima formation and macrophage recruitment. *Cardiovasc Res* 2020; 116: 708–720.
29. He B, Fu GH, Du XF, et al. Halofuginone protects HUVECs from H2O2-induced injury by modulating VEGF/JNK signaling pathway. *J Chin Med Assoc* 2019; 82: 92–98.
30. Shaul PW. Role of the endothelium in the metabolic syndrome: IIB or not IIB. *Am J Med Sci* 2015; 349: 3–5.
31. Liu Y, Jia SD, Yao Y, et al. Impact of high-sensitivity C-reactive protein on coronary artery disease severity and outcomes in patients undergoing percutaneous coronary intervention. *J Cardiol* 2020; 75: 60–65.
32. Frangos JA, Eskin SG, McIntire LV, et al. Flow effects on prostacyclin production by cultured human endothelial cells. *Science* 1985; 227: 1477–1479.
33. Kawabe J, Ushikubi F and Hasebe N. Prostacyclin in vascular diseases. - Recent insights and future perspectives. *Circ J* 2010; 74: 836–843.
34. Mohanty I, Singh J and Rattan S. Downregulation of thromboxane A2 and angiotensin II type 1 receptors associated with aging-related decrease in internal anal sphincter tone. *Sci Rep* 2019; 9: 6759.
35. Gao Y, Liu H, Wang H, et al. Baicalin inhibits breast cancer development via inhibiting IkB kinase activation in vitro and in vivo. *Int J Oncol* 2018; 53: 2727–2736.
36. Ma W, Liu X and Du W. Baicalin induces apoptosis in SW480 cells through downregulation of the SP1 transcription factor. *Anticancer Drugs* 2019; 30: 153–158.
37. Zhu Y, Fang J, Wang H, et al. Baicalin suppresses proliferation, migration, and invasion in human glioblastoma cells via Ca (2+)-dependent pathway. *Drug Des Devel Ther* 2018; 12: 3247–3261.
38. Hsu H, Huang J, Shu HB, et al. TNF-dependent recruitment of the protein kinase RIP to the TNF receptor-1 signaling complex. *Immunity* 1996; 4: 387–396.
39. Luo S, Li S, Zhu L, et al. Effect of baicalin on oxygen-glucose deprivation-induced endothelial cell damage. *Neuroreport* 2017; 28: 299–306.
40. Ding L, Jia C, Zhang Y, et al. Baicalin relaxes vascular smooth muscle and lowers blood pressure in spontaneously hypertensive rats. *Biomed Pharmacother* 2019; 111: 325–330.
41. Liu P, Yan S, Chen M, et al. Effects of baicalin on collagen I and collagen III expression in pulmonary arteries of rats with hypoxic pulmonary hypertension. *Int J Mol Med* 2015; 35: 901–908.
42. Zhang Y, Li P, Guo Y, et al. MMP-9 and TIMP-1 in placenta of hypertensive disorder complicating pregnancy. *Exp Ther Med* 2019; 18: 637–641.