We are IntechOpen,
the world's leading publisher of
Open Access books
Built by scientists, for scientists

6,900
Open access books available

185,000
International authors and editors

200M
Downloads

154
Countries delivered to

Our authors are among the

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities

BOOK CITATION INDEX
CLARIVATE ANALYTICS
INDEXED

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Complementary Therapy with Traditional Chinese Medicine for Neonatal Hypoxic Ischemic Encephalopathy

Chun-Ting Lee, Yu-Chiang Hung and Wen-Long Hu

Additional information is available at the end of the chapter

Abstract

Hypoxic ischemic encephalopathy (HIE) is one of the most significant causes of morbidity, mortality, and lifelong disability in newborns. The diagnosis of neonatal HIE is based on the dysfunction of neurogenic signs and classification according to the Sarnat staging system, which evaluates conscious level, neuromuscular control, complex reflexes, autonomic function, seizures, electroencephalogram readings, and duration of neurologic sign. There is no standard treatment for neonatal HIE, but it is widely accepted that hypothermia therapy is a safe and effective method for treating neonates with HIE. Traditional Chinese medicine (TCM) has recently been used to treat cases of neonatal HIE, especially herbal medicine prescriptions. Acupuncture is a common method used in TCM and is another promising therapy for neonatal HIE due to its demonstrated effective treatment of the disease in animal models. While there is a lack of direct evidence in clinical practice, we have observed acupuncture to be useful in adult HIE and in animal studies; therefore, we believe a clinical trial designed to evaluate the effectiveness of acupuncture in neonatal HIE treatment is worthwhile. Taken together, TCM is a promising technique that can be integrated into the conventional therapies for neonatal HIE.

Keywords: acupuncture, complementary therapy, herbal medicine, neonatal hypoxic ischemic encephalopathy, traditional Chinese medicine

1. Introduction

1.1. Definition and epidemiology of neonatal hypoxic ischemic encephalopathy

Hypoxic ischemic encephalopathy (HIE) occurs when the cerebral blood flow is disrupted, causing a subsequent lack of oxygen to the affected brain area. Neonatal HIE is one of the most significant causes of morbidity, mortality and lifelong disability of newborns, which can include visual impairment, learning impairment, epilepsy, mental retardation, blindness, and cerebral palsy (CP) [1–3]. The incidence of HIE is approximately in 2–9/1000 live births and its frequency increases up to 26/1000 newborns in developing countries [1, 3–10]. Nearly 40% of HIE newborns cannot survive the neonatal period and another 30% suffer from long-term neurological disorders [4, 11, 12].

1.2. Cause of neonatal HIE

HIE is caused by a number of reasons, including severe hypoxia, hypotension, or infection during prenatal development; uterine rupture, cord occlusion or prolapse, abruption or placental insufficiency during perinatal development; shock; and respiratory or cardiac arrest during postnatal periods [3, 13].

1.3. Pathophysiology of neonatal HIE

The pathogenesis of HIE can be divided into the following steps after injury (**Figure 1**) [1, 3, 4, 9, 10]:

i. First 60 min: Due to lack of glucose and oxygen delivery to the brain, anaerobic respiration cannot produce sufficient adenosine triphosphate (ATP) and causes failure of ATP-dependent Na^+/K^+-pumps [1, 3, 4, 9, 10]. This phenomenon results in Ca^{2+} and Na^+ influx and cell membrane depolarization [1, 3, 4, 9, 10]. When the membrane depolarizes, the cells release excitatory glutamate [1, 3, 4, 9, 10]. Glutamate can activate N-methyl-D-aspartate (NMDA) and a-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate (AMPA) receptors, which increases Ca^{2+} influx into cells and causes cell apoptosis [1, 3, 4, 9, 10]. Furthermore, hypoxia inducible factor-1α (HIF-1α) is also upregulated in these conditions, which will then bind to HIF-1β to form HIF-1α/β complex and traffic to nucleus, where it activates downstream genes, such as erythropoietin (*EPO*) and vascular endothelial growth factor (*VEGF*), to rescue this situation after brain injury [9]. Hydrogen sulfide (H_2S) is a novel neuromodulator that is produced by cystathionine β-synthase (CBS) in brain tissue, especially the hippocampus, and can modulate NMDA receptor activity [14]. H_2S plays an important role in ischemic brain damage and the inhibition of H_2S levels could serve as a therapeutic strategy to protect neuron damage in HIE [15].

ii. Between 1 and 48 h: Acute inflammation, oxidative metabolism, and continuation of activated apoptotic cascades take place in this stage of HIE [1, 3, 4, 9, 10]. Because of the Ca^{2+}

accumulation in cells, production of nitric oxide (NO) by neuronal nitric oxide synthase (nNOS) is elevated and generates reactive oxygen species (ROS) caused by mitochondria (mt) injury [1, 3, 4, 9, 10]. Furthermore, lipid peroxidation is induced by intracellular ROS level elevation [1, 3, 4, 9, 10], and *Bcl-2* expression levels are reduced, while *Bax* expression is increased, leading cells to undergo apoptosis [9]. Carbon monoxide (CO) is an endogenous molecule that is generated from the degradation of heme by heme-oxygenase (HO) might serve as an neuroprotective reagent because it can reduce inflammation, anti-apoptosis, and induce vasodilation in HIE rats [16].

iii. Days to months: At this point, chronic inflammation, late cell death, remodeling and repair of the injured brain tissue, and astrogliosis (abnormal increase of astrocytes due to brain damage) occur [1, 3, 4, 9, 10]. Brain-derived neurotrophic factor (BDNF) and glial cell line-derived neurotrophic factor (GDNF) are two important factors that have beneficial effects on brain repair and remodeling in HIE [17–20].
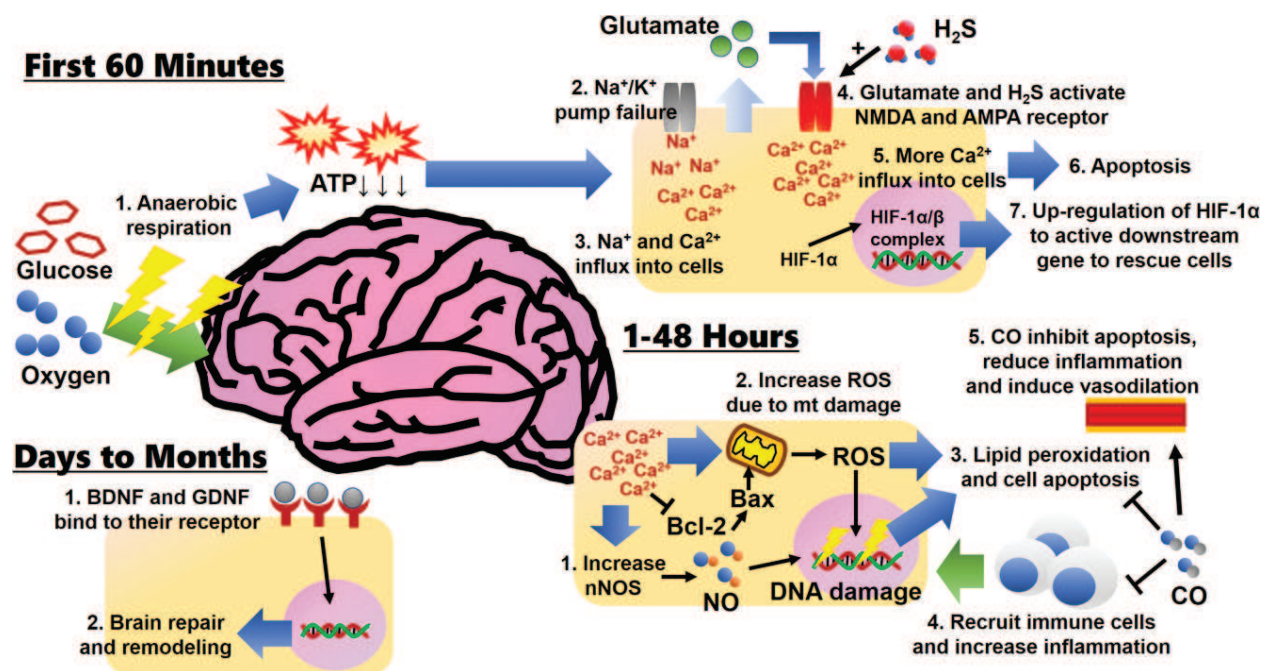

