Extended|Longevity

Cognilace Product Information Sheet

Cognilace™ contains **Phytotherapeutic** Extracts of ***Astragulus membracanus, Salvia miltiorrhiz, Radic Paoenia rubras, Polygonum multiflorum, Dryobalanops aromatica (Borneal), Callus spatholobi and Cinnamomum vera*.** The principal action of **Cognilace** is in modulating the Integrated Stress Response (ISR) by modulating the PERK pathways that induce the sustained PERK signaling associated with chronic or severe endoplasmic reticulum (ER) insults. Imbalances in ER proteostasis can propagate to extracellular environments through the secretion of proteins in non-native conformations that accumulate as toxic oligomers and aggregates associated with proteotoxicity in etiologically diverse protein aggregation diseases, including many amyloid diseases.

Consistent with a role for PERK in dictating both protective and pro-apoptotic responses to specific ER insults, imbalances in PERK activity caused by genetic, environmental, or aging-related factors is implicated in the pathogenesis of diverse diseases. Sustained PERK signaling associated with chronic or severe ER insults is implicated in neurodegeneration associated with diseases such as Alzheimer's disease and prion disease.

The PERK signaling arm of the unfolded protein response (UPR) has a critical role in defining cellular survival in response to pathologic insults that disrupt endoplasmic reticulum (ER) proteostasis (i.e., ER stress). PERK is activated in response to ER stress through a mechanism involving PERK dimerization and autophosphorylation. Once activated, PERK phosphorylates the α subunit of eukaryotic initiation factor 2 (eIF2α). This results in both a transient attenuation in new protein synthesis and the activation of stress-responsive transcription factors such as ATF4. PERK-dependent ATF4 activation induces expression of stress-responsive genes involved in diverse biologic functions including cellular redox, amino acid biosynthesis, and apoptotic signaling. Apart from eIF2α, PERK also phosphorylates NRF2 to promote cellular redox regulation during ER stress. Through this integration of transcriptional and translational signaling, PERK has a central role in dictating cellular proteostasis and survival in response to varying levels of ER stress. During acute ER insults, PERK signaling is important for regulating protective biologic functions including metabolite homeostasis, cellular redox homeostasis and mitochondrial function.

Alterations in PERK signaling can challenge extracellular proteostasis by reducing the secretion of proteins in native, functional conformations and increasing the extracellular accumulation of soluble oligomers associated with the pathogenesis of diverse protein aggregation diseases. Imbalances in PERK signaling are implicated in the onset and pathogenesis of etiologically diverse diseases. PERK inhibition during ER stress increases the secretion of the disease relevant amyloidogenic proteins in non-native conformations that accumulate extracellularly as soluble oligomers. This indicates that PERK signaling has an important role in dictating extracellular proteostasis by controlling the conformational integrity of secreted proteins. Genetic, aging-related, or pharmacologic conditions that reduce PERK signaling could lead to pathologic imbalances in extracellular proteostasis that contribute to human disease.

The Phytotherapeutic ingredients in **Cognilace** include:

Astragalus membranaceus Suppression of PERK-ATF4-CHOP pathway by Astragaloside IV (AS-IV) is associated with inhibition of ER stress-induced podocyte apoptosis. The protective effect of AS-IV on ER stress-induced podocyte apoptosis is associated with inhibition of PERK-ATF4-CHOP pathway.
Astragaloside IV(AS-IV) is a novel saponin purified from Astragalus membranaceus.

Salvia miltiorrhia, operates by increasing blood flow and dissipating stasis improving heart and blood and it is mainly used to treat cardiovascular and cerebrovascular diseases. Studies have found that these compounds mainly include tanshinone I, tanshinone IIA, tanshinone IIB. It promotes microcirculation, dilates coronary arteries, enhances blood flow, prevents uptake and oxidation of LDL, and protects from ischemia-reperfusion injury *Salvia miltiorrhia* also contains a neuroprotective agent. Salvianolic B, a was found to promote neuronal stem progenitor cells proliferation in vitro and in vivo.

