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Review Article

Cerebral-protective effects of hydroxysafflor yellow A

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Abstract: Nowadays, as an important challenge, cerebral diseases are rapidly increasing, with high mortality and huge treatment costs. Moreover, most of the chemical drugs applied in the treatment of cerebral diseases with single-target are always ineffective and toxic. Natural medicines, characterized by multiple targets and low toxicity and are generally considered as promising treatments for a variety of human diseases. Therefore, developing novel and effective drugs derived from plants for treating cerebral diseases is of great importance. Hydroxysafflor yellow A (HYSA) is a natural agent isolated from the roots of from the flower of the safflower plant (*Carthamus tinctorius* L.), a traditional Chinese herbal medicine with the effect of promoting blood circulation and removing blood stasis. Numerous *in vitro* studies and *in vivo* animal experiments have proved that HYSA is beneficial against the progression of cerebral ischemic diseases, vascular dementia (VD), Alzheimer's disease (AD), Parkinson's disease (PD), traumatic brain injury (TBI), etc. The underlying mechanisms primarily involve regulating TLR9/NF-κB, AK2/STAT3, SIRT1-HIF-1α-VEGFA, PI3K/Akt/mTOR, TREM2/TLR4/NF-κb, JAK2/STAT3/NF-κB, BDNF/TrkB/DRD3, JNK/ERK, TLR4/NF-κB pathways and so on. Overall, we demonstrate a systematic overview of the pharmacological actions and the molecular mechanisms of HYSA on diverse cerebral diseases, providing direction to future research of HYSA.

Keywords: hydroxysafflor yellow A (HYSA); cerebral diseases; pharmacological action; systematic overview

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Introduction

Brain is regarded as the most complex organ of the human body's structure and function, and where human wisdom lies. Further studies on the pathogenesis of cerebral diseases, and effective treatment methods have become a hot spot all over the world.[1] Notably, major cerebral diseases, such as cerebral ischemic disease, dementia Parkinson's disease (PD), traumatic brain injury (TBI), with high mortality rates and high-cost treatment, have shown a rapid increase and become an important challenge in today's society and medicine.[2-4] However, chemical drugs for the treatment of cerebral diseases, such as idebenone, diazepam, doxepin, and memantine hydrochloride, are highly toxic and mono-targeted, producing limited efficacy. Natural medicines such as

curcumin, quercetin, resveratrol, rutin, celastrol, berberine, and nuciferine, derived from natural plants and characterized by multi-targets and low toxicity, are usually regarded as promising treatments for a variety of human diseases.[5-9] Therefore, attention should be paid to the exploration and development of natural agents with therapeutic potential against cerebral diseases.

Safflower (SY, *Carthamus tinctorius* L.) is a traditional herbal medicine and blood stasis for thousands of years across Asia especially in China. The flower of the safflower plant, *Carthamus tinctorius* L., and its extracts has been extensively used known as a blood stasis promoting drug has been used to treat several diseases such as cerebrovascular and cardiovascular disorders for more than 2000 years. Hydroxysafflor yellow A (HSYA) (Figure1), a water-soluble monomer responsible for the main beneficial effects of SY, was first separated from safflower by Meselhy MR, et al in 1993.[10] It is the most active ingredient of safflower. In 2005, safflower yellow injection containing 45 mg HSYA per 50 mg was approved as a new drug by the State Food and Drug Administration of China and began to be widely used for treating cardiac diseases such as angina pectoris. The systematic evaluations demonstrated that this injection was significantly effective for cerebral infarction.[11] In recent years, a great number of studies demonstrated that HYSA possessed cerebral-protective potentials against cerebral ischemic diseases, vascular dementia (VD), Alzheimer's disease (AD), Parkinson's disease (PD), traumatic brain injury (TBI). However, there is not a review summarizing the cerebral-protective effect of HYSA, which will greatly hinder the development and utilization of HYSA.

In this review, we managed to give a comprehensive summary and analysis of the cerebral-pharmacological properties of HYSA *in vivo* and *in vitro*, supporting the potential potentials of HYSA in cerebral diseases. This review will also shed light on the development and utilization of natural agent in the treatment of cerebral diseases.