Figure 1. Pathophysiology of neonatal hypoxic ischemic encephalopathy. Generally speaking, the pathophysiology of neonatal HIE can be divided into three major steps. **(1) In the first 60 min:** HIE is caused by reduced glucose and oxygen delivery to the brain, which causes anaerobic respiration. This phenomenon will reduce ATP production from one molecule of glucose (38 ATP → 2 ATP). The reduction of ATP will initially influence the ion content in cells, and then glutamate will accumulate outside the cells and induce cell apoptosis by activating the NMDA and AMPA receptors to transport more Ca^{2+} into cells. However, HIF-1α will be upregulated to modulate downstream genes involved in cell rescue. **(2) In the next 1–48 h:** due to Ca^{2+} accumulation in cells, nNOS and ROS increase, which causes lipid peroxidation and induce cell apoptosis. Furthermore, excess Ca^{2+} will reduce *Bcl-2* expression and increase *Bax* expression, also leading cells to undergo apoptosis. In addition, CO might play an important role in preventing immune cell recruitment, decrease the inflammatory response, inhibit cell apoptosis, and promote vasodilation. **(3) In the days to months following the initial HIE onset:** BDNF and GDNF might be involved in many signaling cascades responsible for brain tissue repair and remodeling. * Partial figure design was provided by Hsiao-Han Hsu.

1.4. Diagnosis and classification of neonatal HIE

Any abnormal heart rate or other signs of neonate distress during delivery and respiratory problems, improper Apgar scores, seizures, unconsciousness and so on after birth are warning sings to suspect neonatal HIE. There is no currently available bedside test for accurate diagnosis of neonatal HIE [1]. The diagnosis of HIE is based on the signs of neurogenic dysfunction such as abnormality of muscle power and tone, reduced consciousness and respiration, functional disruption of the cranial nerve, and seizures [1, 21]. Metabolic acidosis and low Apgar scores are associated with neuronal dysfunction; moreover, metabolic acidosis is significantly related to HI injury [1, 21]. Furthermore, the image pattern of magnetic resonance imaging (MRI) may provide further evidence for HIE diagnosis [1]. Classification of neonatal HIE follows the Sarnat staging system, which is divided into three categories—stage I (mild), stage II (moderate), and stage III (severe)—that are used to evaluate the following parameters: level of consciousness, neuromuscular control, complex reflexes, autonomic function, seizures, electroencephalogram readings, and duration [1, 22].

1.5. Treatment of neonatal HIE

1.5.1. Systemic support

The basic care of neonatal HIE is systemic support, which is very important to maintain the cerebral blood flow that ensures glucose and oxygen supply to the brain to prevent further injury [1]. Neonates with HIE produce less carbon dioxide (CO_2) due to changes in energy metabolism and need less ventilator support to maintain suitable levels of CO_2 [1, 23]. Insufficient CO_2 (hypocapnia) is related to high mortality and poor development of neuron function [1, 23, 24]. In addition, too much oxygen (hyperoxia) is also hazardous in neonates with HIE because it can enhance oxidative stress and free radical formation that might increase mortality and poor outcome [1, 24]. Therefore, maintaining suitable CO_2 and O_2 levels at $PaCO_2$ 40–55 mmHg and PaO_2, 50–100 mmHg, respectively, may prevent further brain injury in neonates with HIE [1]. Blood pressure must also be maintained to avoid hypotension in newborn HIE because it could prevent further ischemic brain injury [1]. Unfortunately, there is no evidence of what the ideal mean arterial blood pressure (MAP) is in cases of neonatal HIE [1].

1.5.2. Fluids and nutrition

For the best long-term outcomes, the initial optimal rate of fluid therapy is not established but the most common practice is to start intravenous 10% dextrose solution combined with sodium and add proper electrolytes based on the results of serum electrolytes [1]. It is suggested that carefully managing fluid therapy in neonates with HIE is helpful in preventing brain edema [1, 25]. Research has shown that hypoglycemia is associated with a high Sarnat stage grade and is an important factor for severe brain injury [1, 26, 27]. Under normal physiological conditions, the adult brain uses nearly 100% glucose as an energy source, but in

neonate brains, glucose may account for only 70% [1, 28]. Despite neonate brains being able to use other substrates as energy such as lactate or ketones, these alternative substrates may not compensate for the lack of glucose [1, 28]. In other words, monitoring fluid and glucose strictly is very important in preventing brain edema and hypoglycemia in newborns with HIE and might be helpful in reducing further brain damage [1].

1.5.3. Hypothermia

It is widely accepted that hypothermia therapy is a safe and effective way to treat neonatal HIE and could reduce morbidity and mortality [1, 3, 29–31]. Many studies have shown that keeping neonatal HIE subjects 2–3° below the normal brain temperature can prevent further neurological damage; one of the possible mechanisms for this might be associated with reduce carbon biomass related to acetyl moieties such as pyruvate and acetyl-CoA [3, 32–34]. Other possible mechanisms of neuroprotection from HIE symptoms like inactive microglia cells could be the reduction of apoptosis pathways by decreased caspase-3 activity, decreased NMDA receptor activity, preservation of lipoprotein membrane integrity, and decreased inflammatory responses [35–40]. Therapeutic hypothermia is a part of current standard treatments of neonates with moderate to severe HIE [41].

1.5.4. Medication for seizure control

The best medication for seizure control in neonates with HIE is not well standardized [1]. Phenobarbital, a frequently prescribed drug by physicians, can only control seizure attacks in 27% of patients [1]. Two promising anti-seizure drugs, topiramate and levetiracetam, need more clinical trials to prove their efficacy in neonates with HIE [1]. In one animal study and one human pilot clinical trial, topiramate was shown to work synergistically with hypothermia therapy [1, 42]. Levetiracetam is reported to reduce neuron cell apoptosis and decrease excitotoxicity in general, and one animal study showed these effects are also appearing in neonatal HIE rats [1, 43].

2. Traditional Chinese medicine in the treatment of neonatal HIE

2.1. TCM perspective of neonatal HIE

Neonatal HIE can be classified into "tai jing, 胎驚", "tai shian, 胎癇", "jing feng, 驚風", and "huan mi, 昏迷" in TCM. In mild and moderate grades of neonatal HIE, the common TCM diagnostic pattern are "deficiency of qi and blood, 氣血不足" and "qi obstruction and blood stasis, 氣滯血瘀". The best therapeutic principles are "supplementing qi and nourishing blood, 益氣養血" and "promoting qi circulation to remove blood stasis, 行氣化瘀". In severe grade one, the most common diagnostic pattern is "phlegm stasis causing wind, 痰瘀生風" and the therapeutic principle is "tranquilize mind and arresting convulsion, 化痰定驚". To

reach this goal, TCM physicians can use herbal medicine or acupuncture in the treatment of neonatal HIE, which we will discuss in the following section.

