TANG [HUMANITAS MEDICINE]

Original Article

Study on the Anti-hypertension mechanism of *Prunella Vulgaris* based on entity grammar systems

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ABSTRACT

Literatures and experimental studies have shown that *Prunella* has an effect on anti-hypertension, however, its components are complicated, so that it is still difficult to clear the specific roles of its various components in blood pressure regulation in. So we decide to systematically study the anti-hypertension mechanism of *Prunella*. We integrated multiple databases and constructed molecular interaction network between the chemical constituents of *Prunella Vulgaris* and hypertension based on entity grammar systems model. The network has 262 nodes and 802 edges. Then we infer the interactions between chemical compositions and disease targets to clarify the anti-hypertension mechanism. Finally, we found *Prunella* could influence hypertension by regulating apoptosis, cell proliferation, blood vessel development and vasoconstriction, etc. Thus this study provides reference for drug development and compatibility, and also gives guidance for health care at a certain extent.

Keywords *Prunella Vulgaris*, hypertension, mechanism, entity grammar systems

INTRODUCTION

Chinese medicine has showed more effective in chronic and polygenic diseases, but the underlying mechanisms of action are rarely investigated systematically (Li et al., 2014). With the advancements in understanding of pathobiology of human diseases, people find that most diseases are not simply caused by one single factor (Goh et al., 2007), such as hypertension, diabetes, cardiovascular disease (CVD) and some others. The Chinese medicine treatments can be regarded as a complexity against complexity pattern between multi-target therapy such as Chinese medicine and the complex biological networks of human diseases.

The development and applications of systems biology (Kitano, 2002) and network biology (Baraba´si et al., 2004) have provided new ideas and methods for elucidating the acting mechanism of Chinese medicine. In the post-genomic era, it is easier to obtain a large number of relevant data. Data-driven analysis has become an important way and an auxiliary method to elucidate the acting mechanism and therapeutic basis of T traditional Chinese medicine.

Hypertension is one of the common chronic diseases. Stroke, myocardial infarction, heart failure and chronic kidney disease are the main complications of hypertension, which will be life-threatening at a certain extent. The World Health Organization took Hypertension Prevention and Control as the theme of World Health Day in 2013 for the first time, and appealed to human to reduce the risk of cardio-cerebral vascular diseases by controlling hypertension, which highlighted the importance of prevention and treatment of hypertension. There were about 266 million high blood pressure patients in 2012 in China, but the control rate of blood pressure was less than 10%, so lowering blood pressure and improving the control rate of hypertension are the main task of Chinese hypertension.

Prunella is spike of fruit with dried flowers, and belongs to *Labiatae*, which firstly contained in Sheng *Nong's Herbal*, and named by "dried after the summer solstice". Its property is cold, it tastes bitter and pungent, and distributes along liver and gallbladder meridian, and plays a role in clearing anger and loosing knot, so it is used to treat red eyes, throat, dizziness, headache, gall tumors and other clinical diseases (Chinese Pharmacopoeia Commission, 2010). The book written by Shi-Zhen Li and compiled by Shi Yu, *Compendium of Materia Medica–Essence of vemacular translation* reads: *Prunella* could be applied to treat hypertension clinically. Studies show that *Prunella* vulgaris extracts may lower blood pressure of SHIR rats by reducing angiotensin II and increasing nitric oxide (NO). And *Prunella* alcohol extract liquid has certain antagonistic effect on aortic contraction which was caused by norepinephrine, potassium chloride, calcium chloride. Experimental results show that *Prunella Asiatica Nakai* can decrease blood pressure of rabbit (He et al., 2002). The study of Xu tipped *Prunella* alcohol extracts may produce endothelium-dependent vasodilation by NO-guanylate cyclase pathway (Xu et al., 2010). You used *Prunella* aqueous extracts to study spontaneously hypertensive rats, and its results show *Prunella* lowers blood pressure at some degree (You et al., 2011). But the anti-hypertension mechanism of *Prunella* has no systematical analysis. Therefore, the study will build molecular-based network between *Prunella* and hypertensive based on entity grammar systems, and infer the interactions of molecules to explain the anti-hypertension mechanism of *Prunella* systematically.