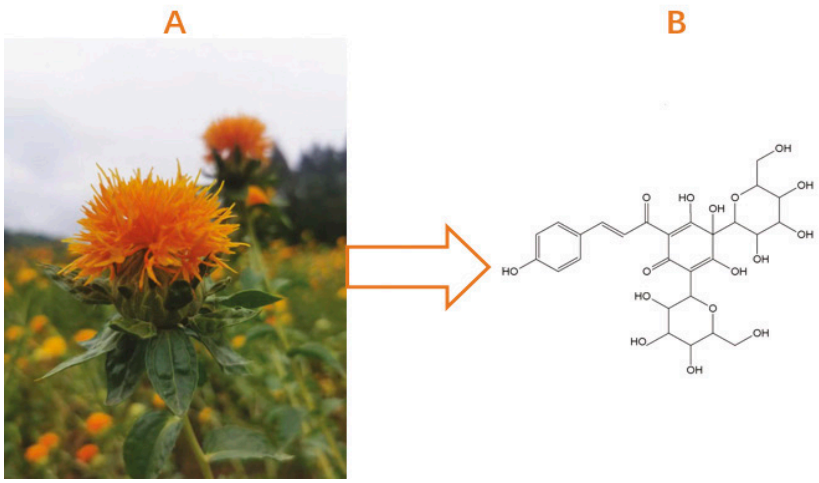

Figure 1 Hydroxysafflor yellow A (HYSA) and its sources

(A) *Carthamus tinctorius* L. (safflower); (B) Hydroxysafflor yellow (the main effective compound of *Carthami Flos*)

Effect of HYSA on cerebral ischemia

The strong inhibitory effect on ischemic brain injury of HYSA has become popular research topics. With the similar potency to nimodipine, HSYA was found to exert significant neuroprotective effects on focal cerebral ischemic rats caused by permanent middle cerebral artery occlusion (MCAO) as expressed by the reduced neurological deficit scores, infarct area, edema extend and levels of Bax, Caspase-3, ICAM-1, IL-1ß, TNF-α and NF-κB, suppressed expressions of Bax, caspase-3 and ICAM-1, IL-1ß, TNF-α and NF-κB, up-regulated glucose metabolism and expressions of GFAP, NGF and Bcl-2.[12-14] (Table 1)

Additionally, HYSA inhibited neurons injury stimulated by glutamate, sodium cyanide (NaCN) and OGD via preventing cell death and LDH release in cultured rat fetal cortical cells.[13] Another *in vitro* study showed HSYA protected PC12 cells from apoptosis induced by OGD followed by reperfusion through suppressing intracellular oxidative stress and mitochondria dependent pathway[15] Further studies showed the inhibitor of Glycogen Synthase Kinase 3 Beta GSK3β partly reversed the protection of HSYA on I/R by modulating NF-κB and caspase-3 *in vivo* and *in vitro*.[16] Further, intraperitoneal injection of HYSA activated Toll-like receptor 9 (TLR9) in microglia of ischemic cortex at 6 hours and inhibited the NF-κB pathway in the acute cerebral ischemia and reperfusion rats. Consistently, TLR9-siRNA reversed the anti-inflammatory action of HSYA in primary microglia induced by OGD.[17] Also, HSYA reduced hippocampal expression levels of light chain 3 (LC3), hypoxia-inducible factor-1 (HIF-1), BCl2/ adenovirus E1B 19kDa interacting protein 3 (BNIP3), and neurogenic locus notch homolog protein 1 (Notch1) in the MCAO rats. And molecular modeling indicated that HSYA could be bound strongly to HIF-1, BNIP3, and Notch1 but weakly to LC3.[18] Further, HSYA treatment suppressed the expression of the Janus Kinase2 (JAK2)-mediated signaling and promoted the expression of suppressor of cytokine signaling 3 (SOCS3) in the MCAO rats. However, inhibiting JAK2-mediated signalingabolished the influence of HYSA on SOCS3 activity, suggesting that induction of the JAK2/signal transducer and activator of transcription 3 (STAT3) pathway by HSYA was vital in provoking SOCS3-negative feedback signaling.[19] It was investigated that the anti-cerebral ischemic effect of HYSA might result from its suppression of thrombin generation and thrombin-mediated inflammatory reaction including NF-κB p65 nuclear translation, p65 binding activity, elevation of ICAM-1mRNA and protein levels and neutrophils infiltration through decreasing angiotensin II.[20] In addition to the inhibitory effect on thrombosis formation, the reasons for the therapeutic effects of HYSA on the MCAO rats were related to its beneficial action on the prostacyclin2 (PGI_2)/ thromboxane A2 (TXA_2) and blood rheological changes *in vivo* and platelet aggregation *in vivo* and *in vitro*.[21] Notably, mitochondria, is likely to be involved in the underlying mechanism. The structurally and functionally ameliorative influence of HYSA on the cortex mitochondria in rats damaged by cerebral ischemia, which might be related to inhibition of overloaded Ca^{2+} and scavenging of free radicals included increase in the membrane fluidity and the activities of respiratory enzymes and decrease in the edema degree and the membrane phospholipid decomposability.[22] Also, HYSA could ameliorate the behavioral and cognitive indexes including neurological scoring, latency time on rotarod

