



Understanding the multi-herbal composition of Buyang Huanwu Decoction: A review for better clinical use



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ABSTRACT

Ethnopharmacological relevance: Buyang Huanwu Decoction (BHD) is a multi-herbal composition commonly prescribed in the treatment of cerebrovascular diseases such as stroke. Although studies have been conducted at the cellular (*in vitro*), animal and human (*in vivo*) level, there was no detailed analysis on how the composition and proportion of BHD is modified according to target diseases.

Aim of study: The purpose of this study is to investigate the composition and proportion of each herb in BHD to summarize how the original BHD was modified according to the target disease.

Materials and methods: Electronic literature searches were performed in three databases, collecting sixty-eight studies for the final analysis. The studies were divided into three types: cell studies, animal experiments and clinical trial. In the analysis, the decoction formula including the composition and the weight proportion of the herbs in BHD used in the studies and the target diseases were examined.

Results: The result showed that in cell studies, the targets were mostly cell differentiation, cell injury and immune activation. In animal studies, cerebrovascular diseases such as cerebral ischemia were the most identified target diseases followed by nervous system and cardiovascular diseases. While the proportions of the herbs in BHD used in these studies were in general similar to the original formula, some studies reduced the amount of Astragali Radix to half of the original amount. Modified BHDs were used in four studies for cerebrovascular and peripheral nerve diseases. However, no significant correlation has been observed between the target diseases and the change of the proportion of the herbs in BHD.

Conclusions: The most commonly used formula was the original composition of BHD, and modified BHDs were reported to be used to treat cerebrovascular and nervous diseases. Further studies about the effects of BHD by composition and proportion of herbs are needed in the future.

1. Introduction

Buyang Huanwu Decoction (BHD) is a type of herbal medicine which in recent years is used to treat stroke, vascular dementia and coronary artery disease. Clinical studies of BHD reported significant improvement of symptoms especially to cerebrovascular diseases such as stroke (Hao et al., 2012; Li et al., 2014; Shu, 2010; Zhang et al., 1995). In previous studies, effects of BHD such as increase of regional cerebral flow, protective effect of microglial cell and suppression of thrombosis were reported through experiments (Cha et al., 2011; Han et al., 2018; Hung et al., 2015; Kim et al., 2001; Oh and Park, 2012;

Park et al., 2000; Son and Park, 2009). In systematic reviews and meta-analyses about BHD targeting cerebral ischemic animal model (Wei et al., 2013), BHD had substantial neuroprotective effect which were significant for all doses in animal models. In addition to studies on cerebrovascular diseases, various studies about protective effects of cardiomyoblast cell, hyperlipidemia, endometriosis, dementia and injuries of spinal cord and peripheral nerve were conducted, which unanimously showed promising effects of BHD (Chen et al., 2001; Jung et al., 1997; Lee et al., 2005; Lim et al., 2010; Seo et al., 2008; Dong et al., 2016). The study of Li et al. (2014) stated that BHD has possibilities to be applied to diseases such as stroke and cardiovascular

Abbreviations: AG, Angelicae Gigantis Radix; AGR, Acori Graminei Rhizoma; AR, Astragali Radix; ARR, Achyranthis Radix; BHD, Buyang Huanwu Decoction; CF, Carthami Flos; CNR, Cinnamomi Ramulus; CR, Cnidii Rhizoma; LB, Lumbricus; PR, Paeoniae Radix Rubra; PS, Persicae Semen; SR, Saposhnikovia Radix; PGR, Polygalae Radix; SMR, Salviae Miltiorrhizae Radix; VEGF, vascular endothelial growth factor

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Table 1
Descriptive table of the ingredients in Buyang Hwanwu Decoction (BHD).

Formula	Korean Name	Chinese Name	Latin Name	Academic Name	Parts used
Original BHD	Dang-gwi	Dang-gui	Angelicae Gigantis Radix	<i>Angelica acutiloba</i> (Siebold & Zucc.) Kitag.	Root
	Hwang-gi	Huang-qi	Astragali Radix	<i>Astragalus membranaceus</i> (Fisch.) Bunge	Root
	Hong-hwa	Hong-hua	Carthami Flos	<i>Carthamus tinctorius</i> L.	Flower
	Cheon-gung	Chuan-xiong	Cnidii Rhizoma	<i>Cnidium officinale</i> Makino	Rhizome
	Gu-in or Ji-ryong	Di-long	Lumbricus	<i>Lumbricus terrestris</i>	Body
	Jeog-jag-yak	Chi-shao-yao	Paeoniae Radix Rubra	<i>Paeonia lactiflora</i> Pall.	Root
	Do-in	Tao-ren	Persicae Semen	<i>Prunus persica</i> (L.) Batsch	Seed
Modified to BHD	U-seul	Niu-xi	Achyranthis Radix	<i>Achyranthes bidentata</i> Blume	Root
	Seok-chang-po	Shi-chang-pu	Acori Graminei Rhizoma	<i>Achyranthes japonica</i> (Miq.) Nakai	Rhizome
				<i>Acorus gramineus</i> Solander	
				<i>Acorus tatarinowii</i> Schott	
	Shi-ho	Chai-hu	Bupleurum chinensis	<i>Bupleurum chinense</i> DC.	Root
	Gye-ji	Gui-zhi	Cinnamomi Ramulus	<i>Cinnamomum cassia</i> (L.) J.Presl	Seed
	Swae-yang	Suo-yang	Cynomorium songaricum	<i>Cynomorium songaricum</i> Rupr.	Stem
	Sok-dan	Xu-duan	Dipsacus asper	<i>Dipsacus asper</i> Wall	Root
	Du-chung	Du-hong	Eucommia ulmoides	<i>Eucommia ulmoides</i> Oliv.	Bark
	Sam-chil	San-qi	Panax notoginseng	<i>Panax notoginseng</i> (Burkill) F.H.Chen	Root
	Ban-ha	Ban-xia	Pinellia ternata	<i>Pinellia ternata</i> (Thunb.) Makino	Rhizome
	Won-ji	Yuan-zhi	Polygalae Radix	<i>Polygala tenuifolia</i> Willd.	Root
	Dan-sam	Dan-shen	Salviae Miltiorrhizae Radix	<i>Salvia miltiorrhiza</i> Bunge	Root
	Bang-pung	Fang-feng	Saposhnikoviae Radix	<i>Saposhnikovia divaricata</i> (Turcz.) Schischk	Root

diseases due to Qi deficiency and blood stasis pattern, through the principle of activating blood circulation by Qi tonifying effect, the applications of which are enabled through a dosage form of BHD with enriched Astragali Radix (AR; *Astragalus membranaceus* (Fisch.)). This implies that the therapeutic effect of a herbal formula can be extended to target a variety of diseases and that the clinical application of BHD can be broadened by changing the composition and proportion of the herbs.

The first record of BHD can be found in *Yilin Gaicuo* (Correction on Errors in Medical Classics), a medical text written by Wang Qingren during Qing Dynasty in China. BHD is composed of seven kinds of medicine: AR, the hairy roots of Angelicae Gigantis Radix (AG; *Angelica acutiloba* (Siebold & Zucc.) Kitag.), Paeoniae Radix Rubra (PR; *Paeonia lactiflora* Pall.), Cnidii Rhizoma (CR; *Cnidium officinale* Makino), Persicae Semen (PS; *Prunus persica* (L.) Batsch, *Prunus davidiana* (Carrière) Franch.), Carthami Flos (CF; *Carthamus tinctorius* L.) and Lumbricus (LB; *Lumbricus terrestris*) (Wang, 2016). It is stated in *Yilin Gaicuo* (Correction on Errors in Medical Classics) that BHD “treats hemiplegia, facial nerve palsy, sluggish speech, drizzling saliva around mouth, dry stool, frequent urination and enuresis” (Wang, 2016). Furthermore, variations of the original formula of BHD are presented in *Yilin Gaicuo* for the treatment of wider range of symptoms. For example, one record in *Yilin Gaicuo* stated that “that one qian, of Saposhnikoviae Radix (SR; *Saposhnikovia divaricata* (Turcz.) Schischk.) should be added when using BHD to treat the early stage of hemiplegia.” (Wang, 2016).

