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A REVIEW OF THE PHARMACOLOGICAL MECHANISM OF TRADITIONAL CHINESE MEDICINE IN THE INTERVENTION OF CORONARY HEART DISEASE AND STROKE

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Abstract

In recent years, several researches have showed that Buyang Huanwu Decoction (BHD) possesses multiple target points in the intervention of diseases, and has same treatment effects on cerebrovascular diseases and cardiovascular diseases. But, there was no full report about the mechanistic and material basis in Brain-Heart concurrent treatment. The objective of the present study was to examine the pharmacological mechanism of traditional Chinese medicine in the intervention of coronary heart disease and stroke. We combined the HIT, PubChem, David Database resource and the networked pharmacology method to ultimately find out BHD's thirty-five potential brain-heart concurrent treatment target points, and preliminarily reveal BHD's material basis for treatment of cerebrovascular diseases and cardiovascular diseases. Finally, the study provided new information with the guidance meanings.

Key words: Buyang Huanwu Decoction (BHD), Brain-Heart concurrent treatment, Pharmaceutical effect mechanism, Material basis.

Introduction

Buyang Huanwu Decoction (BHD) was from *Corrections of Medical Field· Discussion of Paralysis and Flaccid Paralysis*, which was written by Wang Qingren (1768-1831). A famous doctor in the Qing dynasty. BHD includes 200 g *Astragalus mongholicus*, 10 g Angelica tail, 7.5 g Root of common peony, 5 g lumbricus, 5 g Safflower, 5 g peach seed and 5 g *Ligusticum chuanxiong* Hort. with functions of tonifying Qi, invigorating the circulation of blood and dredging collaterals. Usually, it was used to treat cerebrovascular diseases, such as ischemic stroke, qi deficiency and blood stasis, cerebral infarction and etc (Zehong and Yinghui, 2006; Xiaoqing, 2005a). Besides, BHD had good treatment in diseases like angina, obstruction of qi in the chest, hypertension, and congestive heart failure（Hongbin,et al 2005; Huijuan,2007). Based on physiological and pathological research of cerebrovascular cardiovascular, the theory of Brain-Heart concurrent treatment had been put forward according to clinical practices (Di and peng,et al 2013). It had been confirmed that BHD had exact curative effects on Brain-Heart concurrent treatment, which was accorded with the theory of treating different diseases with same method in Traditional Chinese Medicine (TCM). Most of the scholars thought that Qi deficiency and blood stasis were the foundation of stroke (Xiaoqing, 2005b; Yunke, 2006) and benefiting Qi for activating blood circulation as the most fundamental method for curing the sequel of stroke (Meikui, et al 2002).There were also other researches that showed that BHD's treatment of disease was on multiple levels, meaning that BHD had multiple target points in the intervention of diseases (Wanxia and Rongheng, 2008). So far, there was no full coverage about the molecular basis of BHD in Brain-Heart concurrent treatment. Therefore, it is particularly important to conduct research of Buyang Huanwu Decoction (BHD)'s pharmaceutical effect mechanism and material basis on molecular level. The study combined the HIT, PubChem, David Database resource and the networked pharmacology method to ultimately find out a quick and accurate Database Resource Using Method for identifying the targets of drug actions. Also, BHD's thirty-five potential brain-heart concurrent treatment target points had been found out according to this method to offer theory basis for the research BHD's pharmaceutical effect mechanism and material basis.

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Materials and Methods

Data Resource (HIT Database, PubChem Database and David Database) and Search Method

HIT database

We logged on to HIT homepage (http://lifecenter.sgst.cn/hit/) and input each TCM herbs of BHD prescriptions. Thus, we got each TCM's main chemical component. For example, if we input herb "Root of common peony", we get eight major components, i.e., paeonol, paeoniflorin, acetic acid, catechin, (+)-catechin, (-)-catechin, gallocatechin and epigallocatechin. Then, "paeonol" would be taken as an example for illustrating the detailed retrieval process.

PubChem database

We logged on to PubChem Homepage (http://www.ncbi.nlm.nih.gov/pccompound) and searched for "paeonol". We got the paeonol's CID number (11092) from the site, and we linked back to PubChem homepage and clicked "chemical structure search" below "PubChem Tool". From the display, we clicked on "CID, SMILES, INCHI" below "identity similarity", and input 11092 in the blank, unfold "option" menu. We chose similarity greater than 90 and other options were default (Table 1). At last, we clicked "search" to enter next level (Haibo, et al 2012)..