and percentages of alterations behavior, decrease MDA and TNF-αand reduce the infarct volume in I/R rats subjected to MCAO, whereas carboxyatractyloside (CAT), an mitochondrial permeability transition pore (mPTP) opener, attenuated the pharmacological activities of HYSA in the model, suggesting the neuroprotective effect of HSYA against I/R injury might be related to its antioxygenation together with inhibition of the opening of mPTP.[23]

Blood-brain barrier, which is damaged by an ischemic stroke, was also the target of HYSA. After OGD/R in Brain microvascular endothelial cell (BMECs), HSYA significantly increased viability, and decreased the generation of ROS, opening of mPTP and translocation of CytC. Moreover, HSYA inhibited CypD, potentiated MEK, increased ERK phosphorylation, and hindered mitochondrial-modulated apoptosis in BMECs.[24] Further studies showed that Silent information regulator 2 homolog 1 (SIRT1)-HIF-1α-VEGFA and PI3K/Akt (protein kinase B) / molecular Target of Rapamycin(mTOR) signaling pathways were involved in the effects of HSYA on angiogenesis of BMECs treated by OGD/R. HSYA could promote cell proliferation, adhesion, migration and tube formation ability of BMECs and increase the levels of VEGF, Ang and PDGF in BMECs under OGD/R. Further, HSYA up-regulated the expressions of SIRT1, HIF-1α, VEGFA mRNA and protein after OGD/R, which were reduced after SIRT1 inhibition.[25] Also, HSYA effectively reversed the cellular morphological and ultrastructural alterations, increased cell survival, and normalized the permeability of BMECs. Mechanistic studies revealed that HSYA inhibited OGD/R-induced autophagy and apoptosis and increased the levels of p-AKT and p-mTOR proteins, which could be abolished by PI3K inhibitor.[26] Importantly, when combined with AV-IV, HSYA elicited synergetic effects in retaining survival of BMECs by decreasing the expression of PHLPP-1 and strengthening Akt signaling.[27]

Effect on dementia

Recent findings have discovered the anti-dementia properties of HYSA and provided a foundation for its clinical use in both of vascular dementia (VD) and Alzheimer's disease (AD). Compared with the VD rats, the HSYA-treated VD rats induced by permanent bilateral carotid occlusion (2-VO) exerted reduced escape latency, more time spent in the platform quadrant , prolonged swimming distance in the water maze, and increased long-term potentiation (LTP) which could stimulate longlasting synaptic efficacy and plasticity and finally ameliorate learning and memory at CA3CA1 synapses in the hippocampus. The later study exhibited that HSYA could up-regulate expression of VEGFA, N-methyl-Daspartic acid receptor 1 (NR1), brain-derived neurotrophic factor (BDNF) and N-methyl-d-aspartate receptor (NMDAR) GluN2B in the hippocampal, which enhanced LTP and increased synaptic plasticity consequently.[29]