Herbal decoctions in clinics are often modified to treat the patients' symptoms, and this is done by adjusting the weight and types of herbs from the original formula found in medical classics. The result is that the therapeutic effect of the modified formula is more individualized to each patient to which the formula is adjusted, since the modification thoroughly considered the characteristics of each patient's symptoms. Modified BHD, which include new herbs to the original formula, has also been applied to a number of studies: Polygalae Radix (PGR; *Polygala tenuifolia* Willd.) and Acori Graminei Rhizoma (AGR; *Acorus gramineus* Solander, *Acorus tatarinowii* Schott) were added to BHD for treating Alzheimer's disease and impairment of learning and memory studies, and Salviae Miltiorrhizae Radix (SMR; *Salvia miltiorrhiza* Bunge), Achyranthis Radix (ARR; *Achyranthes bidentata* Blume) and Cinnamomi Ramulus (CNR; *Cinnamomum cassia* (L.) J.Presl) were added to BHD for treating cerebral ischemia and infarction studies (Choi et al., 2011; Han and Park, 2010; Moon and Lee, 2000; Oh et al., 2015; Seo et al., 2008).

On the other hand, the modification of the herbal formula through changing the proportion of the amount of each herb also leads to the change of therapeutic effects. Normally a herb providing principal action in the herbal formula, or the sovereign herb, is used in a large quantity, while other herbs with the role of helping the principal are used in small quantities (Kim et al., 2015). The importance of the amount of the herbs within the formula implies the change of effects according to the ratio of the amounts of herbal components even among the herbal medicines with similar compositions. For example, Guizhi-tang and Xiaojianzhong-tang share similar components while the effects are distinctively different, which can be explained by the ratio of the amount of herbal components. The amount of PR in Xiaojianzhong-tang is doubled compared to that in Guizhi-tang, and in addition, Oryzae Gluten (OG; *Oryza sativa* Linné, *Oryza sativa* Linné var. *glutinosa* Matsumura) is added for tonification. As a result, Guizhi-tang disperses wind and cold, while Xiaojianzhong-tang is used for the treatment of interior deficiency (Hong et al., 2010; Kim et al., 2011).

Among the seven herbs in BHD, AR is the sovereign herb with the largest amount for the purpose of treating blood stasis caused by Qi deficiency, by tonifying Qi (Wang, 2016). The proportion of the components in the original BHD—AR, AG, PR, CR, PS, CF and LB is 120:6:4.5:3:3:3:3, and the amount of AR is very much larger than the other herbs (Table 1). Medical classic explains that the weight of the AR can be adjusted from one liang to eight liang according to the symptoms (Wang, 2016) and such adjustment can be found in recent prescriptions. In some studies, the amount of AR was reduced to less than tenth of that of the other herbs, a much smaller amount compared to original formula; in other studies, the proportion of the other six herbs were adjusted from the original formula (Chen et al., 2001; Li et al., 2016; Wu et al., 2009).

Among the previously published BHD studies, most were experimental and clinical studies which investigated the therapeutic effectiveness of the formula. Similarly, previous reviews (Li et al., 2014; Wei et al., 2013) focused on the therapeutic effectiveness and target diseases of BHD. On the other hand, no analysis has been done on the composition and proportion of the herbs that is adjusted to target different diseases. Therefore, this study aimed to conduct an analysis on the modification of the herbs in the BHD and the target diseases by reviewing the studies which used BHD in their experiment. The final goal of this study is to enhance the understanding of the composition and proportion of each herb in BHD and to provide the database for the expansion of the clinical application of BHD.

2. Methods

Electronic literature searches for studies of BHD were performed in three databases: PubMed, Embase and Cochrane Library. The date of the studies were included in the search so that studies before the date July 24, 2018 was included, and search words were as follows: 'Buyang Huanwu', 'BYHW*', 'BYHW decoction', 'BYHW', 'Bu yang Huan wu', 'Bu-yang Huan-wu', 'Bu-yang-Huan-wu', 'Buyanghuanwu', 'Bo yang whan oh tang', 'Bo-yang-whan-oh-tang', 'Boyangwhanohtang', 'Boyangwhanoh-tang', 'Bo yang hwan oh tang', 'Bo-yang-hwan-oh-tang', 'Boyanghwanoh-tang', 'Bo yang hwan o tang', 'Bo-yang-hwan-o-tang', 'Boyanghwanotang', 'Boyanghwanotang'. First, the duplicates of the searched studies were excluded from the database. Further exclusion of the studies was based on the following exclusion criteria: a) not related to BHD, b) non-experimental studies such as reviews or chemical component studies, c) not original articles such as comments, letters or editorials, d) articles of which the full text were unavailable, and e) studies are not written in Korean or English.

The final selected studies were divided into *in vitro* study, animal study and clinical trials. From the selected studies, information such as the subjects, target diseases or disease models in the case of animal studies, the extraction methods and durations of administration were collected. The collected information was analyzed while focusing on the modified composition and proportions of the herbs. Furthermore, the relationship between the modification of the composition and proportions of the herbs and the target diseases were examined. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist was used to guide the reporting of the review (Moher et al., 2009).

3. Results

From the databases, a total of 622 studies were collected from the initial search. Except 213 duplicate studies, 341 studies: no relationship to BHD ($n = 143$), non-experimental studies such as reviews or chemical component studies ($n = 48$), not original articles ($n = 9$), full article unavailable ($n = 97$), written in Chinese ($n = 44$), out of 401 studies, were excluded by predetermined inclusion/exclusion criteria, so that 68 studies were included in the analysis (Fig. 1). From the year 2001, studies on BHD have been published steadily every year except for 2005, and the number of the published studies have increased although there are annual deviations (Fig. 2).

3.1. Outcome of analysis on reported studies based on study methods

Out of the 68 studies included in the analysis, 17 studies were cell studies (*in vitro*). Among 17 *in vitro* studies, nine were on cells extracted from the animals after the administration of the herbal decoction (post treatment *ex vivo*, *in vitro*). The other eight studies either used cells or blood samples taken from animals without prior administration of the herbal decoction (pre-treatment *ex vivo*, *in vitro*), or immortalized cells (Table 2). 50 studies were animal studies (Table 3), and one study was a clinical trial, specifically a case report (Table 4).

3.1.1. Analysis of cell studies

Cell studies were divided into two types: studies using cells derived from the animals with the administration of herbal decoction ($n = 9$), studies using cells or blood samples extracted from the animals without the administration of herbal decoction or normal cultured cells ($n = 8$). In target diseases analysis of animal-derived cell studies after administration of herbal decoction to animals, cerebral ischemia was targeted in two out of nine studies reporting an increase of vascular endothelial growth factor (VEGF) expression (Yang et al., 2015) and suppression of NF- κ B and TNF- α (Jin et al., 2013) after administration of BHD. Other studies targeted cell immune system, differentiation and proliferation.

In detail, activation of humoral immunity response by stimulation of B lymphocyte (Kim et al., 2002), promotion of growth and differentiation of neural progenitor cells (Sun et al., 2007a; Sun et al., 2007b), and suppressed proliferation of vascular smooth muscle cells by suppression of EPK1/2 pathway (Chen et al., 2011) after administration of BHD were identified (Table 2).

In 8 studies treating decoction to cells or bloods extracted from animals without administration of herbal decoction to the animals, the main outcome were cerebral ischemia, promotion of cell differentiation, and cell protective effect (Fig. 3). In detail, protective effects of Schwann cells by activating SOD and suppressing Caspase 3 to oxidative injury (Yang et al., 2011b), immune effects related to activation of lymphocytes and increases of IL-2 (Ha et al., 2001; Kim et al., 2004), and promoted differentiation of bone marrow mesenchymal stem cells by MAPK pathway regulation (Zheng et al., 2012a) after treatment of BHD were identified (Table 2).

In the analysis of extraction methods, when a variety of extraction methods were used in one study, the methods were counted as one method if multiple methods were used consecutively for one experiment. If different methods were used for each extraction and experiments were conducted separately, the methods were counted separately. Among 17 studies, ten studies used hot water extraction and four studies did not describe their extraction method. The remaining three studies used ethanol extraction, precipitation and chromatography respectively (Fig. 4A).

In the analysis of route of administration, intragastric administration was identified in 8 studies, and administration method was not described in one study (Fig. 4B).