2.2. Acupuncture therapy for neonatal HIE

2.2.1. Clinical trial

Currently, there are no suitable clinical trials that have demonstrated that acupuncture can improve the prognosis of neonatal HIE, as acupuncture has only been evaluated in older infants who survived HIE [44]. CP is one of the consequences of HIE that acupuncture might have some beneficial effects in children [45–49]. Clinical evidence showed that acupuncture therapy intervention could improve the quality of life and promote improvements in speech and language impairment, neural function, motor disability, and cognition [45, 46, 50–53]. Although there is no current clinical trial evidence that acupuncture therapy could be used in neonates with HIE, there are many basic research studies have already demonstrated that acupuncture has the potential to be an intervention option for neonatal HIE.

2.2.2. The possible mechanism of acupuncture therapy for neonatal HIE

Because it is widely accepted by patients, physicians and scientists that acupuncture therapy can be used to improve many brain-related diseases such as stroke and Alzheimer disease [54, 55], many researchers are devoted to investigating the possibility of treating neonates with HIE with acupuncture therapy (**Table 1**).

In 2010, Liu et al. [56] showed that electro-acupuncture (EA) could protect against brain damage caused by HIE by reducing hydrogen sulfide (H_2S) generation in neonatal rats. In this study, they treated acupoints Dazhui (DV14, 大椎) and Baihui (DV20, 百會) using needles 0.25 mm in diameter and 10 mm long and an electrical wave frequency 2/100 Hz at an intensity of 3 mA for 30 min/day with 14 continuous days starting the second day after the neonatal HIE rat model was established [56]. The results showed that EA could increase cerebral blood flow and motor function when compared to the no treatment group [56]. They also measured the expression of CBS, an enzyme that can produce H_2S in brain tissue and is elevated in HIE, in the EA-treated group and found reduced expression compared to the untreated control [56]. In 2011, the same therapeutic protocol was also associated with the NO/nNOS system; EA could reduce NO levels and nNOS expression of the cortex compared with the no treatment group [57]. In addition, the expression of nNOS might be related to the nuclear factor-κB (NF-κB) pathway that EA could reduce the nNOS expression level via reducing the NF-κB generation [58]. In 2014, DV14 and DV20 stimulated by EA elevated CO levels and HO-1 in HIE neonatal rats, which might protect against neuron damage [59]. Chao et al. [60] showed that applying manual acupuncture (MA) using needles 0.18 mm in diameter and 13 mm long at Baihui (DV20, 百會) and Shuaigu (GB8, 率谷) for 30 min/day with 30 s twirling and rotation every 5 min during each MA treatment, 2 days before HIE established and 7 days after HIE was induced, could reduce neonatal rat brain injury. They found that this treatment protocol could balance K^+ after HIE, probably through activation of the δ-opioid receptor (DOR) in the brain [60].

Acupoints	Treatment protocol	Possible mechanism	Reference
Dazhui (DV14, 大椎), Baihui (DV21, 百會)	Needles: 0.25 mm in diameter and 10 mm long	**1.** Reduce H_2S level by decreasing the expression level of CBS	[56–59]
	Method: EA with electrical wave frequency 2/100 Hz and intense 3 mA	**2.** Reduce NO level by decreasing the expression of nNOS through the NF-κB pathway	
	Treatment time: 30 min/day with 14 days	**3.** Increase CO level in cortex by enhancing HO-1 expression	
Baihui (DV20, 百會), Shuaigu (GB8, 率谷)	Needles: 0.18 mm in diameter and 13 mm long	Attenuating ischemic disruption of K^+ homeostasis via activated DOR	[60]
	Method: MA with twirling and rotating for 30 s every 5 min during each MA treatment		
	Treatment time: 30 min/day, 2 days before established HIE and 7 days after established HIE		
Baihui (GV 20, 百會), Dazhui (GV 14, 大椎), Quchi (LI 11, 曲池), Yongquan (KI 1, 湧泉)	Needles: 13 mm long, diameter not available in Ref.	GDNF, RET receptor and Akt were increased expression	[61]
	Method: EA with asymmetric bidirectional continuous pulse wave frequency 5–10 Hz and intensity 3–5 V at GV20 and LI11		
	Treatment time: 10 min/day with 21 days		
Baihui (GV 20, 百會), Si shencong (Ex-HN 1, 四神聰)	Needles: 0.3 mm in diameter and 25 mm long	**1.** Attenuated brain cell apoptosis	[62]
	Method: MA with twirling at a rate of 2 spins/s for 15 s when needles insertion in each acupoint and the needles were twirled for 3 min every 10 min	**2.** Up-regulated BDNF and GDNF expression level	
	Treatment time: 30 min/day with 28 days (MA performed for 5 days and 2 days of rest)		

Table 1. The commonly used acupoints and possible mechanisms of neonatal hypoxic ischemic encephalopathy acupuncture.

An article published by Xu et al. [61] showed that EA could protect against neuron damage after HIE and might be associated with the GDNF/rearranged during transfection (RET) receptor pathway. This study choose Baihui (GV 20, 百會), Dazhui (GV 14, 大椎), Quchi (LI 11, 曲池), and Yongquan (KI 1, 湧泉) for acupuncture therapy using needles 13 mm long, and EA with asymmetric bidirectional continuous pulse waves with a frequency of 5–10 Hz and an intensity 3–5 V, which was performed at GV20 and LI11 for 10 min/day for continuous 21 days [61]. These results showed that after treatment, the RET receptor and its key downstream phosphatidylinositol 3 kinase (PI-3 K)/protein kinase B (Akt), increased in expression in a dose dependent manner (sham EA compared with EA treated for 1, 3, 7, and 21 days) [61].

Based on these data, the authors suggested that the longer duration acupuncture treatment had better therapeutic effects on reducing neuron damage after HIE [61].

Zhang et al. [62] found that acupuncture at Baihui (GV 20, 百會) and Si shencong (Ex-HN 1, 四神聰) could reduce neuron damage after HIE. One day after neonatal HIE rat model was established, therapy included 0.3 × 25 mm needles that were twirled at a rate of two spins per second for 15 s, and then retained for 30 min at GV20 and Ex-HN1 [62]. At the needle retention interval, the needles were twirled three times for 3 min [62]. The acupuncture therapy was performed for five consecutive days followed by 2 days of rest and was performed over a total of 28 days [62]. The results showed that neurobehavioral function, and learning and memory abilities were improved after 20 days of treatment [62]. In addition, this study suggested that the possible mechanism of the acupuncture treatment might be associated with anti-apoptosis and upregulated GDNF and BDNF expression levels in the brain [62].

2.3. Herbal medicines for neonatal HIE

2.3.1. Clinical trial

Herbal medicines, including single herb and formulas (combination with different ingredient herb), have beneficial effects on brain HI injury. For example, treating neonates with HIE with a combination of Panax notoginseng saponins and conventional therapy can significantly reduce central respiratory failure, circulation dysfunction and gastrointestinal symptoms when compared to neonates treated only with conventional therapy [63]. Furthermore, the level of Ca^{2+} in red blood cells decreased significantly in the Panax notoginseng saponins treated group [63]. Research has also shown that conventional therapy combined with *Salvia miltiorrhiza*, *Ligusticum chuanxiong*, *Ginkgo biloba*, and *Astragalus propinquus* can improve the clinical outcome of HIE [64]. Some formulas such as Xuefu Zhuyu Decoction (血府逐瘀湯), Sheng Mai Yin (生脈飲), and An Gong Niu Huang Wan (安宮牛黃丸) are also known to improve the prognosis of neonates with HIE when combined with conventional therapy [64]. Considerable research has provided us a possible mechanism for how these herbal medicines and formulas work in HIE treatment, and we discuss this in the following sections.