On the basis of PubChem database results, there were 3129 results shown in Table 2. On the right side of webpage, we saw the item "Bio Activity Experiments" under "Refine your results". Then, we clicked "Bioassays Active (226)", and got 226 main active ingredients. Next, we clicked "BioActivity Analysis" under "Action on your results", and finished target analysis for these 226 active components. The item of "target" was the useful result we needed. We then clicked "download" to download the contents. In the downloaded file, data of "active compounds" showed that results 0-35 were meaningful targets. Found with these meaningful targets was a corresponding "sequence GI used in assays", and these GI number was organised for the next step (Haibo, et al 2012). . After it, we found out all the corresponding GI number of main components about herbs in BHD prescription and organised them for the next step.

David Homepage. We logged on to David homepage (http://david.abcc.ncifcrf.gov/summary.jsp) and clicked "upload" under "start analysis". We input all the GI numbers, chose "protein GI Accession" for "step 2", chose "gene list" for "step 3", then started search and observation of results (Table 2). As shown in Table 2, we clicked "genetic association db disease class", for pop up in another page. It can be found that there were numbers of disease categories and the "neurological" and "cardiovascular" disease categories were our goal. So, we clicked the term "gene". Then we obtained all BHD's targets acting on cerebrovascular diseases and cardiovascular diseases (CVD). Finally, we clicked "download file" to completely organise the results. Until now, we totally finished the whole search session and got the aimed results.

Results

According to the analysis of obtained results, we totally got BHD's sixty-eight targets for treating cerebrovascular diseases and eighty targets for treating cardiovascular diseases (CVD). By comparison, we finally found out BHD's thirty-five potential brain-heart concurrent treatment target points shown in Table 1. After the comprehensive screening of databases and artificial comparisons, Brain-Heart concurrent treatment target points of BHD were elaborated, and these targets were not only related to cerebrovascular diseases, but also associated with cardiovascular diseases, which were the material basis for the detection of Brain-Heart concurrent treatment mechanism at the molecular level. Such as tumour necrosis factor β (TNF-β), it had been reported that TNF-β had complicated biological activities, inducing IL-1, IL-6 and other cell factors, widely taking part in the inflammatory reaction, the growth and adjustment of immune system, and the interaction effect of pro-inflammatory factor and anti-inflammatory cytokines, and playing an important role in the formation of atherosclerosis and autoimmune diseases (Lie, et al 2011). Some other studies revealed

Table 1: Thirty five potential brain-heart concurrent treatment target points of BHD

Number	Protein targets
1	Glutathione S-transferase mu 1
2	Aldo-keto reductase family 1, member B1 (aldose reductase)
3	Androgen receptor
4	Cytochrome P450, family 1, subfamily A, polypeptide 1

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5	Cytochrome P450, family 19, subfamily A, polypeptide 1
6	Aldehyde dehydrogenase 2 family (mitochondrial)
7	3-hydroxy-3-methylglutaryl-Coenzyme A reductase
8	Arachidonate 5-lipoxygenase
9	Solute carrier family 6
10	Neurotransmitter transporter, noradrenalin, member 2
11	Solute carrier family 6
12	Neurotransmitter transporter, serotonin, member 4
13	5-hydroxytryptamine (serotonin) receptor 2A
14	Adenosine A2a receptor
15	Macrophage migration inhibitory factor
17	Adrenergic, alpha-2A-, receptor
18	Peroxisome proliferator-activated receptor alpha
19	Prostaglandin-endoperoxide synthase 2
20	Cytochrome P450, family 2, subfamily C, polypeptide 19
21	Dopamine receptor D1
22	Glutathione S-transferase omega 1
23	Cytochrome P450, family 2, subfamily C, polypeptide 9
24	Solute carrier family 5 (choline transporter), member 7
25	Heat shock 70kDa protein 1A; heat shock 70kDa protein 1B
26	Cytochrome P450, family 3, subfamily A, polypeptide 4
27	Adrenergic, alpha-2C-, receptor
28	Tumour necrosis factor (TNF superfamily, member 2)
29	Nuclear factor of kappa light polypeptide gene enhancer in B-cells 1
30	GNAS complex locus
31	Vitamin D (1,25- dihydroxyvitamin D3) receptor
32	Similar to Serine-protein kinase ATM
33	Cytochrome P450, family 1, subfamily A, polypeptide 2
34	Cytochrome P450, family 2, subfamily D, polypeptide 6
35	Estrogen receptor 1
36	Tumour protein p53
37	Peroxisome proliferator-activated receptor gamma
38	ATP-binding cassette, sub-family B (MDR/TAP), member 1