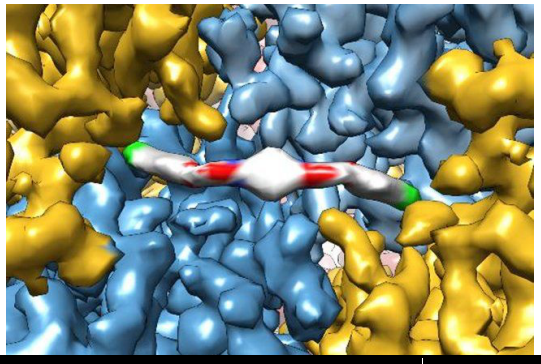
Caulis spatholobi, (SC) has been widely used for the treatment of blood stasis syndrome and dramatically decreased thrombus weight. SC decreased tissue factor (TF) protein expression, inflammatory cells influxes in thrombosed vein wall and serum levels of inflammatory cytokines and CRP. Further, SC up-regulated Sirtuin 1 (SIRT1) protein expression and down-regulated acetylated-NF-κB p65 (Ace-p65) protein expression. SC up-regulated nuclear factor-erythroid 2 related factor 2 (Nrf2) and heme oxygenase-1 (HO-1) protein expressions, and down-regulated phosphorylated-NF-κB p65 (p-p65) protein expression.

Radix paoenia rubras, is mainly used to treat ischemic cerebrovascular disease, including acute cerebral infarction, cerebral thrombosis, concussion, and post-traumatic brain syndrome. It possesses remarkable antithrombotic property in blood. This property could be associated with activating blood flow, anticoagulation activity, the regulation of active substances in vascular endothelium, and maintaining the balance of TXA_2 and PGI_2.

Polygonum multiflorum, Emodin mitigates podocytes apoptosis by inhibiting the PERK-eIF2α signaling pathway in vivo and in vitro. emodin treatment decreased the expression of phosphorylated protein kinase RNA-like endoplasmic reticulum kinase (P-PERK), phosphorylated P-eIF2α, ATF4, and CHOP.

Dryobalanops aromatica (***Borneol)*** Borneol is a monoterpenoid component derived from *Dryobalanops aromatica Gaertn.* It has been widely used in traditional Chinese medicine as a messenger drug, which facilitates the transport of multiple drugs to specific sites and harmonizes the effects of those drugs. Borneol showed tissue-specific Blood-Brain Barrier -opening effect, which was associated with its regulation of the ultrastructure of brain tissues and the expressions of Mdr1a, Mdr1b, and Mrp1. Studies have shown that borneol could increase the permeability of BBB and enhance the therapeutic effect of drugs. At the same time, borneol can maintain the integrity of the BBB structure and cell composition, reduce the BBB permeability, and protect the BBB and brain tissue.

Cinnamomum verum. Contains antioxidants, including polyphenols, phenolic acid and flavonoids.



A cryo-electron microscope rendering of an ISRIB molecule. Image by the Adam Frost lab

University of California San Francisco

Rapid Rejuvenation of Mental Faculties in Aged Mice Implicates Reversible Physiological 'Blockage' Behind Age-Related Cognitive Losses, By Nicholas Weiler

Just a few doses of an experimental drug can reverse age-related declines in memory and mental flexibility in mice, according to a new study by UC San Francisco scientists. The drug, called ISRIB, has already been shown in laboratory studies to restore memory.

In the new study, published Dec. 1, 2020, in the open-access journal eLife, researchers showed rapid restoration of youthful cognitive abilities in aged mice, accompanied by a rejuvenation of brain and immune cells that could help explain improvements in brain function. "The data suggest that the aged brain has not permanently lost essential cognitive capacities, as was commonly assumed, but rather that these cognitive resources are still there but have been somehow blocked, trapped by a vicious cycle of cellular stress," "Our work with ISRIB demonstrates a way to break that cycle and restore cognitive abilities that had become walled off over time."

Could Rebooting Cellular Protein Production Hold the Key to Aging and Other Diseases?