2.3.2. Possible mechanisms of different single herbs for neonatal HIE remedies

In this section, we briefly discuss and summarize some single herbs and their possible pharmacological mechanism on neonatal HIE (**Table 2**).

i. *Panax ginseng* (人參)

Ginseng, the root and rhizome of *Panax ginseng* C A Meyer, has been used as a tonic herb for over 2000 years [65]. Ginsenoside Rg1 is one of the ingredients that is extracted from Ginseng and might improve brain repair after HIE [65]. Rg1 could increase neural viability, promote angiogenesis, and induce neurogenesis by increasing HIF-1α expression [65]. In addition, the expression of HIF-1α expression by Rg1 via cellular signaling pathway such as PI-3 K/Akt and extracellular signal-regulated kinase (ERK) was demonstrated [65].

ii. *Salvia miltiorrhiza* (丹参)

Salvia miltiorrhiza is a common drug used for promoting blood circulation and removing blood stasis "活血化瘀" [66, 67]. Research has shown that tanshinone IIA, an important component of *Salvia miltiorrhiza*, might have neuronal protective, anti-apoptosis effects by inhibiting caspase-3 activity after HIE [66]. In addition, tanshinone IIA can reduce inflammation by decreasing the expression level of TNF-α and IL-1β in HIE brain tissue [67].

iii. *Ligusticum chuanxiong* (川芎)

Ligustrazine, a component extracted from *Ligusticum chuanxiong*, has known to have effect of neuron protection [68, 69]. *Ligusticum chuanxiong* is a herb which is widely used to active blood and promote qi circulation "活血行氣" [68, 69]. In modern research, ligustrazine can increase the expression level of HIF-1α, which can activate many downstream pathways that protect neuron damage in HI conditions [68]. Furthermore, ligustrazine can reduce neuron cell apoptosis through increasing the *Bcl-2* gene expression and decreasing the *Bax* gene expression [69].

iv. *Astragalus propinquus* (黃耆)

Astragalus propinquus is a tonic herb that is used to invigorate qi for ascending "補氣升陽", and nourish blood and promote granulation "養血生肌" [70]. In a recent study, it was demonstrated that *Astragalus propinquus* can improve neural behavior by increasing the expression level of VEGF and VEGF receptor-2 (VEGFR-2) [70], which play important roles in ameliorating cognitive impairment in ischemic brain tissue *in vitro* and *in vivo* by improving neuronal cell viability and function [71].

v. *Radix Puerariae* (葛根)

Puerarin is extracted from *Radix Puerariae*, which has been demonstrated to reduce neuronal apoptosis after HI injury [72, 73]. The possible mechanism of puerarin is the downregulation of Bax and Caspase-3 levels by increasing the expression of BDNF [72]. In addition, puerarin can reduce ROS, prevent excess Ca^{2+} reflux into cells, and decrease inflammatory responses caused during HI injury [72]. Furthermore, the Bim protein can promote cell apoptosis and can also be downregulated by puerarin [73].

vi. *Gastrodia elata* (天麻)

Gastrodia elata belongs to *Orchidaceae* family and is used as a herbal medicine for its pharmacologic function of relieving convulsion and spasm "息風止痙", suppressing liver yang "平抑肝陽", and expelling wind evil and channel "祛風通絡" [74]. It is a promising neuroprotective herb that might have been used in many incurable neural diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), stroke, and seizure because this herb was demonstrated that could reduce neuron cell apoptosis via reducing neuron cell damage by free radical, inhibiting Ca^{2+} influx into cells and decreasing the neuron toxicity by counteracting glutamate effect [75]. The expression of doublecortin in brain tissue can be upregulated by *Gastrodia elata*, and this phenomenon is beneficial for brain injury because it can increase neuron cell migration and differentiation [74].

vii. *Ginkgo biloba* (銀杏)

The extractions from the *Ginkgo biloba* leaf are widely used in the treatment of aging-related diseases such as AD, cerebrovascular disease, and macroangiopathy [76]. The possible mechanism of *Ginkgo biloba* leaf extraction might be associated with its anti-oxidative properties such as scavenging free radicals, regulation of oxidative stress, and anti-lipid peroxidation;

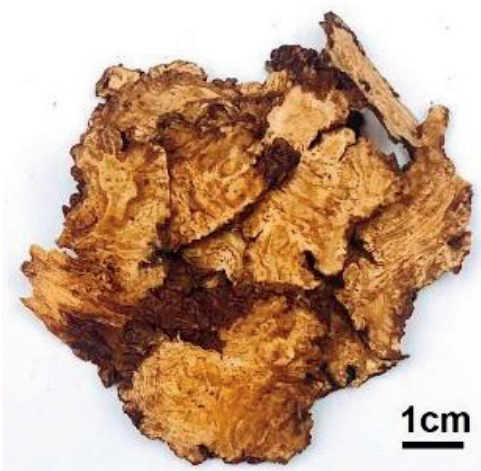| Herbal medicine	Possible mechanism	Reference
Panax ginseng (人参)	**1.** Increases neural viability, promotes angiogenesis, and induces neurogenesis by targeting hypoxia HIF-1α. **2.** Involves the cellular signaling pathway PI-3 K/Akt and ERK upstream of HIF-1α.	[65]
Salvia miltiorrhiza (丹参)	**1.** Neuronal protective effect by inhibiting caspase-3 activity after HIE, which inhibits apoptosis. **2.** Reduces inflammation by decreasing the expression level of TNF-α and IL-1β in HIE brain tissue.	[66, 67]
Ligusticum chuanxiong (川芎)	**1.** Increases the expression of HIF-1α, which can activate many downstream pathways that can protect neuronal damage in HI conditions. **2.** Reduces neuron cell apoptosis by increasing *Bcl-2* gene expression and decreasing the *Bax* gene expression.	[68, 69]

Herbal medicine	Possible mechanism	Reference
Astragalus propinquus (黃耆)	Improves neural behavior by increasing the expression level of *VEGF and VEGFR-2, which might be associated with* ameliorating cognitive impairment in ischemia brain tissue *in vitro* and *in vivo* through improvement of neuron cell viability and function.	[70, 71]
Radix Puerariae (葛根)	1. Decreases apoptosis by down-regulating the level of Bax and Caspase-3, which increases the expression of BDNF. 2. Reduces ROS, prevents excess Ca^{2+} influx into cells, and decreases the inflammatory response to HI injury. 3. Prevents apoptosis by down-regulating the Bim protein.	[72, 73]
Gastrodia elata (天麻)	Increases neuron cell migration and differentiation by elevating the expression of doublecortin.	[74]
Ginkgo biloba (銀杏)	1. Associated with anti-oxidative properties, protection against oxidative DNA damage, and regulation of mt damage. 2. Promotes brain tissue repair by increasing nestin protein expression and inducing neural stem cell proliferation.	[76, 77]

Herbal medicine	Possible mechanism	Reference
Rhodiola rosea (紅景天)	Increases the expression level of HIF-1α in endothelium cells of brain vessels, cerebral cortex, and hippocampus.	[80]
Panax notoginseng (川七)	**1.** Reduces the damage caused by free radicals and decreases Ca^{2+} influx into neuron cells. **2.** Promotes blood circulation in the brain by a vessel dilating effect.	[81]

*All herbal medicine samples were kindly provided by Long Zhi De Chinese Medicine and Biotechnology Co., Ltd.

Table 2. Possible mechanisms of herbs used for neonatal HIE treatment.

protecting DNA damage from oxidative damage; regulating mt damage such as inhibiting mt-induced ROS, and decreasing mt-related apoptosis [76]. In addition, the extract of *Ginkgo biloba* leaves can increase nestin protein expression, which can promote brain tissue repair by inducing neural stem cells proliferation [77].

viii. *Rhodiola rosea* (紅景天)

Rhodiola rosea is a widely used herbal medicine in Asia and Eastern Europe for enhancing physical and mental performance [78]. More recently, this plant has been used as an additive in food, beverages, and dietary supplements [78, 79]. *Rhodiola rosea* extract might function as an HIE treatment by increasing the expression level of HIF-1α in the endothelium cells of brain vessels, cerebral cortex, and hippocampus [80].

ix. *Panax notoginseng* (川七)

Panax notoginseng saponins are important components in *Panax notoginseng* that are a promising reagent for HIE therapy because they have a protective effect that is associated with the

reduction of free radicals and Ca^{2+} influx into neuron cells, which can limit cellular damage after HIE onset [81]. Furthermore, it can also serve as a vasodilator and increase the circulation in the brains of HIE patients [81].