The result of Morris water maze experiment showed HYSA improved learning ability of the AD rats. This agent also inhibited the expression of hippocampus β-site amyloid precursor protein cleaving enzyme (BACE) protein, decrease the level of $A\beta_{1-42}$, reduced cholesterol level in serum and hippocampus, alleviated structural damage to dendritic spines and the loss of synaptic-associated proteins

and ameliorated the disorder of glutamate circulation in the AD rats.[30,31] Also, in the CUMS-induced learning and memory impairments mice, HSYA increased the xpression of BDNF and activated downstream tropomyosin-related kinase B (TrkB) and PI3K/ Akt/mammalian target of rapamycin (mTOR) signaling. HSYA decreased the expression of regulator of calcineurin 1-1L (RCAN1-1L) that could promote the activity of glycogen synthase kinase-3β (GSK-3β). HSYA also attenuated tau phosphorylation by inhibiting the activity of GSK-3β and cyclin-dependent kinase-5 (Cdk5).[32] *In vitro*, HSYA could up-regulate cell viability and improve the morphology in $A\beta_{1-42}$ in BV-2 cells, all of which were regulated by triggering receptor expressed myeloid 2 (TREM2) and switched microglia from an M1 proinflammatory phenotype to an M2 anti-inflammatory phenotype. It inhibited the $A\beta_{1-42}$-induced activation of the TLR4/NF- κB pathway by upregulating TREM2.[33] HYSA had a stimulatory effect on $A\beta_{1-42}$-induced BV-2 cells' viability dose-dependently. It down-regulated the mRNA levels of IL-1β, TNF-α, COX-2 and iNOS and protein expression of COX-2, TNF-α and iNOS, up-regulated IL-4 and IL-10 and protein expression of p-JAK2 and p-STAT3, in order to exert anti-inflammatory effect in $A\beta_{1-42}$-induced BV-2 cells. Besides, cell viability of neurons and SH-SY5Y inhibited by conditioned meadium of $A\beta_{1-42}$-induced BV-2 cells was obviously promoted by HSYA while the apoptosis percentage in the above neurons cells were greatly strengthened by HSYA. However, the anti-inflammatory and neuroprotective activities of HSYA, which might be a consequence of JAK2/ STAT3 pathway involvements, could be attenuated by AG490, an inhibitor of JAK2.[34] This drug also displayed a protective effect against $A\beta_{25-35}$-induced neurotoxicity in cultured rat pheochromocytoma (PC12) cells by increasing cell viability, stabilizing mitochondrial function and inhibiting oxidative stress characterized by reduced levels of lactate dehydrogenase (LDH), intracellular reactive oxygen species ROS and MDA, and neuronal apoptosis as well as increased ratio of Bcl-2/Bax.[35] *In vivo*, the cognitive impairment manifested as the shortened the escape latency, the reduced number to cross the hidden platform and time spent in the target quadrant induced by homocysteine (Hcy) was significantly reversed by HSYA. The further study confirmed that HYSA attenuated Aβ40 and Aβ42 levels in hippocampus partially via suppressing PS1 protein levels, rescued apoptosis, and increased long-term potentiation (LTP) in the AD model [36]. HSYA ameliorated memory deficits of $A\beta_{1-42}$-induced AD mice according to the reduction of mean escape latency, and target quadrant time, and the increase of the percent distance in the Morris water maze test. The mechanism could be explained by the reduction of expression of Iba-1,GFAP, IL-1β,TNF-α and iNOS and increase of expression of IL-4 and IL-10 caused by HSYA, which resulted in suppression of the activation of microglia and astrocytes and inhibition of inflammatory factors in the hippocampi. The further research demonstrated HYSA could promote JAK2 and STAT3 phosphorylation, up-regulate I κB expression, and inhibit p65 nuclear translocation. Moreover, HSYA showed no obvious inhibitory effect on $A\beta_{1-42}$-induced p65 nuclear translocation with JAK2 inhibitor AG490, whereas, without the inhibitor, HSYA inhibited p65 nuclear trans-

location in BV-2 microglia, suggesting that STAT3 played a necessary role in the inhibition of NF-κB activation of HSYA.[37](Table 1)