Based on a cellular quality control mechanism called the integrated stress response the ISR normally detects problems with protein production in a cell — a potential sign of viral infection or cancer-promoting gene mutations — and responds by putting the brakes on cell's protein-synthesis machinery. This safety mechanism is critical for weeding out misbehaving cells, but if stuck in the on position in a tissue like the brain, it can lead to serious problems, as cells lose the ability to perform their normal activities. Animal studies by Walter and Rosi, have implicated chronic ISR activation in the persistent cognitive and behavioral deficits seen in patients after TBI, by showing that, in mice, brief ISRIB treatment can reboot the ISR and restore normal brain function almost overnight. The cognitive deficits in TBI patients are often likened to premature aging, which led Rosi and Walter to wonder if the ISR could also underlie purely age-related cognitive decline. Aging is well known to compromise cellular protein production across the body, as life's many insults pile up and stressors like chronic inflammation wear away at cells, potentially leading to widespread activation of the ISR. "We've seen how ISRIB restores cognition in animals with traumatic brain injury, which in many ways is like a sped-up version of age-related cognitive decline," said Rosi, who is but asking whether the drug could reverse symptoms of aging itself was just a logical next step."

Improves Cognition, Boosts Neuron and Immune Cell Function

In the new study, researchers led aged animals to escape from a watery maze by finding a hidden platform, a task that is typically hard for older animals to learn. But animals who received small daily doses of ISRIB during the three-day training process were able to accomplish the task as well as youthful mice, much better than animals of the same age who didn't receive the drug.

The researchers then tested how long this cognitive rejuvenation lasted and whether it could generalize to other cognitive skills. Several weeks after the initial ISRIB treatment, they trained the same mice to find their way out of a maze whose exit changed daily – a test of mental flexibility for aged mice who, like humans, tend to get increasingly stuck in their ways. The mice who had received brief ISRIB treatment three weeks before still performed at youthful levels, while untreated mice continued to struggle.

To understand how ISRIB might be improving brain function, the researchers studied the activity and anatomy of cells in the hippocampus, a brain region with a key role in learning and memory, just one day after giving animals a single dose of ISRIB. They found that common signatures of neuronal aging disappeared literally overnight: neurons' electrical activity became responsive to stimulation, and cells showed more robust connectivity with cells around them while also showing an ability to form stable connections with one another usually only seen in younger mice. The researchers are continuing to study exactly how the ISR disrupts cognition in aging and other conditions and to understand how long ISRIB's cognitive benefits may last. Among other puzzles raised by the new findings is the discovery that ISRIB also alters the function of the immune system's T cells, which also are prone to age-related dysfunction. The findings suggest another path by which the drug could be improving cognition in aged animals and could have implications for diseases from Alzheimer's to diabetes that have been linked to heightened inflammation caused by an aging immune system. "This was very exciting to me because we know that aging has a profound and persistent effect on T cells and that these changes can affect brain function in the hippocampus," said Rosi. "At the moment, this is just an interesting observation, but it gives us a very exciting set of biological puzzles to solve."

Broad Effects Exemplify 'Serendipity' of Basic Research of the University of California's QB3 biotech innovation hub, following Walter's 2013 study showing that the drug seemed to instantly enhance cognitive abilities in healthy mice. To Rosi, the results from that study implied some walled-off cognitive potential in the brain that the molecule was somehow unlocking, and she wondered if this extra cognitive boost might benefit patients with neurological damage from traumatic brain injury.

ISR'S WIDE-RANGING IMPLICATIONS

Chronic ISR activation and resulting blockage of cellular protein production may play a role in a surprisingly wide array of neurological conditions. Here are the conditions where there is already evidence that the ISR plays a role, and which could potentially be treated with an ISR-resetting agent:

Frontotemporal Dementia
Alzheimer's Disease
Amyotrophic Lateral Sclerosis (ALS)
Age-related Cognitive Decline
Multiple Sclerosis
Traumatic Brain Injury
Parkinson's Disease
Down Syndrome
Prion Disease

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PERK Signaling Regulates Extracellular Proteostasis of an Amyloidogenic Protein During Endoplasmic Reticulum Stress