2.3.3. Possible mechanism of different herbal formulas for neonatal HIE

Formula is a combination of different single herbs used to treat many kinds of diseases. The beneficial of formula is that after combing different herbs together which could reduce toxicity and side effect if we only used too many same single herbs. Here we briefly introduce some herbal formulas that are beneficial in neonatal HIE therapies (**Table 3**).

i. Xuefu Zhuyu Decoction (血府逐瘀湯)

Xuefu Zhuyu Decoction is from "Correction on Errors in Medical Classics (醫林改錯)" written by Qing-Ren Wang (王清任) [64]. Because this formula is widely used to promote blood circulation and remove blood stasis "活血化瘀", this formula could reduce the viscosity of blood and lead to an increase the blood circulation [64]. Studies have shown that this formula could improve neural behavior in neonatal rats with HIE on day 6 after neonatal HIE rat model was established, compared to the saline treated control group [82]. In addition, Xuefu Zhuyu Decoction could maintain or slightly increase nerve growth factor (NGF) expression on day 6, while NGF expression levels decreased in the saline-treated control group [82]. These results suggest that Xuefu Zhuyu Decoction might protect neuron cells after HI injury by up-regulating NGF expression [82]. NGF is a neurotrophy, which can support the differentiation and survival of neuron cells and have anti-apoptotic and anti-oxidative effect which is showed to have beneficial effects on neonatal HIE rat [83].

ii. Sheng Mai Yin (生脈飲)

This formula consists of *Panax ginseng* (人參), *Liriope spicata* (麥門冬), and *Schisandra chinensis* (五味子) and is widely used to supplement qi and nourish yin "益氣養陰", reduce resuscitation and recuperate depleted yang "回陽固脫", and promote blood circulation and remove blood stasis "活血化瘀" [64]. A pharmacologic study showed that this formula can eradicate free radicals, inhibit lipid peroxidation, improve microcirculation, and increase

Formulas	Possible mechanism	Reference
Xuefu Zhuyu Decoction (血府逐瘀湯)	**1.** Increases blood circulation by decreasing blood viscosity. **2.** Improves neural behavior by up-regulating NGF expression.	[64, 82]
Sheng Mai Yin (生脈飲)	**1.** Eradicates free radicals, inhibits lipid peroxidation, improves microcirculation, and increases cell resistance to hypoxia. **2.** Rescues brain hypoxia and ischemic injury by improving the metabolism of the heart, increasing myocardial cells contraction, and cardiac output.	[64]
An Gong Niu Huang Wan (安宮牛黃丸)	Eradicates free radicals and reduces edema in the brain by decreasing vascular permeability and increasing hypoxia resistance.	[64, 84]

Table 3. Possible mechanisms of herbal formulas for neonatal HIE treatment.

neuron cell resistance to hypoxia and other cellular stress [64]. In addition, Sheng Mai Yin can also improve the metabolism of heart and increase myocardial cells contraction and cardiac output to rescue hypoxia and ischemic injury of the brain [64]. Taken together, Sheng Mai Yin can prevent nerve cells damage after HIE via reducing neuron cell apoptosis, increasing neuron cell resistance to hypoxia and stress, increasing brain circulation [64].

iii.   An Gong Niu Huang Wan (安宮牛黃丸)

An Gong Niu Huang Wan is a formula that can remove qi and blood obstruction, smooth circulation, and stop pains with aromatics "芳香開竅", awaking brain and reliving spasm "醒腦止痙", clear away heat and toxic materials "清熱解毒" and cool blood and promoting qi circulation "涼血行氣" [64]. A biomedical study showed that An Gong Niu Huang Wan could eradicate free radicals in brain tissue and reduce brain edema by decreasing vascular permeability and increasing neuron cell resistance to hypoxia [64, 84].

3. Discussion and conclusion

Current advances in medical technology have increased, but there is still no standard and effective treatment for neonatal HIE. The widely accepted treatment for neonatal HIE is hypothermia therapy that has been demonstrated to reduce morbidity and mortality in newborns [1, 3, 29–31]. Many researchers and physicians hope to find the best way to treat this disease and devote themselves to the investigation and development of new therapeutic agents and stem cells transplantation therapy [1]. Recently, many basic researches showed that TCM (including herbal medicine and acupuncture) treatment was involved in many molecular pathways which might be beneficial to neonatal HIE for example, reducing H_2S and NO level, increasing CO level, keeping ion homeostasis, up-regulating BDNF, GDNF and NGF, scavenging free radicals and so on in neural cells to prevent cells apoptosis and further damage. Due to abovementioned reasons, integrating Chinese Medicine to treat neonatal HIE is one promising method toward a better prognosis. Here we review many kinds of herbal medicines and formulas used in clinical practice in China and show that in with standard treatment, these herbs and formulas can improve the prognosis of neonatal HIE. In addition, acupuncture therapy is also a promising method to treat neonates with HIE, but unfortunately there are no suitable clinical trials that report the effect of acupuncture on neonatal HIE. However, it is worth mentioning that acupuncture therapy of adults with HIE is very useful [85]. In our experience, the Acupoints of Regain Consciousness (ARC) "醒腦開竅方" and Acupoints of Recover from Paralysis (ARP) "疏經活絡方" established by Dr. Wen-Long Hu are very useful in cases of adult HIE, and these acupoints are listed as the following: ARCs including 12 Jing-Well points (十二井穴), Frontal-top belt (額頂帶), Top-temporal belt (頂顳帶) and Renzhong (DU 26, 人中); and ARPs including Quchi (LI 11, 曲池), Hegu (LI 4, 合谷), Zusanli (ST36, 足三里), Sanyinjiao (Sp 6, 三陰交), Yanglingquan (GB 34, 陽陵泉) and three brain needle (腦三針) [85].

To conclude, although there is still a lack of clinical studies for demonstrating that acupuncture is suitable and beneficial for the treatment of neonates with HIE, many animal studies have demonstrated that acupuncture has potential as a treatment for neonatal HIE in clinical

practice, and its effectiveness for treating the symptoms of neonatal HIE should be evaluated. Based on current research and our clinical practice, we believe integrating conventional therapy with TCM is a promising therapeutic method for neonatal HIE.

Author details

Chun-Ting Lee[1], Yu-Chiang Hung[1,2] and Wen-Long Hu[1,3,4]*

*Address all correspondence to: oolonghu@gmail.com

1 Department of Chinese Medicine, Kaohsiung Chang Gung Memorial Hospital and School of Traditional Chinese Medicine, Chang Gung University College of Medicine, Kaohsiung, Taiwan

2 School of Chinese Medicine for Post Baccalaureate, I-Shou University, Kaohsiung, Taiwan

3 Fooyin University College of Nursing, Kaohsiung, Taiwan

4 Kaohsiung Medical University College of Medicine, Kaohsiung, Taiwan

References

[1] Douglas-Escobar M, Weiss MD. Hypoxic-ischemic encephalopathy: A review for the clinician. JAMA Pediatrics. 2015;**169**(4):397-403

[2] Zhao M, Zhu P, Fujino M, Zhuang J, Guo H, Sheikh I, Zhao L, Li XK. Oxidative stress in hypoxic-ischemic encephalopathy: Molecular mechanisms and therapeutic strategies. International Journal of Molecular Sciences. 2016;**17** (12):pii: E2078