3.1.2. Analysis of animal experiment studies

Target diseases of 50 animal experiment studies are presented in Table 3. Cerebrovascular diseases were the most common target disease in 26 studies (52%), and 20 studies out of 26 targeted cerebral ischemia. Out of cerebral ischemia studies, 14 studies targeted cerebral ischemia/reperfusion (causing cerebral ischemia by occlusion of cerebral artery and reperfusion blood), and 2 studies targeted focal cerebral ischemia. In the studies of cerebral ischemia, effectiveness of BHD was mainly estimated by infarction size, neurological deficit and proliferation of neural cells. For cerebral ischemic models after the administration of BHD, activation of VEGF in study by Cai et al. (2007), increased expression of angiopoietin in study by Shen et al. (2014) and increase of glutamate transporter and synthase expression in study by Ding et al. (2015) were reported. In other cerebrovascular disease studies, increase of ERK2 and CaMKII in hippocampus CA1 in vascular dementia by Tang et al. (Tang et al., 2013) and activation of VEGF transporter intracerebral hemorrhage study by Cui et al. (2015) were also identified.

A total of 13 studies (26%) targeted nervous system diseases. Among these studies, seven studies targeted spinal diseases and three studies targeted peripheral nerve diseases. In studies on spinal diseases, protective effects by suppression of apoptosis factor (Dong et al., 2016) and increased expression of Notch1 (Guo et al., 2015) in spinal injury model and suppression of CDK5 in spinal ischemia/reperfusion models (Wang and Jiang, 2013) after administration of BHD were examined. One study about sciatic nerve injury model by Chang et al. (2016) reported that distal extension of axons was improved and expression of GAP-43 increased in BHD treated group. In the Alzheimer's disease study by Fei et al. (2018), increased expression of LRP1 and ApoJ were examined; in the encephalitis study by Wang et al. (Wang et al., 2018b), suppression of TLR4/Myd88/NF- κ B pathway were reported.

Eight studies (16%) targeted cardiovascular diseases. Six studies targeted heart diseases such as myocardial ischemia and coronary heart disease. The target outcomes were anti-inflammatory effects of BHD through the activation of SOD and suppression of the expression of CD40 and CD40L to myocardial ischemia models in study by Liu et al. (2011) and decrease of heart weight/body weight ratio and left

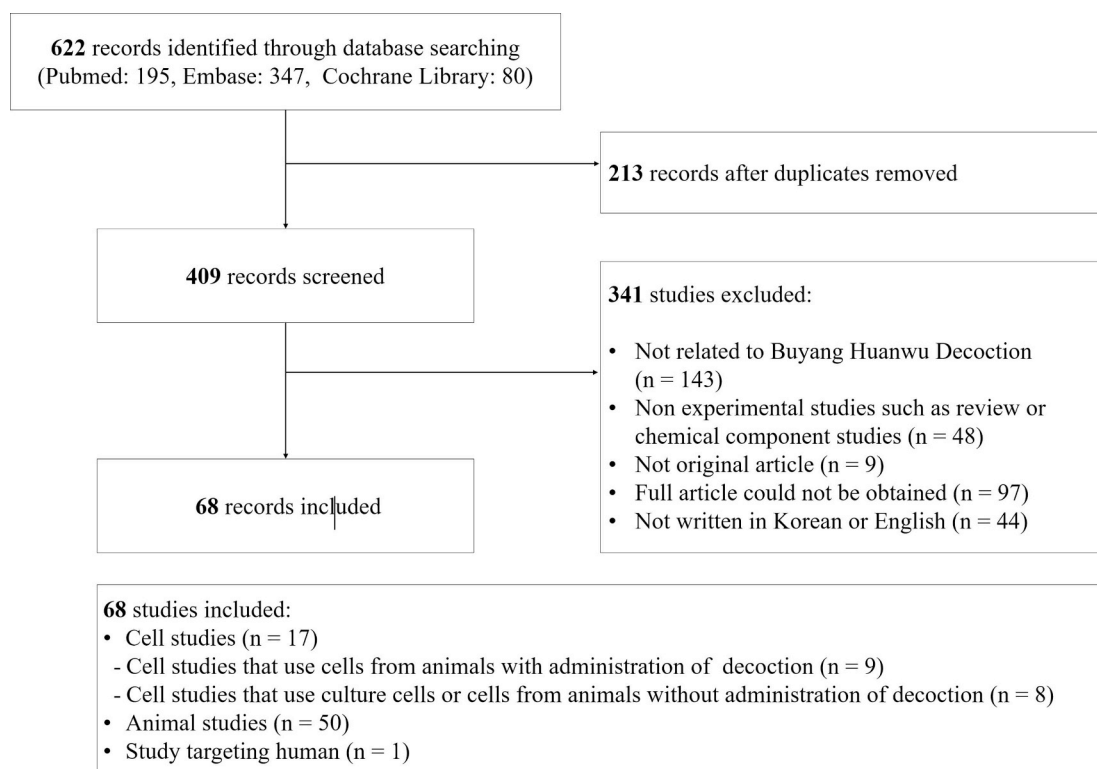


Fig. 1. Flow diagram for selection of studies.

ventricle dimension in myocardial infarction models in study by Zhou et al. (2012). Furthermore, decreased expression of collagen in pulmonary fibrosis models (Wang et al., 2018a) and suppressed angiogenesis to hepatocellular carcinoma (Min et al., 2016) were investigated (Fig. 3).

In the 51 animal experiment studies, 43 used material extracted in hot water, while 2 used differential extraction in organic solvents and 6 others had not described their method of extraction (Fig. 4A). In only one study was intraperitoneal administration used while all others were intragastric (Fig. 4B).

3.1.3. Clinical trial

One case study (Hijikata et al., 2006), reporting on outcomes in three individuals diagnosed with refractory epilepsy, was analyzed (Table 4). Each of the patients suffered a specific symptom pattern, which were diagnosed as Moyamoya disease, hemiplegia-hemiconvulsion-epilepsia syndrome (frontal lobe spikes) and loss of consciousness with fatigue and stress (temporal lobe activity). All patients were

diagnosed with blood stagnation pattern. Upon the BHD treatment to all three patients, decreased frequency and severity of seizures were reported. Moyamoya disease is characterized by frequent recurring seizures. BHD treatment for two months decreased the frequency of seizures and abated the problems with loss of appetite and indigestion. In the case of hemiconvulsion-epilepsia syndrome, fatigue and stress trigger an increase in the frequency of seizures. Not only did a year of BHD treatment reduce frequency of seizures but this was evident by examination of frontal lobe activity. In the latter case of temporal lobe epilepsy, two years of BHD treatment resulted in symptomatic relief. However, no details on extraction method, dosage form or route of administration of BHD were declared.

3.2. Analysis of BHD used in included studies

3.2.1. Weight proportion of medicines & target diseases

Twenty studies followed the same proportion as the original formula (AR:AG:PR:CR:PS:CF:LB = 120:6:4.5:3:3:3) and in the other 13

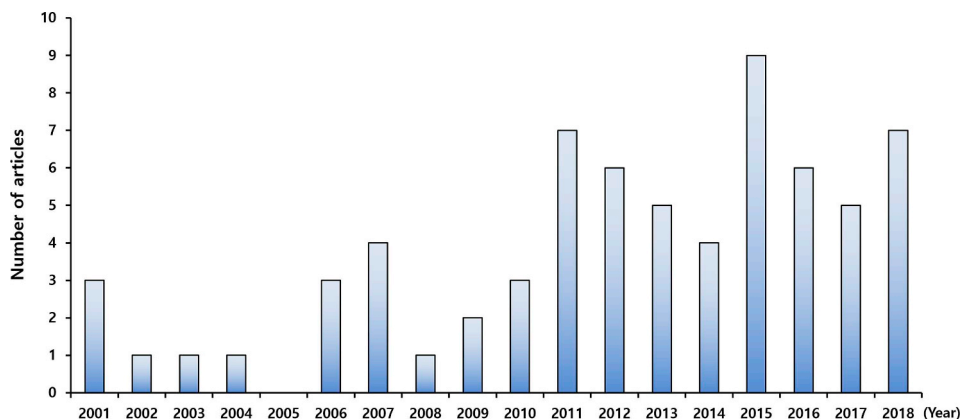


Fig. 2. Publication date of articles.