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The PERK arm of the unfolded protein response (UPR) regulates cellular proteostasis and survival in response to endoplasmic reticulum (ER) stress. However, the impact of PERK signaling on extracellular proteostasis is poorly understood. We define how PERK signaling influences extracellular proteostasis during ER stress using a conformational reporter of the secreted amyloidogenic protein transthyretin (TTR). We show that inhibiting PERK signaling impairs secretion of destabilized TTR during thapsigargin (Tg)-induced ER stress by increasing its ER retention in chaperone-bound complexes. Interestingly, PERK inhibition increases the ER stress-dependent secretion of TTR in non-native conformations that accumulate extracellularly as soluble oligomers. Pharmacologic or genetic TTR stabilization partially restores secretion of native TTR tetramers. However, PERK inhibition still increases the ER stress-dependent secretion of TTR in non-native conformations under these conditions, indicating that the conformation of stable secreted proteins can also be affected by inhibiting PERK. Our results define a role for PERK in regulating extracellular proteostasis during ER stress and indicate that genetic or aging-related alterations in PERK signaling can exacerbate ER stress-related imbalances in extracellular proteostasis implicated in diverse diseases.

The PERK signaling arm of the unfolded protein response (UPR) has a critical role in defining cellular survival in response to pathologic insults that disrupt endoplasmic reticulum (ER) proteostasis (i.e., ER stress). PERK is activated in response to ER stress through a mechanism involving PERK dimerization and autophosphorylation[1,2]. Once activated, PERK phosphorylates the α subunit of eukaryotic initiation factor 2 (eIF2α). This results in both a transient attenuation in new protein synthesis and the activation of stress-responsive transcription factors such as ATF4[3–5]. PERK-dependent ATF4 activation induces expression of stress-responsive genes involved in diverse biologic functions including cellular redox, amino acid biosynthesis, and apoptotic signaling[3,6,7]. Apart from eIF2α, PERK also phosphorylates NRF2 to promote cellular redox regulation during ER stress[8,9]. Through this integration of transcriptional and translational signaling, PERK has a central role in dictating cellular proteostasis and survival in response to varying levels of ER stress. During acute ER insults, PERK signaling is important for regulating protective biologic functions including metabolite homeostasis, cellular redox homeostasis and mitochondrial function[8,10–12]. However, chronic PERK activation caused by severe or persistent ER stress promotes apoptotic signaling primarily through the PERK-dependent transcriptional regulation of pro-apoptotic factors[13,14].

Consistent with a role for PERK in dictating both protective and pro-apoptotic responses to specific ER insults, imbalances in PERK activity caused by genetic, environmental, or aging-related factors is implicated in the pathogenesis of diverse diseases. Sustained PERK signaling associated with chronic or severe ER insults is implicated in neurodegeneration associated with diseases such as Alzheimer's disease and prion disease[15,16]. As such, pharmacologic inhibition of PERK has emerged as a potential strategy to ameliorate neurodegeneration-associated pathologies involved in these disorders[15]. In contrast, genetic and pharmacologic evidence demonstrates that reductions in PERK signaling also influence disease pathogenesis. Loss-of-function mutations in *PERK* promote neonatal diabetes in mouse models and the human disease Wolcott-Rallison syndrome[17,18]. Similarly, hypomorphic *PERK* alleles are implicated in the tau-associated neurodegenerative disorder progressive supranuclear palsy

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Original Paper

Down-Regulation of PERK-ATF4-CHOP Pathway by Astragaloside IV is Associated with the Inhibition of Endoplasmic Reticulum Stress-Induced Podocyte Apoptosis in Diabetic Rats

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Key Words
Astragaloside IV • Endoplasmic reticulum stress • PERK-ATF4-CHOP pathway • Podocyte apoptosis • Diabetic nephropathy