[3] Yildiz EP, Ekici B, Tatli B. Neonatal hypoxic ischemic encephalopathy: An update on disease pathogenesis and treatment. Expert Review of Neurotherapeutics. 2017;**17**(5):449-459

[4] Li B, Concepcion K, Meng X, Zhang L. Brain-immune interactions in perinatal hypoxic-ischemic brain injury. Progress in Neurobiology. 2017;**159**:50-68

[5] Wu YW, Backstrand KH, Zhao S, Fullerton HJ, Johnston SC. Declining diagnosis of birth asphyxia in California: 1991-2000. Pediatrics. 2004;**114**(6):1584-1590

[6] Graham EM, Ruis KA, Hartman AL, Northington FJ, Fox HE. A systematic review of the role of intrapartum hypoxia-ischemia in the causation of neonatal encephalopathy. American Journal of Obstetrics and Gynecology. 2008;**199**(6):587-595

[7] Thornberg E, Thiringer K, Odeback A, Milsom I. Birth asphyxia: Incidence, clinical course and outcome in a Swedish population. Acta Paediatrica. 1995;**84**(8):927-932

[8] Lee AC, Kozuki N, Blencowe H, Vos T, Bahalim A, Darmstadt GL, Niermeyer S, Ellis M, Robertson NJ, Cousens S, Lawn JE. Intrapartum-related neonatal encephalopathy

incidence and impairment at regional and global levels for 2010 with trends from 1990. Pediatric Research. 2013;**74**(Suppl 1):50-72

[9]   Wu Q, Chen W, Sinha B, Tu Y, Manning S, Thomas N, Zhou S, Jiang H, Ma H, Kroessler DA, Yao J, Li Z, Inder TE, Wang X. Neuroprotective agents for neonatal hypoxic-ischemic brain injury. Drug Discovery Today. 2015;**20**(11):1372-1381

[10]   Allen KA, Brandon DH. Hypoxic ischemic encephalopathy: Pathophysiology and experimental treatments. Newborn and Infant Nursing Reviews. 2011;**11**(3):125-133

[11]   Higgins RD, Raju T, Edwards AD, Azzopardi DV, Bose CL, Clark RH, Ferriero DM, Guillet R, Gunn AJ, Hagberg H, Hirtz D, Inder TE, Jacobs SE, Jenkins D, Juul S, Laptook AR, Lucey JF, Maze M, Palmer C, Papile L, Pfister RH, Robertson NJ, Rutherford M, Shankaran S, Silverstein FS, Soll RF, Thoresen M, Walsh WF, Eunice Kennedy Shriver National Institute of Child, H.; Human Development Hypothermia Workshop, S. Moderators, hypothermia and other treatment options for neonatal encephalopathy: An executive summary of the Eunice Kennedy Shriver NICHD workshop. The Journal of Pediatrics. 2011;**159**(5):851-858

[12]   Rocha-Ferreira E, Hristova M. Antimicrobial peptides and complement in neonatal hypoxia-ischemia induced brain damage. Frontiers in Immunology. 2015;**6**:56

[13]   Volpe JJ. Encephalopathy of prematurity includes neuronal abnormalities. Pediatrics. 2005;**116**(1):221-225

[14]   Kimura H. Hydrogen sulfide induces cyclic AMP and modulates the NMDA receptor. Biochemical and Biophysical Research Communications. 2000;**267**(1):129-133

[15]   Qu K, Chen CP, Halliwell B, Moore PK, Wong PT. Hydrogen sulfide is a mediator of cerebral ischemic damage. Stroke. 2006;**37**(3):889-893

[16]   Queiroga CS, Tomasi S, Wideroe M, Alves PM, Vercelli A, Vieira HL. Preconditioning triggered by carbon monoxide (CO) provides neuronal protection following perinatal hypoxia-ischemia. PLoS One. 2012;**7**(8):e42632

[17]   Han BH, D'Costa A, Back SA, Parsadanian M, Patel S, Shah AR, Gidday JM, Srinivasan A, Deshmukh M, Holtzman DM. BDNF blocks caspase-3 activation in neonatal hypoxia-ischemia. Neurobiology of Disease. 2000;**7**(1):38-53

[18]   Almli CR, Levy TJ, Han BH, Shah AR, Gidday JM, Holtzman DM. BDNF protects against spatial memory deficits following neonatal hypoxia-ischemia. Experimental Neurology. 2000;**166**(1):99-114

[19]   Wang X, Guo S, Lu S, Zhou J, Li J, Xia S. Ultrasound-induced release of GDNF from lipid coated microbubbles injected into striatum reduces hypoxic-ischemic injury in neonatal rats. Brain Research Bulletin. 2012;**88**(5):495-500

[20]   Li SJ, Liu W, Wang JL, Zhang Y, Zhao DJ, Wang TJ, Li YY. The role of TNF-alpha, IL-6, IL-10, and GDNF in neuronal apoptosis in neonatal rat with hypoxic-ischemic encephalopathy. European Review for Medical and Pharmacological Sciences. 2014;**18**(6):905-909

[21] Volpe JJ. Neonatal encephalopathy: An inadequate term for hypoxic-ischemic encephalopathy. Annals of Neurology. 2012;**72**(2):156-166

[22] Sarnat HB, Sarnat MS. Neonatal encephalopathy following fetal distress. A clinical and electroencephalographic study. Archives of Neurology. 1976;**33**(10):696-705

[23] Pappas A, Shankaran S, Laptook AR, Langer JC, Bara R, Ehrenkranz RA, Goldberg RN, Das A, Higgins RD, Tyson JE, Walsh MC, Eunice Kennedy Shriver National Institute of Child, H.; Human Development Neonatal Research, N. Hypocarbia and adverse outcome in neonatal hypoxic-ischemic encephalopathy. The Journal of Pediatrics. 2011;**158**(5):752-758 e751

[24] Klinger G, Beyene J, Shah P, Perlman M. Do hyperoxaemia and hypocapnia add to the risk of brain injury after intrapartum asphyxia? Archives of Disease in Childhood. Fetal and Neonatal Edition. 2005;**90**(1):F49-F52

[25] Kecskes Z, Healy G, Jensen A. Fluid restriction for term infants with hypoxic-ischaemic encephalopathy following perinatal asphyxia. Cochrane Database of Systematic Reviews. 2005;**3**:CD004337

[26] Basu P, Som S, Choudhuri N, Das H. Contribution of the blood glucose level in perinatal asphyxia. European Journal of Pediatrics. 2009;**168**(7):833-838

[27] Salhab WA, Wyckoff MH, Laptook AR, Perlman JM. Initial hypoglycemia and neonatal brain injury in term infants with severe fetal acidemia. Pediatrics. 2004;**114**(2):361-366

[28] McGowan JE, Perlman JM. Glucose management during and after intensive delivery room resuscitation. Clinics in Perinatology. 2006;**33**(1):183-196

[29] Azzopardi DV, Strohm B, Edwards AD, Dyet L, Halliday HL, Juszczak E, Kapellou O, Levene M, Marlow N, Porter E, Thoresen M, Whitelaw A, Brocklehurst P, Group TS. Moderate hypothermia to treat perinatal asphyxial encephalopathy. The New England Journal of Medicine. 2009;**361**(14):1349-1358

[30] Gunn AJ, Wyatt JS, Whitelaw A, Barks J, Azzopardi D, Ballard R, Edwards AD, Ferriero DM, Gluckman PD, Polin RA, Robertson CM, Thoresen M, CoolCap Study G. Therapeutic hypothermia changes the prognostic value of clinical evaluation of neonatal encephalopathy. The Journal of Pediatrics. 2008;**152, 58**((1)):55, e51-58