Table 2
Cell studies using Buyang Hwanwu Decoction (BHD).

Author (Year)	Animal or cell, Target disease (Disease model)	Extraction method, Route of administration, treatment duration	Addition of other herbs	Results
Cell studies including administration of decoction to animal (n = 9)				
Kim et al. (2002)	MC, Splenocyte, Antigen-specific immune response (Immunization with hen egg-white lysozyme)	HW, i.g., 7 days (mice)	–	Enhanced anti-HEL-specific humoral immune responses via the direct stimulation of B lymphocytes
Sun et al. (2007a)	WS, Neural progenitor cell, Cell growth and differentiation (–)	HW, i.g., For total of 7 doses (rat), 24, 48 h (cell)	–	Promoted growth and differentiation of neural progenitor cell
Sun et al. (2007b)	WS, Neuroepithelial stem cell, Cell growth and differentiation (–)	HW, i.g., For total of 7 doses (rat), 24, 48 h (cell)	–	Promoted neurite outgrowth and differentiation of neuroepithelial stem cell
Chen et al. (2011)	SD, Vascular smooth muscle cell, Cell proliferation (–)	-, i.g., For total of 7 doses (rat), 24, 48 h (cell)	–	Prevented vascular smooth muscle cell proliferation
Jin et al. (2013)	SD, HT22 cell, CIR (MCAO)	-, i.g., 7 days (rat)	–	Attenuated inflammatory response and cellular apoptosis
Yang et al. (2015)	SD, Mesenchymal stem cell, FCI (Bilateral carotid artery ligation)	HW, -, 10 days (rat)	–	Enhanced angiogenesis, angiogenic miRNA and expression of vascular endothelial growth factor
Li et al. (2016)	WS, Differentiated PC12 cell, Neurotoxicity (Exposure to 6-OHDA)	-, i.g., 3 days (rat), 25 h (cell)	–	Blocked 6-OHDA-induced neurotoxicity via Akt/GSK3 β pathway
Yu et al. (2017)	SD, Cortical astrocyte, Oxygen-glucose deprivation/reoxygenation (Incubation with isotonic oxygen-glucose deprivation/reoxygenation solution)	HW, i.g., 3 days (rat)	–	Up-regulated glutamate transporter-1 and glutamine synthetase via p38 MAPK activation and protective effect to astrocytes
Zhang et al. (2018)	SD, Human aorta vascular smooth muscle cell, Age-associated migration and invasion (–)	HW, i.g., 7 days (rat)	–	Suppressed migration and invasion by increase of SIRT1 level
Cell and blood studies without administration of decoction to animal (n = 8)				
Ha et al. (2001)	MC spleen cell, Cytotoxic activity of lymphocytes (Anti-CD3 antibody)	HW, -, 3 days, 4 h	–	Promoted non-specific cytotoxic T lymphocyte activity
Kim et al. (2004)	MC spleen cell, Proliferation and activation of spleen cell and lymphocytes (Anti-CD3 antibody)	HW, -, 1, 2, 3 days	–	Enhanced B cell mitogenic activity and activated T cell response by B cell regulation
Zhang et al. (2007)	New Zealand rabbits blood, Binding platelet activating factor to receptor (–)	–	–	Revealing Carthami Flos, Astragali Radix, Persicae Semen, Lumbricus, Angelicae Gigantis Radix are major influencing factors to inhibit binding of ^3H -platelet activating factor to its receptor
Yang et al. (2011a)	WS schwann cell, Oxidative injury (Addition of hydrogen peroxide)	Hot water extraction-ethanol extraction, -, 12 h	–	Protective effect to Schwann cells from oxidative injury
Li (2012)	WS cerebral cortex and cerebellum cell, CIR (Bilateral common carotid arteries occlusion)	HW, -, 2 h	–	Enhanced protective effect against cell membrane fluidity changes by scavenging free radicals
Zheng et al. (2012a)	SD bone marrow mesenchymal stem cell, Differentiation of bone marrow mesenchymal stem cell (–)	Alcohol precipitation-ion exchange resin chromatography, -, 7, 14, 28 days	–	Activated differentiation of bone marrow mesenchymal stem cell into neuron-like cells
Zheng et al. (2012b)	SD bone marrow mesenchymal stem cell, Cell differentiation (–)	Alcohol precipitation- acid-base precipitation- resin-bed method, -, 28 days	–	Revealing active principle region in decoction that has greater effect to differentiation of bone marrow mesenchymal stem cell into neural-like cell <i>in vitro</i> than original decoction formula
Shen et al. (2016)	Human umbilical vein endothelial cell, Hydrogen peroxide-induced apoptosis (Exposure to hydrogen peroxide)	HW, -, 24 h	–	Protective effect to hydrogen peroxide-induced apoptosis

CIR: Cerebral ischemia/reperfusion, FCI: Focal cerebral ischemia, HW: Hot water extraction, i.g.: Intragastric administration, MAPK: mitogen-activated protein kinase, MC: Mice, MCAO: Middle cerebral artery occlusion, SD: Sprague Dawley rats, WS: Wistar rats, -: not described.

Table 3
Animal studies including administration of Buyang Hwanwu Decoction (BHD) to animal.

Author (Year)	Animal, Target disease (Disease model)	Extraction method Route and duration of administration	Addition of other herbs	Results
Chen et al. (2001)	SD, SNI (Stumps of sciatic nerve)	-, i.g., 5 weeks	O	Increased regeneration of nerves
Zhang et al. (2001)	WS, Arterial thrombosis (-)	-, i.g., 14 days	-	Improved thrombosis
Li et al. (2003)	WS, Forebrain ischemia (Four-vessel occlusion)	HW, i.g., 7 days	-	Recovered neuronal injury
Fan et al. (2006)	Rabbits, SIR (Abdominal aorta occlusion)	HW, i.g., 9 days	-	Recovered spinal cord injury
Zhang (2006)	SD, CIR (Common carotid artery occlusion)	HW, i.g., 5 days	-	More protective effect of neuron than Astragali Radix group and blood activation group
Cai et al. (2007)	WS, FCI (MCAO)	HW, i.g., 1, 3, 7, 14 days	-	Improved recovery of neurological function and neuronal injury
Chen et al. (2008)	SD, SCI (Right lateral funiculus transection)	HW, i.g., 8 weeks	-	Increased recovery of spinal cord injury
Wang and Jiang (2009)	SD, SIR (Abdominal aorta occlusion)	HW, i.g., 72 h	-	Increased neuroprotective effect
Wu et al. (2009)	SD, Aortic intimal hyperplasia (Insersion of domestic balloon catheter into aorta)	Water/alcohol/chloroform extraction-cation exchange resin, 14 days	-	Inhibition of aortic intimal hyperplasia
Cai and Liu (2010)	SD, FCI (MCAO)	HW, i.g., 1, 3, 7, 14 days	-	Promoted angiogenesis
Zhang et al. (2010a)	SD, Coronary heart disease (Exhaustive swimming exercising)	HW, i.g., 21 days	-	Reduced C-reactive protein and CD40
Zhang et al. (2010b)	SD, CIR (Modified Zea-Longa method)	HW, i.g., 10 days	-	Up-regulated vascular endothelial growth factor and Ki-67 expressions
Choi et al. (2011)	SD, FCI (MCAO)	HW, 1) I.p., 15 min before MCAO and 15 min after reperfusion, 2) I.g., 30 min or 120 min after MCAO	O	Reduced cerebral infarct size and neurological deficit
Liu et al. (2011)	SD, Myocardial ischemia (Injection of isoproterenol)	HW, i.g., 14 days	-	Antioxidative action, regulation of lipid metabolisms, and inhibition of inflammatory pathway
Wang et al. (2011a)	MC, CIR (RMCA occlusion)	HW, i.g., 1, 7, 14 days	-	Increased neuroprotective effect of neurofunctional and genomic approach
Wang et al. (2011b)	SD, Coronary heart disease (Exhaustive swimming exercise)	HW, i.g., 21 days	-	Improvement of hemorheological disorders and energy metabolism
Yang et al. (2011b)	MC, Myocardial ischemia (Injection of isoproterenol)	HW, i.g., 14 days	-	Increased protective effect of myocardial injury
Chen (2012)	MC, CIR (RMCA occlusion)	HW, i.g., 1 day	-	Restored abnormal metabolites
Zhao et al. (2012)	SD, CIR (MCAO)	HW, i.g., 72 h	-	Improved neurological defect score and infarction volume
Zhou et al. (2012)	WS, Myocardial infarction (Left anterior descending artery ligation)	HW, i.g., 12 weeks	-	Alleviated ventricular remodeling
Liu et al. (2013)	WS, FCI (MCAO)	HW, i.g., 1, 7, 14, 28 days	-	Promoted proliferation and differentiation of neural stem cells and increased synaptic plasticity
Tang et al. (2013)	Rats, Vascular dementia (Four-vessel occlusion)	HW, i.g., 30 days	-	Increased recovery of learning and memory
Wang et al. (2013)	SD, CIR (MCAO)	HW, i.g., 7 days	-	Attenuated excitatory toxicity and reduced areas of cerebral infarction
Wang and Jiang (2013)	SD, SIR (Abdominal aorta occlusion)	HW, i.g., 3 days	-	Improved spinal function and decreased Cdk5
Fan et al. (2014)	SD, - (-)	HW, i.g., 15 days	-	Identified safety and function of detoxification and antioxidant in liver
Kong et al. (2014)	SD, CIR (MCAO)	HW, i.g., 21 days	-	Promoted neuronal differentiation related to migratory process of neural precursor cells
Liu et al. (2014)	WS, FCI (MCAO)	HW, i.g., 7 days	-	Improved the neurological behavior; reduced the infarction volume, increased E2 and ER concentration
Shen et al. (2014)	SD, CIR (MCAO)	HW, i.g., 7, 14, 21, 28 days	-	Reduced infarct and atrophy volumes and neurological deficit, increased microvessel density protein expression of angiotensin-1
Chen et al. (2015)	MC, CIR (RMCA occlusion)	HW, i.g., 1, 3 days	-	Revealing effects of cerebral ischemic stroke by protein analysis
Cui et al. (2015)	MC, Intracerebral hemorrhage (Injecting collagenase type VII into right globus pallidus)	HW, i.g., 1, 3, 7 days	-	Promoted neurological recovery and angiogenesis
Ding et al. (2015)	SD, FCI (MCAO)	HW, i.g., 1, 3, 5, 7 days	-	Revealing protective role of astrocytes by glutamate transporter-1 and glutamate synthetase in association with PACAP-38
Guo et al. (2015)	SD, SCI (Injury of T10 spinal cord)	HW, i.g., 1, 7, 14, 28 days	-	Up-regulated Notch1 gene expression by affecting microenvironment
Liu et al. (2015)	SD, Hypoxic ischemic encephalopathy (Permanent suture of left carotid artery)	-, i.g., 1, 3, 7 days	-	Delayed hypoxic ischemic encephalopathy onset and preserved motor function