Abstract
Background: Endoplasmic reticulum (ER) stress-induced podocyte apoptosis plays a critical role in the development of diabetic nephropathy (DN). Here, we tested the hypothesis that suppression of PERK-ATF4-CHOP pathway by Astragaloside IV (AS-IV) is associated with inhibition of ER stress-induced podocyte apoptosis in streptozotocin (STZ)-induced diabetic rats. ***Methods:*** Diabetic rats were treated with AS-IV at 5 and 10 $mg \cdot kg^{-1} \cdot d^{-1}$, p.o., for 12 weeks. Albuminuria examination, hematoxylin & eosin staining and TUNEL analysis were performed. Immunohistochemistry, western blot, and real-time PCR were used to detect renal expression of ER chaperone GRP78 and ER-associated apoptosis proteins. ***Results:*** Treatment with AS-IV ameliorated albuminuria and renal histopathology in diabetic rats. Diabetic rats had significant increment in podocyte apoptosis as well as phosphorylated PERK and eIF2α in the kidneys, which were attenuated by AS-IV treatment. Furthermore, diabetic rats were found to have increased protein and mRNA expressions of GRP78 and ER-associated apoptosis proteins, such as ATF4, CHOP and TRB3, which were also attenuated by AS-IV treatment. Increased Bax expression and decreased Bcl-2 expression were detected in diabetic rats, and these changes were partially restored by AS-IV treatment. ***Conclusion:*** The protective effect of AS-IV on ER stress-induced podocyte apoptosis is associated with inhibition of PERK-ATF4-CHOP pathway. Down-regulation of PERK- ATF4-CHOP pathway by AS-IV may be a novel strategy for the treatment of DN.

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Extended Longevity

Effects of *Salvia miltiorrhiza* on CNS Neuronal Injury and Degeneration: A Plausible Complementary Role of Tanshinones and Depsides*

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Key words
- *Salvia miltiorrhiza*
- Lamiaceae
- tanshinones and depsides
- CNS neuronal injury and degeneration
- *in vivo* studies
- biochemical mechanisms
- pharmacokinetics

Abstract

Salvia miltiorrhiza is a very important herbal drug of traditional Chinese medicine. Bioactive constituents are represented by two main groups of secondary metabolites, the lipophilic diterpenic quinones known as tanshinones and the hydrophilic depsides known as salvianolic acids. *S. miltiorrhiza* extracts and single constituents have been shown to have positive effects in central nervous system neuronal injury and degeneration in several animal models by various biological mechanisms. Both tanshinones and depsides protect against β-amyloid-induced toxicity, but their mechanisms are complementary due to their different structure, the lipophilic tanshinones and the hydrophilic depsides. A number of anti-inflammatory mechanisms is also reported for both tanshinones and depsides. Common mechanisms are the effects on cytokines, inducible nitric oxide synthase, and glial fibrillary acidic protein. In addition, depsides are inhibitors of nitric oxide and cyclooxygenase-2, while tanshinones inhibit hypoxia-inducible factor-1α and nuclear factor kappa β. Both constituents can also modulate the protection of the central nervous system from oxidative stress with different but complementary mechanisms: tanshinones can enhance the activities of superoxide dismutase and glutathione peroxidase, while depsides can decrease reactive oxygen species.
Furthermore, neuronal death underlies the symptoms of many human neurological disorders, including Alzheimer's, Parkinson's, and Huntington's diseases, stroke, and amyotrophic lateral sclerosis. Both classes of constituents can enhance the antiapoptotic B-cell leukemia protein-2 family members and decrease the translocation of cytochrome c, and, in addition, depsides decrease caspase-3 and intracellular Ca^{2+}. Again, both classes of constituents have an activity on vascular endothelial growth factor but it is opposite, whereas tanshinones are inhibitors of acetylcholinesterase.
Besides the extensive studies reporting on the biological mechanisms of depsides and tanshinones, pharmacokinetics studies are still very limited and not conclusive, especially for brain distribution. Further research is warranted to address the mechanisms of the multitarget actions of *S. miltiorrhiza* constituents and to translate this knowledge into clinical practice.