Effect on Parkinson's Disease

HSYA had an essentially neuroprotective role in 6-OHDA-induced Parkinson's Disease (PD) rats manifesting as the reduced apomorphine-induced turns and increased levels of dopamine (DA) and its metabolites, 4-dihydroxyphenyl acetic acid (DOPAC) and homovanillic acid (HVA) as well as increased number of tyrosine hydroxylase-positive cells. Likewise, GDNF (glial cell line-derived neurotrophic factor) and BDNF (brain-derived neurotrophic factor) in striatum were enhanced in the PD rats.[38] Meanwhile, HSYA could improve motor dysfunction of the PD mice model induced by rotenone evidenced as the reduced climbing time in the pole test and the increased rotarod time and total distance and average speed in the open field test and protect dopamine neurons by increasing the number of TH-containing dopaminergic neurons in substantia nigra and the dopamine content in the striatum in PD mice. It was suggested that BDNF/Tr kB/DRD3 signaling pathway was responsible for the pharmacological effect of HSYA because the expressions of BDNF, p-TrkB/TrkB, DRD3, p-PI3K/PI3K and p-AKT/AKT in the rotenone-induced PD mice were enhanced by HSYA.[39] Additionally, after coadministration of HSYA with L-DOPA, the 6-hydroxydopamine-lesioned rat model of PD exerted the attenuated dyskinesia, the prolonged motor response duration and the down-regulated expression of the dopamine D receptor in the striatum, compared with the PD rats administrated by L-DOPA only. [40] HSYA enhanced expression of tyrosine hydroxylase (TH) in substantia nigra (SN) and corpus striatum (STR), reduced levels of iNOS, COX-2 and NF-κB and DA neuronal apoptosis in the PD rats. In 6-OHDA-treated SH-SY5Y cells, HSYA decreased the levels of p-p38 and p-JNK and upregulated that of p-ERK.[41]

The formation of autophagosomes was augmented by HYSA in the rotenone-induced PD rats. Additionally, HYSA increased levels of TH, p-JNK1/JNK1, Beclin1, Atg7, Atg12-5, p-Bcl-2/Bcl-2, and the LC3-II/LC3-I ratio and reduced the expression of α-syn.[42] Moreover, HSYA treatment attenuated the LPS-induced dopaminergic neurons damage and inhibited levels of IL-1β, TNF-α and NO and the expressions of NF-κB p65 and iNOS.[43] (Table 1)

Effect on traumatic brain injury

HSYA showed excellent protective effects against TBI. In the TBI rats, HSYA attenuated BBB permeability via increasing the production of the TJPs, including occludin, claudin-1 and zonula occludens protein 24 h after. Additionally, HSYA could suppress levels of IL-1β, IL-6, and TNF-α, and also down-regulate the expression of inflammation-related Toll-like receptor 4/nuclear factor kappa-B (TLR4/NF-κB) protein, decreased oxidative stress markers and inhibited the expression of apoptosis proteins.[44,45] Also, HYSA acutely attenuated blood-brain barrier permeability, oxidative stress, inflammation and apoptosis in traumatic brain injury in rats. Another report confirmed that HYSA increased activities of mitochondrial ATPase and tissue plasminogen activator (t-PA) and decreased plasma plasminogen activator inhibitor-1 (PAI-1) activity and MMP-9 expression in the hippocampus of the TBI rats.[46] HSYA alleviated the neurological deficits of TBI rats. Fifteen potentially significant metabolites focusing on 4 key targets, including NOS1, ACHE, PTGS2 and XDH, as well as their related core metabolites and pathways were involved in the anti-TBI effects of HSYA.[47] (Figure 2)