(continued on next page)

Table 3 (continued)

Author (Year)	Animal, Target disease (Disease model)	Extraction method Route and duration of administration	Addition of other herbs	Results
Oh et al. (2015)	SD, Vascular dementia (Permanent occlusion of bilateral common carotid arteries)	HW, i.g., 4 weeks	O	Increased neuroprotective property by chronic cerebral hypoperfusion
Shen et al. (2015)	MC, Acute ischemic stroke (RMCA occlusion)	HW, i.g., 7 days	-	Revealing neuroprotective mechanism by analysis of gene and pathway
Zhang et al. (2015)	SD, SCI (Complete transection at T10 vertebra of spinal cord)	HW, i.g., 7, 14, 28 days	-	Enhanced differentiation of neural stem cell into neurons and oligodendrocytes
Chang et al. (2016)	SD, SNI (Crush injury of sciatic nerve)	HW, i.g., 5 days	-	Improved axonal regeneration on axons and Schwann cells and functional recovery
Dong et al. (2016)	WS, SCI (Injury by impactor)	HW, i.g., 4 weeks	-	Restored hind-limb motor function and decreased expression of apoptosis-related proteins
Min et al. (2016)	MC, Human hepatocellular carcinoma (Orthotopic implantation of intact metastatic tumor tissue)	HW, i.g., 21, 28, 35 days	-	Reduced angiogenesis and metastasis by affecting expression of genes
Zhang et al. (2016)	SD, CIR (MCAO)	HW, i.g., 17 days	-	Enhanced angiogenesis, cerebral circulation and brain tissue repair
Chen et al. (2017)	WS, Cardiac remodeling (Transverse aortic constriction)	HW, i.g., 16 weeks	-	Increased cardioprotective effect against pressure overload
Luo et al. (2017)	SD, Poststroke depression (MCAO, chronic mild stress)	HW, i.g., 21 days	-	Curative effects to poststroke depression by affecting neurotrophic pathway
Pan et al. (2017)	SD, Cerebral ischemia (MCAO)	HW, i.g., 3, 7, 14 days	-	Facilitated neurorehabilitation through improvement in synaptic plasticity
Zhong et al. (2017)	MC, CIR (MCAO)	HW, i.g., 1, 3, 7 days	-	Increased neuroprotective effect by regulating apoptosis
Cui et al. (2018)	SD, Intracerebral hemorrhage (Injection of collagenase type VII into right globus pallidus)	HW, i.g., 21 days	-	Revealing therapeutic effects to hemoglobin complex, oxygen transport and pyruvate metabolism
Fei et al. (2018)	MC, Alzheimer's disease (APP/SP1 transgenic mice)	HW, i.g., 28 days	-	Reduced morphological changes and altered LRP1 and ApoJ expression
Kim and Namgung (2018)	SD, SNI (Transection and coaptation of sciatic nerve)	HW, i.g., 1, 6 weeks	-	Enhanced axonal regeneration by interaction between axons and distal Schwann cells
Wang et al. (2018a)	SD, Pulmonary fibrosis (Endotracheal injection of bleomycin)	HW, i.g., 7, 14, 28 days	-	Improved lung tissue morphology, decreased level of serum collagen and reduced expression of CTGF and p-AKT protein
Wang et al. (2018b)	MC, Experimental autoimmune encephalomyelitis (Injection of pertussis toxin)	HW, i.g., 25 days	-	Inhibition of CNS inflammation and regulation of immune responses
Zhou et al. (2018)	SD, Denervated-dependent skeletal muscle atrophy (Turning two ends of common peroneal nerve)	HW, i.g., 14 days	-	Increased ANGPTL4 expression involving NF- κ B and MURF1 signaling

CIR: Cerebral ischemia/reperfusion, CNS: Central nervous system, CTGF: Connective-tissue growth factor, FCI: Focal cerebral ischemia, HW: Hot water extraction, i.g.: Intragastric administration, i.p.: Intraperitoneal administration, LRP1: Low density lipoprotein receptor-related protein 1, MC: Mice, MCAO: Middle cerebral artery occlusion, RMCA: Right middle cerebral artery, SCI: Spinal cord injury, SD: Sprague Dawley rats, SIR: Spinal ischemia/reperfusion, SNI: Sciatic nerve injury, WS: Wistar rats, -: not described.

Table 4
Buyang Hwanwu Decoction (BHD) study targeting human.

Author (Year)	Patient: Age (sex)	Target disease	Extraction method	Duration of administration	Addition of other herbs	Results
Hijikata et al. (2006)	Case 1) 24 years (women)	Moyamoya disease	-	2 months	-	Decreased catamenial seizure and improved appetite
	Case 2) 37 years (women)	Hemiplegia-hemiconvulsion-epilepsy syndrome	-	1 year	-	Decreased seizure frequency and improved electroencephalogram, showing gradual decline in frontal lobe spikes
	Case 3) 30 years (man)	Loss of consciousness with fatigue and stress	-	2 years	0	Almost complete resolution of complaints

studies, five herbs except for AR and LB were used equally (AR:AG:PR:CR:PS:CF:LB = 120:10:10:10:10:10:4.5). Fourteen studies increased the amount of only the *Paeoniae Radix Rubra* (AR:AG:PR:CR:PS:CF:LB = 120:6:6:3:3:3:3 in 11 studies, and AR:AG:PR:CR:PS:CF:LB = 120:6:5:3:3:3:3 in 3 studies). Other studies decreased the amount of AR less than half of the amount found in the original formula, and a variety of weight proportions were identified (Table 5).