Abbreviations

AChE:	acetylcholinesterase
AD:	Alzheimer's disease
APP:	amyloid precursor protein
Akt:	protein kinase B
Aβ:	β-amyloid
Bax:	Bcl2-associated X protein
BBB:	blood-brain barrier
Bcl-2:	B-cell leukemia protein
BDNF:	brain-derived neurotrophic factor
BPRP:	brain-pancreas relative protein
CA1:	hippocampal CA1 region
Cdk5:	cyclin-dependent kinase 5
CMM:	Chinese materia medica
CNS:	central nervous system
COX-2:	cyclooxygenase-2
CTS:	cryptotanshinone
DTSI:	dihydrotanshinone I
EPO:	erythropoietin
ER:	estrogen receptor
ERK1/2:	extracellular signal-regulated kinase 1 and 2
GFAP:	glial fibrillary acidic protein
GSH-Px:	glutathione peroxidase
GSK-3β:	glycogen synthase kinase-3 beta

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* Dedicated to Professor Dr. Dr. h.c. mult. Adolf Nahrstedt on the occasion of his 75th birthday.

Extended Longevity

frontiers in Pharmacology

ORIGINAL RESEARCH
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l-Borneol Exerted the Neuroprotective Effect by Promoting Angiogenesis Coupled With Neurogenesis via Ang1-VEGF-BDNF Pathway

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At present, Stroke is still one of the leading causes of population death worldwide and leads to disability. Traditional Chinese medicine plays an important role in the prevention or treatment of stroke. *l*-borneol, a traditional Chinese medicine, has been used in China to treat stroke for thousands of years. However, its mechanism of action is unclear. After cerebral ischemia, promoting angiogenesis after cerebral ischemia and providing nutrition for the infarct area is an important strategy to improve the damage in the ischemic area, but it is also essential to promote neurogenesis and replenish new neurons. Here, our research shows that *l*-borneol can significantly improve the neurological deficits of pMCAO model rats, reduce cerebral infarction, and improve the pathological damage of cerebral ischemia. and significantly increase serum level of Ang-1 and VEGF, and significantly decrease level of ACE and Tie2 to promote angiogenesis. PCR and WB showed the same results. Immunohistochemistry also showed that *l*-borneol can increase the number of CD34 positive cells, further verifying that *l*-borneol can play a neuroprotective effect by promoting angiogenesis after cerebral ischemia injury. In addition, *l*-borneol can significantly promote the expression level of VEGF, BDNF and inhibit the expression levels of TGF-β1 and MMP9 to promote neurogenesis. The above suggests that *l*-borneol can promote angiogenesis coupled neurogenesis by regulating Ang1-VEGF-BDNF to play a neuroprotective effect. Molecular docking also shows that *l*-borneol has a very high binding rate with the above target, which further confirmed the target of *l*-borneol to improve cerebral ischemic injury. These results provide strong evidence for the treatment of cerebral ischemia with *l*-borneol and provide reference for future research.

Keywords: l-borneol, cerebral ischemia, pMCAO, angiogenesis, neurogenesis

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Abbreviations: t-PA, Tissue plasminogen activator; FDA, Food and Drug Administration; VEGF, vascular endothelial growth factor; Ang, angiopoietin; BDNF, Brain derived neurotrophic factor; SVZ, subventricular zone; LPS, lipopolysaccharide; BBB, blood brain-barrier; MCAO, middle cerebral artery occlusion; SD, Sprague Dawley; TTC, 2,3,5-Triphenyltetrazolium chloride; ELISA, Enzyme-linked immunosorbent assay; Hematoxylin-eosin, HE; IHC, immunohistochemical; ACE, angiotensin-converting enzyme; PBS, Phosphate buffer solution; SDS, Sodium dodecyl sulfate; PDB, Protein Data Bank; TGF-β1, Transforming growth factor, MMP9, Matrix metalloprotein 9; qRT-PCR, quantitative real-time polymerase chain reaction; VEGFR, vascular endothelial growth factor receptor; MVD, Microvessel density; eNOS, endothelial nitric oxide synthases, NO, nitric oxide