Table 1 Summary about the cerebra-protection of HYSA

Effects	Model	Detials	Ref
Cerebral ischemia	Rat fetal cortical cells stimulated by OGD.	↓ cell death, LDH release	13
	Rat fetal cortical cells stimulated by glutamate and NaCN	↓ cell death, LDH, NO	14
	MCAO rats	↓ neurological deficit scores, infarct area, edema extend, cell apoptosis and expressions of Bax, Caspase-3, ICAM-1, IL-1β, TNF-α, NF- κB ↑ glucose metabolism.GFAP, NGF and Bcl-2	12-14
	MCAO rats	↓ neurological deficit scores, thrombin generation, Ang II NF- κB p65 nuclear translation, p65 binding activity, ↑ ICAM-1 neutrophils infiltration	20,21
	MCAO rats	↓ apoptotic cell number, ↑ Bcl-2/Bax, phosphorylation of Akt and GSK-3β	26
	MCAO rats	↑ glucose metabolism, neurological function, GFAP, NGF and Bcl-2 ↓ cerebral infarction volume, Bax, caspase-3 ICAM-1, IL-1ß, TNF-α, NF-κB	12
	MCAO rats	↑ TLR9; ↓ the NF-κB pathway	17
		↓ neurobehavioral deficits, brain infarct area and tissue damage, hippocampal expression levels of LC3, HIF-1, BNIP3 and Notch1	18
		↓ JAK2/ STAT3 ↑ SOCS3	19
	BMECs after OGD/R	↑ cell viability, MEK, pERK ↓ apoptosis, ROS, opening of mPTP and translocation of cytochrome C, CypD	24
	BMECs during OGD/R	↑ VEGF, Ang, PDGF VEGFA, Ang-2, PDGFB cell proliferation, adhesion, migration and tube formation ability, CD31 and CD34 , SIRT1, HIF-1α	26

Table 1 Summary about the cerebra-protection of HYSA (cont.)

Effects	Model	Details	Ref
	BMECs during OGD/R	↓ permeability, apoptosis, autophagy, LC3, Beclin-1, ↑ p-Akt and p-mTOR proteins	27
	primary microglia stimulated by oGD/R	↑ TLR9; ↓ the NF- κB pathway	17
	OGD-induced PC12 cells	↑ cell viability, Bcl-2, SOD ↓ MDA, apoptotic cells and expressions of Bax, Caspase-3 and cyto c and increasing	15
	MCAO rats	↓ overloaded Ca^{2+} and scavenge capability of free radicals, edema degree and membrane phospholipid decomposability ↑ the membrane fluidity and activities of respiratory enzymes ↑ latency time on rotarod and alteration behavior in Y-maze, levels of GSH and catalase ↓ neurological deficit scores, levels of MDA and TNF-β, and infarct volume	25
Dementia	VD rats by 2-VO	↓ escape latency, prolonged time spent in the platform quadrant and swimming distance in the water maze, ↑ LTP ,VEGF-A, NR1, BDNF, NMDAR	28,29
	$Aβ_{1-42}$-induced AD model rats	↑ learning and memory abilities ↓ Aβ deposition,structural damage to dendritic spines,the loss of synaptic-associated proteins, the disorder of glutamate circulation	30
	$Aβ_{1-42}$-induced AD model rats	↓ BACE protein, $Aβ_{1-42}$	31
	CMS-induced AD model rats	↓ learning and memory impairments, BDNF, TrkB, PI3K/Akt/mTOR, RCAN1-1L, tau phosphorylation, GSK-3β, Cdk5	32
	$Aβ_{1-42}$-induced AD model rats	↓ TLR4/NF-κB transduction pathway ↑ TREM2	33
	AD rats induced by Hcy	↓ escape latency, the number to cross the hidden platform and time spent in the target quadrant, $Aβ_{40}$, $Aβ_{42}$ and PS1 protein levels, cell apoptosis and increasing LTP	36
	$Aβ_{1-42}$-induced AD mice	↓ memory deficits and expressions of Iba-1, GFAP, IL-1, TNF-α and iNOS, increasing expressions of IL-4 and IL-10 and suppressing activation of microglia and astrocytes in the hippocampi	34

Table 1 Summary about the cerebra-protection of HYSA (cont.)