that TNF level in the patients with coronary heart disease had obviously risen, indicating that TNF played an important part in coronary heart disease (Huanmei, et al 2009).The target TNF-β was one of the thirty-five targets in the above method, and it had been confirmed that it had close relationship with both cerebrovascular diseases and cardiovascular diseases, as one of the confirmed Brain-Heart concurrent treatment target points, which verified the veracity of this networked pharmacology method for excavating targets. Except for some reported targets in Table1 from previous documents, there were also many targets with no deep study and report. Therefore, these target pathways would provide new research directions for studying pharmaceutical effect mechanism and material basis of BHD in Brain-Heart concurrent treatment.

Table 2: Corresponding relations between targets, effective components and herbs

No.	Targets	Effective component	Corresponding relation with drugs
1	Glutathione S-transferase 1	Isoimperatorin, isorhamnetin	Angelica tail, Astragalus mongholicus

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2	Aldo-keto reductase family 1, member B1(aldose reductase)	Paeonol, isorhamnetin, kaempferol	Root of common peony, Astragalus, mongholicus
3	Androgen receptor	Paeonol, isorhamnetin, kaempferol	Root of common peony, Astragalus mongholicus
4	Cytochrome P450,family 1, subfamily A, polypeptide1	Paeonol, isorhamnetin, kaempferol	Root of common peony, Astragalus mongholicus
5	Cytochrome P450,family19, subfamily A, polypeptide1	Paeonol, isorhamnetin, kaempferol	Root of common peony, Astragalus, mongholicus
6	Aldehyde dehydrogenase2 family(mitochondrial)	Paeonol, kaempferol	Root of common peony, Astragalus , mongholicus
7	3-hydroxy-3-methylglutaryl- Coenzyme A reductase	Palmitic acid, palmitic acid	Angelica tail, Ligusticum Chuanxiong Hort
8	Arachidonate 5-lipoxygenase	Isorhamnetin, kaempferol	Astragalus, mongholicus
9	Solute carrier family 6 , member 2 (neurotransmitter transporter, noradrenalin)	Thymol, o-cresol	Ligusticum Chuanxiong Hort
10	Solute carrier family 6, member 4 (neurotransmitter transporter, serotonin)	o-cresol	Ligusticum Chuanxiong Hort
11	5-hydroxytryptamine (serotonin) receptor 2A	Paeonol, kaempferol	Root of common peony, Astragalus, mongholicus
12	Adenosine A2a receptor	o-cresol, isoimperatorin, angelicin, paeonol, isorhamnetin, kaempferol	Ligusticum Chuanxiong Hort, Angelica tail, Root of common peony, Astragalus, mongholicus
13	Macrophage migration inhibitory factor (glycosylation- inhibiting factor)	Isorhamnetin, kaempferol	Astragalus, mongholicus
14	Adrenergic, alpha-2A-, receptor	o-cresol	Ligusticum Chuanxiong Hort
15	Peroxisome proliferator- activated receptor alpha	Palmitic acid, palmitic acid , paeonol	Ligusticum Chuanxiong Hort, Angelica tail, Root of common peony
16	Prostaglandin-endoperoxide synthase 2 (prostaglandin G/H synthase and cyclooxygenase)	o-cresol, isorhamnetin, kaempferol	Ligusticum Chuanxiong Hort, Angelica tail
17	Cytochrome P450, family 2, subfamily C, polypeptide 19	Isoimperatorin, angelicin, z-ligustilide, butylphthalide, paeonol, isorhamnetin, kaempferol	Ligusticum Chuanxiong Hort, Angelica tail Root of common peony, Astragalus , mongholicus
18	Dopamine receptor D1	Isoimperatorin, angelicin, isorhamnetin, kaempferol, paeonol	Angelica tail, Root of common peony, Astragalus, mongholicus
19	Glutathione S-transferase omega 1	Juglone, isorhamnetin, kaempferol, catechin, gallocatechin, Epigallocatechin	Peach seed, Root of common peony, Astragalus, mongholicus