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Research Article

Antithrombotic Effect and Mechanism of Radix Paeoniae Rubra

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The compounds of Radix Paeoniae Rubra (RPR) were isolated and identified by bioassay-guided method, and antithrombotic effects and mechanism were investigated by the acute blood stasis rat model. The RPR extract was evaluated by APTT, TT, PT, and FIB assays in vitro. Results indicated that RPR extract exhibited the anticoagulant activity. In order to find active compounds, six compounds were isolated and identified, and four compounds, paeoniflorin (Pae), pentagalloylglucose (Pen), albiflorin (Ali), and protocatechuic acid (Pro), exhibited the anticoagulant activity in vitro. Therefore, the antithrombosis effects of RPR extract and four active compounds were investigated in vivo by measuring whole blood viscosity (WBV), plasma viscosity (PV), APTT, PT, TT, and FIB. Meanwhile, the levels of TXB_2, 6-Keto-$PGF_{1\alpha}$, eNOS, and ET-1 were detected. Results suggested that RPR extract and four active compounds had the inhibition effect on thrombus formation, and the antithrombotic effects were associated with the regulation of vascular endothelium active substance, activating blood flow and anticoagulation effect.

1. Introduction

Thrombosis, the formation or presence of the thrombus in a blood vessel, is a multifactorial disease induced by promoting a combination of stasis and hypercoagulability [1]. Thrombotic diseases, especially heart disease and cerebrovascular thrombosis, have become primary causes of death and their incidence has been increasing each year [2]. It is well known that thrombosis is closely related to activated platelet adhesion, aggregation, secretion functions, and activation of intrinsic and extrinsic coagulation systems, which cause blood coagulation and fibrin formation. Although they have many causes [3], accumulation of thrombus is a key factor in the final analysis.

Many traditional Chinese herbal medicines have been used for thousands of years in clinical practice because of their proven efficacy, wide indications, high safety profile, and low toxicity [4]. Then Traditional Chinese Medicine (TCM) plays an important role in the clinic treatment of blood stasis in China, one of which is the Radix Paeoniae Rubra (RPR), which is the dried root of *Paeonia lactiflora* Pall. and *P. veitchii* Lynch [5]. It had the function of removing pathogenic heat from the blood and treating blood stasis and relieving pain [6, 7].

In Traditional Chinese Medicine, thrombotic disorders are described as blood stasis syndrome [8]. Though aspirin has been widely used as antithrombotic medicine in clinical practice, an increasing number of studies have indicated that some patients subpopulations do not respond to the antithrombotic effects of aspirin and may exhibit a degree of aspirin resistance. Therefore, interest in TCM from natural sources as a feasible alternative therapeutic agent for the prevention of blood stasis disorder in patients with "aspirin resistance" is growing [9].

RPR has some effects on activating blood circulation to dissipate blood stasis; however, the mechanism has been poorly studied. In this paper, antithrombotic effects and mechanism of extracts and the compounds from the RPR root were investigated.

2. Materials and Methods

2.1. Plant Materials. The RPR was purchased from Lerentang Pharmacy, Kaifeng, Henan Province, China, and a voucher specimen was identified by Professor Chang-qin Li of Henan University and deposited in the Herbarium of the Institute of Natural Products, Henan University.

Drug Design, Development and Therapy

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ORIGINAL RESEARCH

Emodin mitigates podocytes apoptosis induced by endoplasmic reticulum stress through the inhibition of the PERK pathway in diabetic nephropathy

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Background: Endoplasmic reticulum stress is associated with podocyte apoptosis in the pathogenesis of diabetic nephropathy (DN). A previous study has demonstrated that emodin has a protective effect in the kidney by suppressing proliferation of mesangial cells and inhibiting the renal tubular epithelial-to-mesenchymal transition. However, the effects of emodin on the podocyte apoptosis in DN and its mechanisms are unknown.

Aim: This study aimed to explore the effect of emodin on DN model KK-Ay mice and high glucose induced podocytes apoptosis via the PERK–eIF2α pathway.

Methods: KK-Ay mice model of DN were treated with emodin at dose of 40 and 80 mg/kg/day for 8 weeks. Urine albumin, serum creatinine, blood urea nitrogen levels and the renal histopathology in mice were performed. In vitro, conditionally immortalized mouse podocytes exposed to HG (30mM) were incubated with emodin. Cell viability was measured by CCK-8 assay. Additionally, we performed RNA interference and measured the apoptosis in cultured podocytes treated with emodin. Immunohistochemistry, immunofluorescence, western blot, and real-time PCR were used to detect gene and protein expression both in vivo and in vitro.