Effects	Model	Details	Ref
	$A\beta_{1-42}$-induced BV-2 cells	↓ IL-1β, TNF-α, COX-2, iNOS , COX-2, TNF-α , iNOS ↑ cell viability, L-4, IL-10, pJAK2, pSTAT3 ↓ cell apoptosis	37 37
	Neurons and SH-SY5Y cells inhibited by conditioned meadium of $A\beta_{1-42}$-induced BV-2 cells $A\beta_{25-35}$-induced PC12 cells	↑ cell viability, mitochondrial function ↓ reducing LDH, intracellular ROS, MDA and neuronal apoptosis	35
TBI	TBI rats	↓ contusion volume, MDA and GSSG PAI-1 , MMP-9 ↑ SOD, CAT, GSH, t-PA, mitochondrial ATPase, GSH/GSSG	46,47
	TBI rats	↑ occludin, claudin-10, zonula occludens protein ↓ interleukin-1β, interleukin-6, IL-1β, IL-6, TNF-α, TLR4/NF- κB, Bax, caspase-3 and caspase-9	47
Other nervous system diseases	LE-induced brain injury in rats	↓ neurological scores, cell apoptosis, HRV ↑ eNOS	48
	CUMS-induced depression rats	↓ TNF-α, IL-6 ,IL-1β,MDA,TLR4/NF- κB ↑ SOD, GSH-Px expression signaling pathway	49

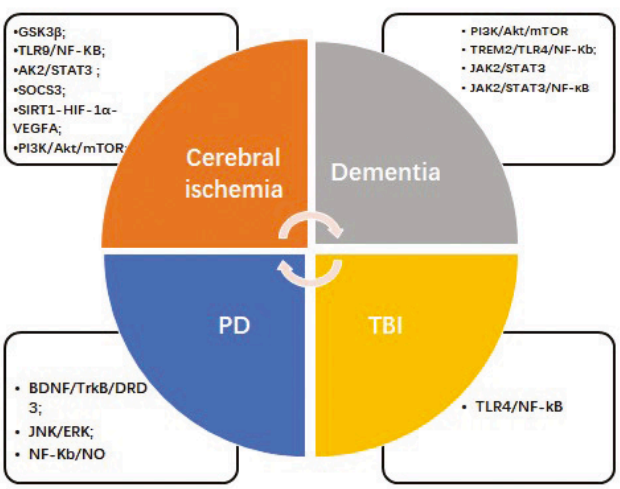

Figure 2 The pathways related to the cerebra-protective effects of HYSA

Additionally, HSYA treatment markedly alleviated brain injury induced by lymphostatic encephalopathy (LE) in rats by dramatically decreasing the neurological scores, attenuating histological change especially cell apoptosis in the rostral ventrolateral medullus (RVLM) and impaired cardiovascular function. Additionally, the decrease of endothelial nitric oxide synthase (eNOS) mRNA and protein expression in the RVLM of rats with LE were prevented by HYSA.[48] In rat model of depression, HSYA improved depressive behavior, and inhibited the activation of HPA signaling, inflammation and oxidative stress in brain of depressed rats and exerted a suppressive role in TLR4/NF-κB signaling pathway.[49]

Conclusion

This paper systematically summarizes the therapeutic potentials of HYSA in the treatment of cerebral diseases *in vitro* and *in vivo*, and clarifies the underlying mechanisms. HYSA is a potentially effective drug in the prevention and treatment of cerebral diseases. Since there is currently no systematic review focusing on the role and mechanism of action of HYSA in cerebral diseases, we provide a comprehensive summary with this goal and an outlook for future HYSA research.

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บทความปริทัศน์

ผลต่อการปกป้องสมองของสารไฮดรอกซีแซฟฟลอล์เยลโล่เอ

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ห้องปฏิบัติการหลักประจำมณฑลด้านทรัพยากรยาแผนจีนภาคตะวันตกเฉียงใต้ มหาวิทยาลัยการแพทย์แผนจีนเฉิงตู