In the analysis of association between weight proportion of herbs and target diseases, studies using the original formula mostly targeted cerebral ischemia, cardiovascular and nervous system diseases. Among the 20 studies using the original formula (AR:AG:PR:CR:PS:CF:LB = 120:6:4.5:3:3:3:3), cerebral ischemia and cardiovascular diseases were target diseases in 3 studies, and spinal injury and sciatic nerve injury were target diseases in two studies each. Encephalitis and thrombosis were target diseases in other studies.

In 11 studies using five herbs in equal amount except for AR and LB (AR:AG:PR:CR:PS:CF:LB = 120:10:10:10:10:10:4.5), the weight proportion of AR was about 69% of the total weight. Compared to the original formula, proportion of AR decreased by about 15% and proportion of the other herbs increased. Out of 11 studies using this proportion, seven studies targeted cerebral ischemia, and Alzheimer's disease and myocardial infarction were also included.

In the studies using an increased weight of PR (AR:AG:PR:CR:PS:CF:LB = 120:6:6:3:3:3:3 in 11 studies and AR:AG:PR:CR:PS:CF:LB = 120:6:5:3:3:3:3 in 3 studies), there was little difference except for a slightly increased weight of PR compared to the original formula. Out of 14 studies using this proportion, 7 studies targeted cerebral ischemia and 3 studies targeted spinal ischemia/reperfusion, which implied that this proportion was often used to ischemic diseases of central nervous system. In addition, carcinoma and muscle atrophy were also identified as target diseases.

Except for the studies using modified formula, nine studies were found in which the weight of AR were reduced (weight of AR about 50%–73% of the total weight). Among these nine studies, five studies were cell studies investigating the activation of lymphocyte, differentiation of bone marrow stem cell and proliferation of vascular cell. The other four studies targeted intracerebral hemorrhage, spinal injury and aortic intimal hyperplasia. The BHD studies using reduced weight of AR also reported significant results.

3.2.2. Modified medicines

Out of 68 studies, modified BHDs were used in 4 studies. In animal experiment studies, 3 studies were identified, and they targeted about sciatic nerve injury (Chen et al., 2001), focal cerebral ischemia (Choi et al., 2011) and vascular dementia (Oh et al., 2015), respectively. The remaining one study was a clinical trial in which modified BHD were used for the treatment of the third case patient suffering from loss of consciousness with fatigue and stress (Hijikata et al., 2006).

In the modified formula, ARR, AGR, PGR, CNR and SMR were commonly added. In two studies adding the five kinds of aforementioned herbs, reduced infarction size and neurological deficit to ischemia/reperfusion models (Choi et al., 2011) and anti-inflammatory effects of hippocampus to vascular dementia models induced by hypoperfusion at cerebral artery (Oh et al., 2015) were reported respectively. Other herbs added to BHD included *Dipsacus asper* (*Dipsacus asper* Wall. ex C.B. Clarke), *Cynomorium songaricum* (*Cynomorium songaricum* Rupr.), *Eucommia ulmoides* (*Eucommia ulmoides* Oliv.), *Panax notoginseng* (*Panax notoginseng* (Burkill) F.H.Chen), *Bupleurum chinensis* (*Bupleurum chinense* DC.), and *Pinellia ternata* (*Pinellia ternata* (Thunb.) Makino) (Table 5).

4. Discussion

This study conducted an analysis on the modification of the composition and proportion of the herbs and the corresponding target

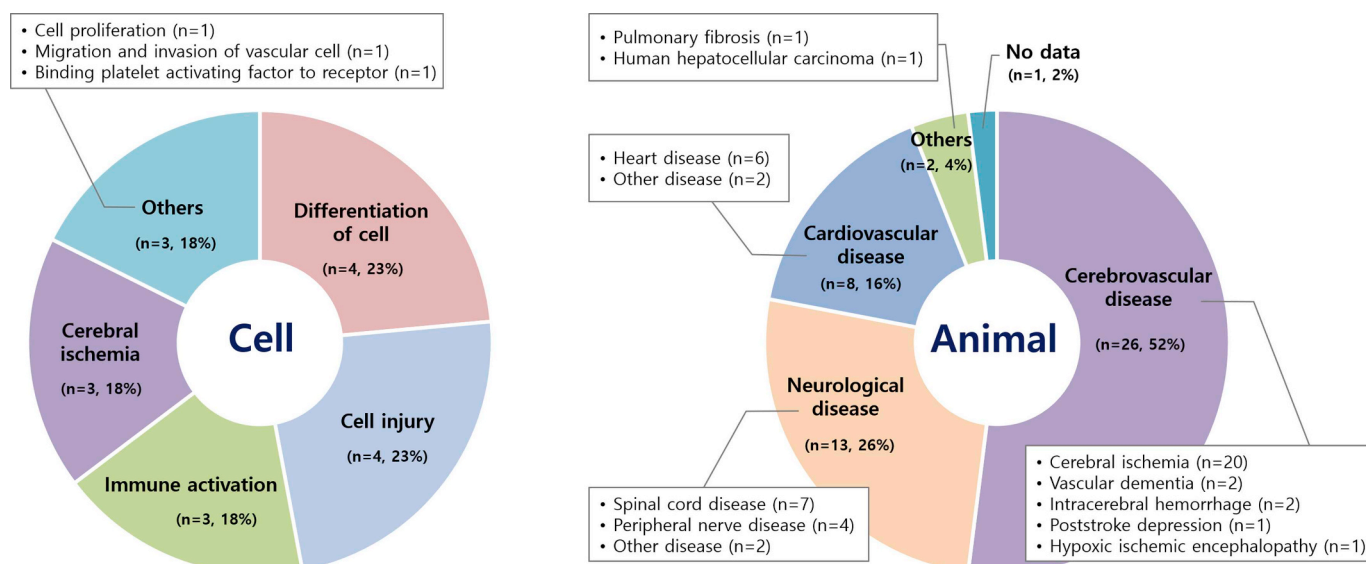


Fig. 3. Target diseases of cell and animal studies.

Target diseases of cell studies (left, n = 17) and animal studies (right, n = 50). Types, numbers, and proportions of target diseases in cell and animal studies were presented by pie graph.

diseases of BHD by reviewing cell (*in vitro*), animal (*in vivo*) and human studies (clinical trials) which used BHD in their experiment. The goal of this study was to enhance the understanding on the composition of BHD and to provide database for the expansion of the clinical application of BHD. The result showed that cerebrovascular diseases such as cerebral ischemia were the most identified target diseases followed by nervous system and cardiovascular diseases. Modified BHD were found in some studies, and these studies targeted cerebrovascular and peripheral nerve diseases. However, from our data there was no significant correlation between the target diseases and the change of the proportion of the herbs in BHD.

BHD is comprised by seven kinds of medicinal herbs and is mainly known for the treatment of blood stagnation caused by Qi deficiency. Medical classics state that AR in BHD plays the most important role in treating Qi deficiency by tonifying Qi. Hairy root of AG, PR, CR, PS, and

CF remove blood stagnation. LB treats hemiplegia caused by stroke by relieving obstruction of collateral vessels. In sum, traditional medicine understands that BHD treats blood stagnation with AR tonifying insufficient Qi and other medicines activating blood and unblocking the meridian (Kim et al., 2011; Wang, 2016).