Results: The results showed that emodin treatment ameliorated urine albumin, serum creatinine, and blood urea nitrogen of DN mice. The pathological damage of kidney tissue was also improved after treatment with emodin. Moreover, emodin increased nephrin expression. Podocytes apoptosis and endoplasmic reticulum stress markers (GRP78) were significantly reduced upon emodin treatment. Furthermore, emodin treatment decreased the expression of phosphorylated protein kinase RNA-like endoplasmic reticulum kinase (P-PERK), phosphorylated P-eIF2α, ATF4, and CHOP. In vitro, emodin treatment was further found to decrease the GRP78 level induced by high glucose or tunicamycin (TM). Besides, emodin and PERK knockdown inhibited the apoptosis of podocytes cultured in high glucose by counteracting the upregulation of phosphorylated PERK, phosphorylated eIF2α, ATF4, and CHOP.

Conclusion: Overall, the findings indicate that emodin mitigates podocytes apoptosis by inhibiting the PERK-eIF2α signaling pathway in vivo and in vitro, and, therefore, exerts a protective action on podocytes in DN.

Keywords: emodin, diabetic nephropathy, endoplasmic reticulum stress, podocyte apoptosis, PERK-eIF2α

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Introduction

Diabetic nephropathy (DN) is a progressive microvascular complication occurring among people with diabetes mellitus and has become a prime cause of end-stage renal disease (ESRD) in the USA.[1] This disease is initially characterized by the appearance of moderately increased albuminuria, followed by overt proteinuria and a gradual

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Spatholobi Caulis dispensing granule reduces deep vein thrombus burden through antiinflammation via SIRT1 and Nrf2

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Abstract

Background: Deep vein thrombosis (DVT) is a kind of blood stasis syndrome. Spatholobi Caulis (SC) has been widely used for the treatment of blood stasis syndrome in China, but the underlying mechanism remains poorly understood.

Purpose: The aim of present study was to investigate the anti-DVT mechanism of Spatholobi Caulis dispensing granule (SCDG).

Study design/methods: A rat model of inferior vena cava (IVC) stenosis-induced DVT and a cell model of oxygen-glucose deprivation (OGD) were performed. Rats were orally administered with SCDG solution once daily for seven consecutive days. IVC stenosis-induced DVT was operated on the sixth day. Thrombi were harvested and weighed on the seventh day. Pathological changes were observed by hematoxylin-eosin (HE) staining. Tumor necrosis factor (TNF)-α and interleukin (IL)-1β of serum were analyzed by enzyme-linked immunosorbent assay. C-reactive protein (CRP) was measured with turbidimetric immunoassay. Protein expressions in thrombosed IVCs and/or OGD-stimulated EA. hy926 cells were evaluated by western blot and/or immunofluorescence analyses.

Results: SCDG dramatically decreased thrombus weight. SCDG decreased tissue factor (TF) protein expression, inflammatory cells influxes in thrombosed vein wall and serum levels of inflammatory cytokines and CRP. Further, SCDG up-regulated Sirtuin 1 (SIRT1) protein expression and down-regulated acetylated-NF-κB p65 (Ace-p65) protein expression. Moreover, SCDG up-regulated nuclear factor-erythroid 2 related factor 2 (Nrf2) and heme oxygenase-1 (HO-1) protein expressions, and down-regulated phosphorylated-NF-κB p65 (p-p65) protein expression. In the OGD cell model, SCDG medicated serum decreased the protein expression of TF. SCDG medicated serum enhanced SIRT1 protein expression and reduced Ace-p65 nuclear protein expression. SCDG medicated serum promoted protein expressions of nuclear Nrf2 and total HO-1, and inhibited translocation of p65. Furthermore, inhibiting SIRT1 and Nrf2 reversed the protective effect of SCDG medicated serum on OGD-induced EA. hy926 cells.