บทคัดย่อ: ปัจจุบันอัตราการเสียชีวิตจากโรคทางสมองเพิ่มสูงขึ้นอย่างรวดเร็ว รวมไปถึงต้นทุนด้านการรักษาพยาบาลโรคทางสมองอยู่ในระดับสูง นอกจากนี้กลุ่มยาสารเคมีส่วนใหญ่ที่ใช้ในการรักษาโรคทางสมองนั้นมีกลไกการออกฤทธิ์โดยไปจับกับเป้าหมายจุดเดียว ทำให้ประสิทธิผลในการรักษาที่ได้ไม่ดีเท่าที่ควรและยังก่อให้เกิดความเป็นพิษ จึงมีการพิจารณานำยาจากสมุนไพรตามธรรมชาติมาใช้ในการรักษา อันเนื่องมาจากยาจากสมุนไพรธรรมชาติออกฤทธิ์โดยไปจับกับเป้าหมายที่หลากหลายและมีความเป็นพิษต่ำ ดังนั้นการพัฒนายาใหม่จากพืชสมุนไพรที่มีประสิทธิผลสำหรับใช้ในการรักษาโรคทางสมองจึงนับว่ามีความสำคัญเป็นอย่างยิ่ง สาร hydroxysafflor yellow A (HYSA) เป็นสารสกัดได้จากดอกของคำฝอย (*Carthamus tinctorius* L.) ซึ่งมีฤทธิ์ตามภูมิปัญญาคือส่งเสริมการไหลเวียนของโลหิตและขจัดเลือดคั่ง จากงานศึกษาวิจัยจำนวนมากในหลอดทดลองและสัตว์ทดลองพบว่าสาร HYSA สามารถชะลอการดำเนินของโรคสมองขาดเลือดเนื่องจากหลอดเลือดสมองตีบหรืออุดตัน ภาวะสมองเสื่อมที่มีสาเหตุมาจากขาดเลือดไปเลี้ยงสมองภาวะสมองเสื่อมชนิดอัลไซเมอร์โรคพาร์คินสัน การบาดเจ็บที่สมอง เป็นต้น โดยส่วนใหญ่ปรับและควบคุมผ่านกลไกที่เกี่ยวข้องคือ TLR9/NF-κB, AK2/STAT3, SIRT1-HIF-α-VEGFA, PI3K/Akt/mTOR, TREM2/TLR4/NF-κb, JAK2/STAT3/NF-κB, BDNF/TrkB/DRD3, JNK/ERK, TLR4/NF-κB เป็นต้น บทความนี้ได้สรุปและรวบรวมข้อมูลไว้อย่างเป็นระบบในด้านฤทธิ์ทางเภสัชวิทยาและกลไกในระดับโมเลกุลของสาร HYSA ที่มีต่อกลุ่มโรคทางสมองต่างๆ เพื่อเป็นแนวทางในการศึกษาค้นคว้าวิจัยสาร HYSA ต่อไปในอนาคต

คำสำคัญ: สาร hydroxysafflor yellow A (HYSA); โรคทางสมอง; ฤทธิ์ทางเภสัชวิทยา; การรวบรวมข้อมูลไว้อย่างเป็นระบบ

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文献综述

羟基红花黄色素 A 的脑保护作用

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摘要：现今，脑病致死率高，花费高，发生率增长迅速，是如今社会面临的重大问题。大多数治疗脑病的化药作用靶点单一，效果差且有一定毒性。天然药物由于靶点较多，低毒，被认为是可用于许多疾病治疗的潜力药物。因此，从天然药物中发现新型有效药物用于脑病治疗非常中药。羟基红花黄色素 A 分离自活血化瘀中药红花。大量体内外实验表明，该单体可缓解脑缺血、血管性痴呆、阿尔茨海默病、帕金森病、创伤性脑损伤等。其机制与调节TLR9/NF-κB, AK2/STAT3, SIRT1-HIF-1α-VEGFA, PI3K/Akt/mTOR, TREM2/TLR4/NF-κb, JAK2/STAT3/NF-κB, BDNF/TrkB/DRD3, JNK/ERK, TLR4/NF-κB 等。本文系统综述了羟基红花黄色素 A 对于多种脑病的作用及机制，为未来该单体的研究提供了方向。

关键词：羟基红花黄色素 A; 脑病；药理作用；综述

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