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20	Cytochrome P450, family 2, subfamily C, polypeptide 9	Paeonol, kaempferol	Root of common peony, Astragalus mongholicus
21	Solute carrier family 5, member 7 (choline transporter)	Paeonol, isoimperatorin, angelicin	Root of common peony, Angelica tail
22	Heat shock 70kDa protein 1A; heat shock 70kDa protein 1B	Paeonol, kaempferol	Root of common peony, Astragalus , mongholicus
23	Cytochrome P450, family 3, subfamily A, polypeptide 4	Paeonol, catechin, gallocatechin, epigallocatechin, isoimperatorin, angelicin, isorhamnetin, kaempferol, z-ligustilide	Ligusticum Chuanxiong Hort, Angelica tail, Root of common peony, Astragalus , mongholicus
24	Adrenergic, alpha-2C-, receptor	o-cresol	Ligusticum Chuanxiong Hort
25	Tumour necrosis factor (TNF superfamily, member 2)	Isoimperatorin	Angelica tail
26	Nuclear factor of kappa light polypeptide gene enhancer in B-cells 1	z-ligustilide, paeonol, isorhamnetin, kaempferol	Ligusticum Chuanxiong Hort, Rootof common peony, astragalus, mongholicus
27	GNAS complex locus	Isorhamnetin	Astragalus, mongholicus
28	Vitamin D receptor (1,25- dihydroxyvitamin D3)	Juglone, paeonol , catechin, gallocatechin, epigallocatechin, isorhamnetin, kaempferol	peach seed, Root of common peony Astragalus mongholicus
29	Similar to Serine-protein kinase ATM (Ataxia telangiectasia mutated) (A-T, mutated) ataxia telangiectasia mutated	Kaempferol	Astragalus mongholicus
30	Cytochrome P450, family 1, subfamily A, polypeptide 2	Isoimperatorin, angelicin, isorhamnetin, kaempferol, paeonol, z-ligustilide, butylphthalide, thymol	Ligusticum Chuanxiong Hort, Angelica tail Root of common peony, Astragalus mongholicus
31	Cytochrome P450, family 2, subfamily D, polypeptide 6	Isorhamnetin, kaempferol	Astragalus mongholicus
32	oestrogen receptor 1	Isorhamnetin, kaempferol, isoimperatorin	Astragalus mongholicus, Angelica tail
33	Tumour protein p53	Juglone, paeonol, isorhamnetin, kaempferol	Peach seed, Root of common peony, Astragalus mongholicus
34	Peroxisome, proliferator- activated, receptor gamma	Thymol, o-cresol, paeonol, kaempferol	Ligusticum Chuanxiong Hort, Root of common peony, Astragalus mongholicus
35	ATP-binding cassette, sub-family B (MDR/TAP), member 1	Paeonol, isorhamnetin, kaempferol	Root of common peony, Astragalus mongholicus

Corresponding relations between targets, effective components and herbs perfectly reveal the effective specific location of main ingredients in TCM. The corresponding relationship can not only associate targets with drug ingredients, but also can provide new references for specific access mechanism study.

Discussion

In recent years, quick development of network pharmacology has provided a lot of valuable information for drug research. The information was provided by HIT database, PubChem database, and David database, which not only have advantage of large amounts of data, but also have

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accurate and comprehensive characteristics. Through comprehensive utilisation of these three database resources, we can find the targets corresponding with the effective composition of herbs quickly and accurately, and can complete the collection of information within a few hours with low requests of computer equipment. This method can greatly improve the efficiency, and get more accurate and comprehensive information. So, it is a kind of fast and effective method to find targets. According to traditional Chinese medicines, different diseases could be treated with same method or herbs, and the point was neither the cause nor disease symptom, but the identification of same pathogenesis for different diseases. So, different diseases with same pathogenesis could be treated with same methods or herbs. The thirty-five targets found in this research are the material basis for BHD's treatment of stroke sequelae and Brain-Heart concurrent treatment. Some reports showed that BHD's treatment of disease was at multiple levels, and this research has accorded active ingredients in BHD with the corresponding targets, offering new information with great guiding significance for the material basis research of BHD. With in-depth study of compound preparations, detection of detailed target points for effective components in compound preparation has become the main tendency. In future study, through full use of network pharmacology methods and database resources, those data mining methods could be applied in the study of material basis and acting mechanism to offer some potential supports for basic research of herbs material.

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