[31] Shankaran S, Laptook AR, Ehrenkranz RA, Tyson JE, McDonald SA, Donovan EF, Fanaroff AA, Poole WK, Wright LL, Higgins RD, Finer NN, Carlo WA, Duara S, Oh W, Cotten CM, Stevenson DK, Stoll BJ, Lemons JA, Guillet R, Jobe AH, National Institute of Child, H.; Human Development Neonatal Research, N. whole-body hypothermia for neonates with hypoxic-ischemic encephalopathy. The New England Journal of Medicine. 2005;**353**(15):1574-1584

[32] Compagnoni G, Pogliani L, Lista G, Castoldi F, Fontana P, Mosca F. Hypothermia reduces neurological damage in asphyxiated newborn infants. Biology of the Neonate. 2002;**82**(4):222-227

[33] Davidson JO, Wassink G, Yuill CA, Zhang FG, Bennet L, Gunn AJ. How long is too long for cerebral cooling after ischemia in fetal sheep? Journal of Cerebral Blood Flow and Metabolism. 2015;**35**(5):751-758

[34] Takenouchi T, Sugiura Y, Morikawa T, Nakanishi T, Nagahata Y, Sugioka T, Honda K, Kubo A, Hishiki T, Matsuura T, Hoshino T, Takahashi T, Suematsu M, Kajimura M. Therapeutic hypothermia achieves neuroprotection via a decrease in acetylcholine with a concurrent increase in carnitine in the neonatal hypoxia-ischemia. Journal of Cerebral Blood Flow and Metabolism. 2015;**35**(5):794-805

[35] Wagner CL, Eicher DJ, Katikaneni LD, Barbosa E, Holden KR. The use of hypothermia: A role in the treatment of neonatal asphyxia? Pediatric Neurology. 1999;**21**(1):429-443

[36] Barrett RD, Bennet L, Davidson J, Dean JM, George S, Emerald BS, Gunn AJ. Destruction and reconstruction: Hypoxia and the developing brain. Birth Defects Research. Part C, Embryo Today. 2007;**81**(3):163-176

[37] Tanaka T, Wakamatsu T, Daijo H, Oda S, Kai S, Adachi T, Kizaka-Kondoh S, Fukuda K, Hirota K. Persisting mild hypothermia suppresses hypoxia-inducible factor-1alpha protein synthesis and hypoxia-inducible factor-1-mediated gene expression. American Journal of Physiology. Regulatory, Integrative and Comparative Physiology. 2010;**298**(3): R661-R671

[38] Tong G, Endersfelder S, Rosenthal LM, Wollersheim S, Sauer IM, Buhrer C, Berger F, Schmitt KR. Effects of moderate and deep hypothermia on RNA-binding proteins RBM3 and CIRP expressions in murine hippocampal brain slices. Brain Research. 2013; **1504**:74-84

[39] Webster CM, Kelly S, Koike MA, Chock VY, Giffard RG, Yenari MA. Inflammation and NFkappaB activation is decreased by hypothermia following global cerebral ischemia. Neurobiology of Disease. 2009;**33**(2):301-312

[40] Orrock JE, Panchapakesan K, Vezina G, Chang T, Harris K, Wang Y, Knoblach S, Massaro AN. Association of brain injury and neonatal cytokine response during therapeutic hypothermia in newborns with hypoxic-ischemic encephalopathy. Pediatric Research. 2016;**79**(5):742-747

[41] Shankaran S, Laptook AR, Pappas A, McDonald SA, Das A, Tyson JE, Poindexter BB, Schibler K, Bell EF, Heyne RJ, Pedroza C, Bara R, Van Meurs KP, Grisby C, Huitema CM, Garg M, Ehrenkranz RA, Shepherd EG, Chalak LF, Hamrick SE, Khan AM, Reynolds AM, Laughon MM, Truog WE, Dysart KC, Carlo WA, Walsh MC, Watterberg KL, Higgins RD, Eunice Kennedy Shriver National Institute of Child, H.; Human Development Neonatal Research, N. Effect of depth and duration of cooling on deaths in the NICU among neonates with hypoxic ischemic encephalopathy: A randomized clinical trial. JAMA. 2014;**312**(24):2629-2639

[42] Filippi L, la Marca G, Fiorini P, Poggi C, Cavallaro G, Malvagia S, Pellegrini-Giampietro DE, Guerrini R. Topiramate concentrations in neonates treated with prolonged whole body hypothermia for hypoxic ischemic encephalopathy. Epilepsia. 2009;**50**(11):2355-2361

[43] Kilicdag H, Daglioglu K, Erdogan S, Guzel A, Sencar L, Polat S, Zorludemir S. The effect of levetiracetam on neuronal apoptosis in neonatal rat model of hypoxic ischemic brain injury. Early Human Development. 2013;**89**(5):355-360

[44] Wong V, Cheuk DK, Chu V. Acupuncture for hypoxic ischemic encephalopathy in neonates. Cochrane Database of Systematic Reviews. 2013;**1**. DOI: CD007968

[45] Sun JG, Ko CH, Wong V, Sun XR. Randomised control trial of tongue acupuncture versus sham acupuncture in improving functional outcome in cerebral palsy. Journal of Neurology, Neurosurgery, and Psychiatry. 2004;**75**(7):1054-1057

[46] Wong VC, Sun JG, Yeung DW. Pilot study of positron emission tomography (PET) brain glucose metabolism to assess the efficacy of tongue and body acupuncture in cerebral palsy. Journal of Child Neurology. 2006;**21**(6):456-462

[47] Wu Y, Jin Z, Li K, Lu ZL, Wong V, Han TL, Zheng H, Caspi O, Liu G, Zeng YW, Zou LP. Effect of acupuncture on the brain in children with spastic cerebral palsy using functional neuroimaging (FMRI). Journal of Child Neurology. 2008;**23**(11):1267-1274

[48] Wu Y, Zou LP, Han TL, Zheng H, Caspi O, Wong V, Su Y, Shen KL. Randomized controlled trial of traditional Chinese medicine (acupuncture and tuina) in cerebral palsy: Part 1–any increase in seizure in integrated acupuncture and rehabilitation group versus rehabilitation group? Journal of Alternative and Complementary Medicine. 2008;**14**(8): 1005-1009

[49] Zhang Y, Liu J, Wang J, He Q. Traditional Chinese Medicine for treatment of cerebral palsy in children: A systematic review of randomized clinical trials. Journal of Alternative and Complementary Medicine. 2010;**16**(4):375-395

[50] Liu L, Liu LG, Lu M, Ran WJ. Clinical observation on infantile cerebral palsy treated with quick meridian needling therapy plus scalp acupuncture. Zhongguo Zhen Jiu. 2010;**30**(10):826-829

[51] Watson P. Modulation of involuntary movements in cerebral palsy with acupuncture. Acupuncture in Medicine. 2009;**27**(2):76-78

[52] Wu Z. Clinical applications of acupoints Baihui (GV 20) and Sishencong (Ex-HN 1). Journal of Acupuncture and Tuina Science. 2010;**8**(6):394-396

[53] Zou XY, Yu ZH, He YM, Yang H, Dong XL. Effect of acupuncture combined language training on cerebral palsy children with language retardation. Zhongguo Zhong Xi Yi Jie He Za Zhi. 2013;**33**(7):924-926

[54] Chavez LM, Huang SS, MacDonald I, Lin JG, Lee YC, Chen YH. Mechanisms of acupuncture therapy in ischemic stroke rehabilitation: A literature review of basic studies. International Journal of Molecular Sciences. 2017;**18**(11):e2270

[55] Zhou J, Peng W, Xu M, Li W, Liu Z. The effectiveness and safety of acupuncture for patients with Alzheimer disease: A systematic review and meta-analysis of randomized controlled trials. Medicine (Baltimore). 2015;**94**(22):e933

[56] Liu Y, Zou LP, Du JB, Wong V. Electro-acupuncture protects against hypoxic-ischemic brain-damaged immature rat via hydrogen sulfide as a possible mediator. Neuroscience Letters. 2010;**485**(1):74-78