The results of our study correspond to this understanding from the medical classics by showing that among the target diseases in selected animal studies, cerebrovascular diseases occupied the largest portion (52%). Among the studies targeting cerebrovascular diseases, 20 studies targeted ischemic cerebrovascular diseases, two studies targeted vascular dementia induced by cerebral artery occlusion, and one study targeted post-stroke depression (PSD). Among the 20 cerebral ischemia studies, 11 studies induced brain injuries by blood reperfusion after occluding cerebral artery. Two studies on hemorrhagic cerebrovascular diseases were about intracerebral hemorrhage caused by injection of

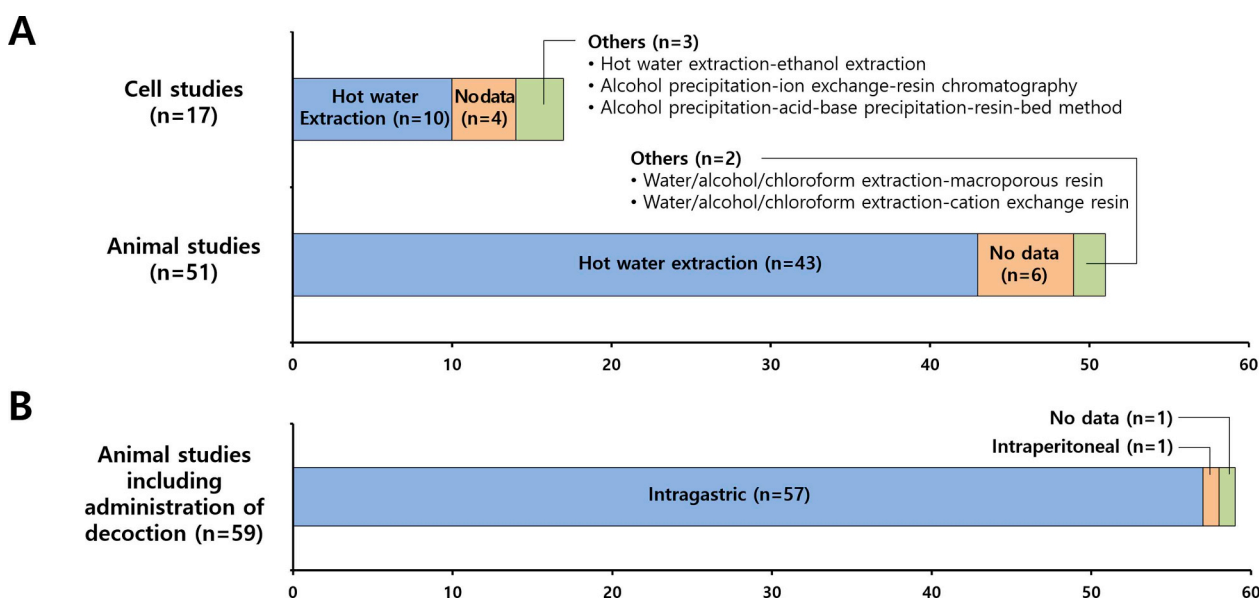


Fig. 4. Methods of extraction and administration in selected studies.

(A) Methods of extraction in selected studies. Extraction methods were analyzed in two groups by targets of studies: Cell studies (n = 17) and animal studies (n = 51). (B) Methods of administration of decoction in selected studies. The studies including administration of decoction to animal were analyzed (n = 59).

Table 5
Proportion of Buyang Hwanwu Decoction (BHD) composition herbs in selected studies.

Types of proportion	AR	AG	PR	CR	PS	CF	LB	Added herbs	Proportion of AR in BHD	Number of articles (reference)
BHD	120 g	6 g	4.5 g	3 g	3 g	3 g	3 g	-	84.21%	11 (Chang et al., 2016; Chen et al., 2008; Fan et al., 2014; Kim and Namgung, 2018; Kong et al., 2014; Li, 2012; Liu et al., 2011; Wang et al., 2018b; Zhang et al., 2001; Zhang et al., 2007; Zhang et al., 2015)
BHD-1	(120)	(6)	(4.5)	(3)	(3)	(3)	(3)	-	68.77%	9 (Ding et al., 2015; Sun et al., 2007a; Sun et al., 2007b; Wang et al., 2013; Yang et al., 2011a; Yang et al., 2011b; Yu et al., 2017; Zhang et al., 2010a; Zhang et al., 2018)
BHD-2	(120)	(10)	(10)	(10)	(10)	(10)	(4.5)	-	83.33%	11 (Cai and Liu, 2010; Cai et al., 2007; Chen, 2012; Chen et al., 2015; Dong et al., 2016; Fei et al., 2018; Pan et al., 2017; Shen et al., 2016; Shen et al., 2014; Wang et al., 2011a; Zhou et al., 2012)
BHD-3	120 g	6 g	6 g	3 g	3 g	3 g	3 g	-	83.92%	9 (Fan et al., 2006; Kim et al., 2002; Kim et al., 2004; Wang and Jiang, 2009, 2013; Yang et al., 2015; Zhang et al., 2016 Zhang, 2006; Zhang et al., 2010b)
BHD-4	(120)	(6)	(6)	(3)	(3)	(3)	(3)	-	80.65%	2 (Shen et al., 2015; Zhao et al., 2012)
BHD-5	120 g	6 g	5 g	3 g	3 g	3 g	3 g	-	72.73%	3 (Min et al., 2016; Zhong et al., 2017; Zhou et al., 2018)
BHD-6	(100)	(6)	(4.5)	(4.5)	(3)	(3)	(3)	-	55.56%	2 (Li et al., 2003; Tang et al., 2013)
BHD-7	(60)	(6)	(4.5)	(3)	(3)	(3)	(3)	-	54.05%	2 (Cui et al., 2015, 2018)
BHD-8	120 g	10 g	10 g	10 g	10 g	4.5 g	10 g	-	-	2 (Liu et al., 2013, 2014)
BHD-O	60 g	9 g	6 g	6 g	9 g	9 g	9 g	-	-	2 (Zheng et al., 2012a, 2012b)
BHD-ND	Others (Only once described proportions)	60 g	9 g	6 g	9 g	9 g	9 g	-	-	2 (Chen et al., 2011; Wu et al., 2009)
mBHD-1	No data	4 g	0.3 g	0.35 g	0.3 g	0.2 g	0.2 g	-	-	5 (Guo et al., 2015; Ha et al., 2001; Jin et al., 2013; Li et al., 2016; Luo et al., 2017)
mBHD-2	(10)	(2)	(1.5)	(1)	(1)	(1)	(1)	-	38.46%	4 (Chen et al., 2017; Liu et al., 2015; Wang et al., 2011b; Wang et al., 2018a)
mBHD-3	4 g	0.3 g	0.35 g	0.3 g	0.2 g	0.2 g	0.2 g	-	47.34%	2 (Choi et al., 2011; Oh et al., 2015)
	9 g	3.5 g	3 g	3 g	4 g	2 g	1.5 g	-	1 (Chen et al., 2001)	1 (Chen et al., 2001)
								-	1 (Hijikata et al., 2006)	1 (Hijikata et al., 2006)

Numbers in () mean that proportion of decoction was described as not weight but ratio in articles. AG: Angelicae Gigantis Radix, AR: Astragali Radix, CF: Carthami Flos, CR: Cnidii Rhizoma, LB: Lumbricus, PR: Paeoniae Radix Rubra, PS: Persicae Semen.

collagenase into the brain tissue. In addition, BHD showed therapeutic effects to diseases in the peripheral nerve system as well as those in the central nervous system. Furthermore, it also had effects on ischemic cardiovascular diseases. Target diseases besides the aforementioned cerebrovascular diseases were nervous system diseases (26%) and cardiovascular diseases (16%). Similar results were reported in the previous studies, in which cerebrovascular diseases occupied a large portion (Li et al., 2014).

The therapeutic effects of a herbal decoction is determined by the composition and weight proportion of the used herbs (Kim et al., 2015). One example of the changing composition would be adding *Armeniaca Semen* (*Prunus armeniaca* L. var. *ansu* Maxim) and *Magnoliae Cortex* (*Magnolia officinalis* Rehder & E.H. Wilson) to Guizhi-tang to direct Qi downward when a patient have symptoms of dyspnea (Shin, 1988). Similarly, BHD was modified in four studies in our data to expand the range of target diseases. These studies include three animal experiment studies and one case report, and the target diseases of the animal experiment studies were cerebral ischemia, sciatic nerve injury and vascular dementia, respectively, which are cerebrovascular and peripheral nervous diseases. In the case report, modified BHD was used to the patient suffering from loss of consciousness with fatigue and stress. Modified BHD in which the five herbs were modified (ARR, AGR, PR, CNR and SMR) were used for the improvement of cerebral ischemia induced by cerebral artery occlusion. ARR, CNR and SMR treat blood stagnation (Kim et al., 2011), all of which the anti-inflammatory and protective effects of brain and vessels were reported in recent studies (Jeong et al., 2008; Li et al., 2018; Oh et al., 2012; Park and Kim, 2014). In addition, neuroprotective effects about AGR and PR to cerebral ischemia were also reported (Han et al., 2000; Kim et al., 2000, 2003). In sum, the modified BHD aimed for enhancing anti-inflammatory and cerebral protection effects to cerebral ischemia injuries.