[57] Liu Y, Zou LP, Du JB. Nitric oxide-mediated neuronal functional recovery in hypoxic-ischemic brain damaged rats subjected to electrical stimulation. Brain Research. 2011; **1383**:324-328

[58] Liu Y, Li W, Hu L, Liu Y, Li B, Sun C, Zhang C, Zou L. Downregulation of nitric oxide by electroacupuncture against hypoxicischemic brain damage in rats via nuclear factork-appaB/neuronal nitric oxide synthase. Molecular Medicine Reports. 2015;**11**(2):837-842

[59] Liu Y, Li Z, Shi X, Liu Y, Li W, Duan G, Li H, Yang X, Zhang C, Zou L. Neuroprotection of up-regulated carbon monoxide by electrical acupuncture on perinatal hypoxic-ischemic brain damage in rats. Neurochemical Research. 2014;**39**(9):1724-1732

[60] Chao D, Wang Q, Balboni G, Ding G, Xia Y. Attenuating Ischemic Disruption of K(+) Homeostasis in the Cortex of Hypoxic-Ischemic Neonatal Rats: DOR Activation vs. Acupuncture Treatment. Molecular Neurobiology. 2016;**53**(10):7213-7227

[61] Xu T, Xu NG, Yang ZH, Wan YZ, Wu QL, Huang KB. Neuroprotective effects of electroacupuncture on hypoxic-ischemic encephalopathy in newborn rats are associated with increased expression of GDNF-RET and protein kinase B. Chinese Journal of Integrative Medicine. 2016;**22**(6):457-466

[62] Zhang Y, Lan R, Wang J, Li XY, Zhu DN, Ma YZ, Wu JT, Liu ZH. Acupuncture reduced apoptosis and up-regulated BDNF and GDNF expression in hippocampus following hypoxic ischemic encephalopathy in neonatal rats. Journal of Ethnopharmacology. 2015; **172**:124-132

[63] Wang QX, Ling HE, Jiang Y, Chen LP. Clinical study on panax notoginseng saponins in the treatment of neonatal hypoxic-iscemic encephalopathy. Chinese Journal Of Contemporary Pediatrics. 2003;**5**(2):117-119

[64] Fan HZ. Review of Herbal Medicine on Hypoxic Ischemic Encephalopathy. Hubei Journal of TCM JUL. 2016;**38**(7):65-66

[65] Tang B, Qu Y, Wang D, Mu D. Targeting hypoxia inducible factor-1alpha: A novel mechanism of ginsenoside Rg1 for brain repair after hypoxia/ischemia brain damage. CNS & Neurological Disorders Drug Targets. 2011;**10**(2):235-238

[66] Wang YJ, Liu YH, Riao RX. Protective effect of tanshinone IIA on neurocyte apoptosis in rats with hypoxic ischemic brain damage and its mechanism. Chinese Pharmacological Bulletin. 2015;**31**(3):443-444

[67] Liau RS, Liou YH, Wang YJ, Shia CM. Effects of tanshinone IIA on IL-1β and TNF-α in cerebral tissue of newborn rats with hypoxic-ischemic encephalopathy. Journal of Apoplexy and Nervous Disease. 2014;**31**(11):1002-1004

[68] Li J, Yu HG, Chen YD. The effect of liguistrazine on the HIF-1α expression in neonatal rats with hypoxic ischemic brain damage. Nanjing Medical University: Natural Sciences. 2009;**29**(11):1542-1544

[69] Jang YS, Ju FL. Effects of Ligustrazine on expressions of Bcl-2 and Bax in brain tissue of rats with hypoxic ischemic encephalopathy. Modern Journal of Integrated Traditional Chinese and Western Medicine. 2010;**9**(24):3025-3027

[70] Li Y, Wang L, Sun L, Chen J, Li HY, Wang C, Fang L. Effect of astragalus injection on the expression of VEGF and VEGF2 in rats with celebral ischemia reperfusion injury. Chinese Journal of Integrative Medicine on Cardio-/Cerebrovascular Disease. 2016;**14**(1):25-28

[71] Yang J, Yao Y, Chen T, Zhang T. VEGF ameliorates cognitive impairment in in vivo and in vitro ischemia via improving neuronal viability and function. Neuromolecular Medicine. 2014;**16**(2):376-388

[72] Xu B, Xiao N, Zhang XP. Neuroprotective effect of puerarin after hypoxia-ischemia in neonatal and its mechanism. Journal of the Fourth Military Medical University. 2009; **30**(23):2757-2760

[73] Chen J, Zhang B, Tao X, Zhao R, Zhang H. Influence of puerarin on brain cell apoptosis and expression of bim protein in hypoxic ischemic encephalopathy neonatal rats. Modern Journal of Integrated Traditional Chineseand Western Medicine. 2009;**18**(35):4335-4338

[74] Ho SS, Li R, Wu D, Wang ZY, Peng ZW, Wang HN, Tang QR. Protective effects of gastrodin on the hippocampal newborn neurons after cerebral ischemia-reperfusion. Progress in Modern Biomedicine. 2015;**15**(31):6241-6244

[75] Jang JH, Son Y, Kang SS, Bae CS, Kim JC, Kim SH, Shin T, Moon C. Neuropharmacological potential of gastrodia elata blume and its components. Evidence-based Complementary and Alternative Medicine. 2015;**2015**:309261

[76] Zuo W, Yan F, Zhang B, Li J, Mei D. Advances in the studies of ginkgo biloba leaves extract on aging-related diseases. Aging and Disease. 2017;**8**(6):812-826

[77] Sung WH, Lu FY, Wang YP, Wu XM. The effect of ginkgo biloba leaf on neonatal rat with hypoxic iscemic encephalopathy. Chinese Journal of Basic Medicine in Traditional Chinese Medicine. 2014;**20**(12):1635-1636

[78] Chiang HM, Chen HC, Wu CS, Wu PY, Wen KC. Rhodiola plants: Chemistry and biological activity. Journal of Food and Drug Analysis. 2015;**23**(3):359-369

[79] Evstatieva L, Todorova M, Antonova D, Staneva J. Chemical composition of the essential oils of Rhodiola rosea L. of three different origins. Pharmacognosy Magazine. 2010; **6**(24):256-258

[80] Yang AJ, Cui H, Cui Y, Ai CS, Ta HC, Huang DJ, Lan MD, Chang WT. Chinese traditional medicine hongjingtian detect on neonatal rats wim hypoxic-ischemic ephalopathy. Journal of Emergency in Traditional Chinese Medicine. 2008;**16**(1):79-80, 86

[81] Hamn JA, Hu WI. The review of the protective effect of panax notoginseng saponins on hypoxia iscemia encephalopathy. Chinese Journal of Integrated Traditional and Western Medicine. 1996;**12**(8):506-507

[82] Wang Z, Wang N, Wang DP. Protective effects of xuefu zhuyu decoction on hypoxic-ischemic brain damage in rats. Zhejiang Journal of Traditional Chinese Medicine. 2009;**44**(11):793-795

[83] Wei L, Ren Q, Zhang Y, Wang J. Effects of hyperbaric oxygen and nerve growth factor on the long-term neural behavior of neonatal rats with hypoxic ischemic brain damage. Acta Cirúrgica Brasileira. 2017;**32**(4):270-279

[84] Yu PL. Comparative study of applying tiaoxue yisui recipe and ssl regimen in treating infantile chronic aplastic anemia and analysis of its therapeutical mechanism. Chinese Journal of Integrated Traditional and Western Medicine. 1997;**17**(6):378-380

[85] Hu WL. Hypoxic ischemic encephalopathy treated with the combination of western and traditional Chinese medicine-case report. Science Journal of Taiwan Traditional Chinese Medicine. 2006;**1**(2):20-25