Yilin Gaicuo states that medicines in BHD could be modified to correspond to the patient's condition from the following sentence: "When a patient first becomes hemiplegic, add one qian of SR. If patient have already been suffering for 2–3 months and have taken too much of medicines with cold qualities, add 4–5 qian of *Aconiti Lateralis Radix Preparata* (processed root of *Aconitum carmichaelii* Debeaux). If too much of wind-dissipating medicines have been applied, add 3–4 qian of *Codonopsis Pilosulae Radix* (*Codonopsis pilosula* (Franch.) Nannf.)." (Wang, 2016) Likewise, the target of the herbal decoction in the present clinical approach is modified through changing the composition or the weight proportion of the formula. On the other hand, there is a lack of study about the different effects of modified BHD formulas. Therefore, it seems necessary to further research on the various therapeutic effects according to the modification of the formulas.

As we mentioned above, there are two ways in the modification of the medicine to increase effectiveness of the herbal decoction to the target disease, and one approach is to add herbs according to the target symptoms such as neuroprotective medicines. For example, in Buzhongyiqi-tang, whose principal herb is AR, CNR and SR are added for excessive sweating and *Alismatis Rhizoma* (*Alisma orientale* (Sam.) Juz.) and *Plantaginis Semen* (*Plantago asiatica* L.) are added for urinary retention (Shin, 1988). Furthermore, the interaction between herbs are considered when adding a herbs to the prescription. For instance, the side effect becomes more severe when *Euphorbiae Pekinensis Radix* (*Euphorbia pekingensis* Rupr.) and *Glycyrrhizae Radix et Rhizoma* (*Glycyrrhiza glabra* L.) are combined because toxicity of *Euphorbiae Pekinensis Radix* remains in the body for a longer time (Kim et al., 2011). This implies the possibility of reduced therapeutic effects or increased side effects when AR is combined with other herbs; however, few studies have been conducted on the interaction between AR and other herbs.

Sometimes it is necessary to avoid adding further herbs to the BHD mix to curb potential negative interactions. Thus, BHD optimisation by modifying relative weight proportions of the herbs is a superior approach. For example, Pingwei-san and Duijinyinzi consist of the same

medicines: *Atractylodis Rhizoma* (*Atractylodes lancea* (Thunb.) DC.; *Atractylodes chinensis* (DC.) Koidz, *Atractylodes japonica* Koidz), *Magnoliae Cortex*, *Citri Unshius Pericarpium* (*Citrus unshiu* (Yu. Tanaka ex Swingle) Marow.) and *Glycyrrhizae Radix et Rhizoma*. However, the principal herb in Pingwei-san is *Atractylodis Rhizoma*, which treats food stagnation; the principal herb in Duijinyinzi is *Citri Unshius Pericarpium*, which treats internal damage due to alcohol (Kim et al., 1998, 2011; Na, 2013; Shin, 1988). As with the previously mentioned approach, there are few studies about the modification of weight proportion of the herbs in BHD. Therefore, further studies are required to increase the clinical value of BHD.

On the other hand, it is noteworthy to mention that although AR occupies the largest portion in BHD, the studies reducing its weight have also reported valid results. Yilin Gaicuo states that the weight of AR in BHD could be adjusted flexibly at the following explanation:

"if a patient is unwilling to take AR, use 1–2 liang, and then gradually increase to 4 liangs. If the effect is too low, double the daily dosage of the decoction. [While one may wonder] why it is not 8 liangs, doubled dosage may be taken for 5–6 days and then reduced to the normal dosage." (Wang, 2016)

If the therapeutic effects are maintained with the reduced weight of AR which originally occupies 84% of the total weight in BHD, questions on the original weight of 120 g in the original formula may be raised; indeed, a modified formula of BHD is in the market as over-the-counter drug in Japan, which contains AR about 26% of total weight (Kang et al., 2007; Kim et al., 2008). In addition, reduced AR may prevent the possible adverse effects for AR that have been reported including bleeding (Lu and Lu, 2014), lowered blood pressure and increase of body temperature (Denzler et al., 2016). Therefore, further studies are required on the effectiveness of the decreased weight of AR and the effectiveness of BHD on the target diseases.

Limitations of the studies included in our review are as follows. First, there were only a few explanations about the modified formula in the studies. Future studies need to elaborate on the modification and the consequential changes of target diseases. In the case report included in our review, no descriptions were provided about the production and administration of BHD such as dosage and number of doses for a day, extraction method and dosage form, which need to be explained in the future studies. Second, Latin name and binomial name of the herbs were mixed throughout the studies. For instance, AR was written as: '*Astragali Radix*', '*Astragalus Membranaceus* (Fisch.) Bunge', '*Radix Astragali seu Hedysari*', '*Milkvetch Root*', '*Huangqi*', etc. Among the studies using modified BHD in Table 5, two studies wrote modified herbs in Latin name, while others wrote in binomial name, which may cause confusion. For example, when only written in binomial name, '*Cinnamomum cassia* (L.) J. Presl', we can't distinguish '*Cinnamomi Cortex*' (bark of the plant) from '*Cinnamomi Ramulus*' (little branch of the plant). Similarly, '*Achyranthis Radix*' does not provide the origin of the herbs in the name such as '*Achyranthes bidentata* Blume' or '*Achyranthes japonica* (Miq.) Nakai'. To prevent these problems, it is desirable to describe herbs in both Latin and binomial names in studies.

Third, the used part of AG was unclear. The original formula states that the hairy roots of AG called '*Danggui-wei*' should be used in BHD. Its effects were explained differently by its parts: the main body roots have blood-tonifying effect, hairy roots activate blood and resolve blood stagnation and using it as a whole tonifies and harmonizes blood (Kim et al., 2011). One study investigating the effects of different parts of *Angelica gigas* Nakai to ischemic stroke rat models showed that hairy root is the most effective for suppression of ischemic brain injuries compared to other parts, showing the effects may be different by the parts within one herb (Shin and Park, 2014). However, most studies included in our review did not specify which part was used in the study, and it is appropriate to specify in the studies which part of the AG was used, such as use the hairy root as recorded in original formula.

Lastly, there was a lack of information about the extraction and

process of BHD. In the case of hot water extraction, the medicine constituents and yield depend on quantity of water, temperature and time of extraction and process after extraction. Even though the same amount of BHD was administered to animals, there could be a difference in BHD concentration due to variation in the extraction and process method. As there were limited information regarding the method of production in some studies, it is necessary for the future studies to present exact process of making BHD. If there is uniformity in its making processes, difference in BHD between studies will decrease.

Although BHD is known as a commonly used formula in China, most studies could not be searched or included due to full-text access issue. However, most studies selected in this study were conducted in China, so this study is believed to reflect the current state of Chinese studies; therefore, it can be assumed that this limitation of language did not have a great effect on the actual study collection. Nevertheless, a lack of diversity of the collected studies can be improved by including Chinese database in the future studies.

In conclusion, this is the first study to investigate the modified composition and weight proportion of each herbs and the target diseases of BHD. This study is significant in focusing on analyzing modified composition and weight proportion of BHD in the published studies. Most studies used the original formula, and some studies reported neuroprotective effects of modified BHD targeting cerebrovascular and nervous diseases. However, there was no significant correlation between the effects or target diseases by proportions of the herbs in BHD. More BHD studies about the effects by composition and proportion of medicines are needed, and further studies on the target diseases besides cerebrovascular diseases should be conducted. From this study, the target diseases and increased clinical application of BHD may be expanded in the future.

Declarations of competing interest

None.

Author's contribution

Ye-Seul Lee and Seong-Cheon Woo performed data analysis and drafted the manuscript. Song-Yi Kim contributed to the conception of the work and assisted with protocol development. Ji-Yeun Park designed the study, coordinated the acquisition of all study data, interpretation of results and writing of the article. All co-authors were involved in critical revision of initial drafts.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jep.2020.112765>.

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