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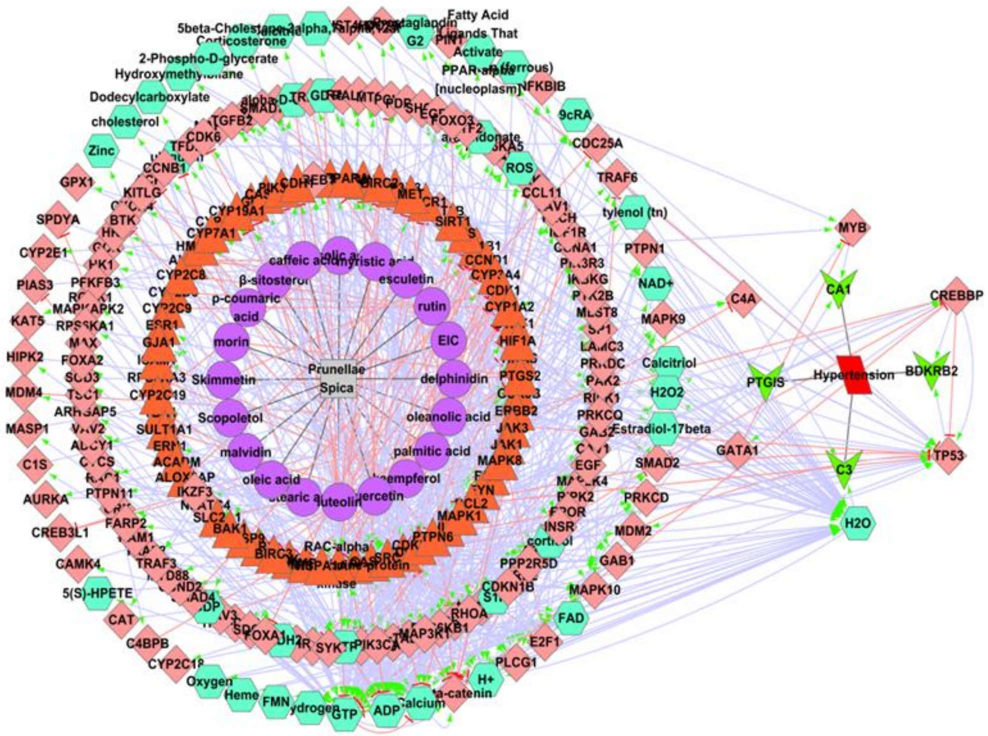

Fig.1 The molecular interaction network between the chemical constituents of *Prunella Vulgaris* and hypertension

Data sources

We integrated databases TCMSP (http://tcmspnw.com), TTD (http://bidd.nus.edu.sg/group/TTD /ttd.asp), and so on for *Prunella*-related data and disease-related data, through STITCH database (http://stitch.embl.de/) we got the data of interactions between compounds and targets. Based on the biological response data and signaling pathways data from hipathDB database (http://hiPathDB.kobic.re.kr.) to build the molecular network between Prunella and hypertension, *link (A, B, X)* as the form of application. Finally, the molecular network can be visualized through the software Cytoscape_v2.8.3.

Molecular network construction based on entity grammar systems

Entity grammar systems

Entity grammar systems is a formalized syntax system and proposed for biological systems, which was indicated by five-tuple $G = (V_N, V_T, F, P, S)$, and all the characters are non-terminal character set, terminal character set, manipulate subset, rule set, and initial character respectively (Wang, 2004). When we do not distinguish or without regard to the terminal character and non-terminal character, entity grammar systems can be represented as four-tuple $G = (V, F, P, S)$, where $V = V_N \cup V_T$.

Network construction

In the study, V represent nodes of each type in the network, namely Chinese medicine, chemical compositions of Chinese medicine and their targets, disease and its related proteins, small molecules and other related proteins, F represent various types of relationships between the network nodes, such as include / interaction / activation / inhibition etc., *P* is the rules or formulas for inference, which is used for deducing the relationship between *Prunella* targets and hypertension targets based on above entities, and we took it an example that if A to B and B to C is the same effect (the same effect is all positive or negative), it concludes that the regulatory way of A to C is positive, otherwise it is negative, and the action distance of A to C is the sum of distances from A to B and B to C. The specific processes of entity grammar systems can refer the principle of dTGS in the article of study on mechanism of Tianzhu Powder in treatment of vascular dementia based on system pharmacology (Zhang et al., 2015).

Above-mentioned *Link (X, Y, Z, W)* can be described as an action mode of source node X with Z (activation represents forward and inhibition represents reverse) by W-step reaction working on a target node *Y*. (*W* represents the transitive of positive or negative regulation of the nodes in network and the cumulative of transitional steps, W is set to 5 in the study, the results will not be considered if $W >= 6$). The source node and the target node will be labeled respectively, by the reasonable setting of *W* to find all signal paths starting with point *X*, ending point *Y* and *Z* as the mode of action and the pathway when the value of *W* is the minimum. Finally, the results of forward reasoning process of compound C to disease-related protein D import Cytoscape_v2.8.3 to achieve the visualization of molecular biological network.

RESULTS AND DISCUSSION

The resulting network includes targets of *Prunella* chemical compositions and hypertensive-related proteins as shown in Fig.

1. The biomolecule network has 262 nodes and 802 edges. Different shapes represent different types of nodes. The square represents traditional Chinese medicine *Prunella*, circles represent chemical compositions of *Prunella*, triangles represent targets of the chemical compositions, diamonds represent proteins, hexagons represent small molecules, irregular quadrilaterals represent targets of disease, and parallelogram represents hypertensive disease. Arrows show the direction of action, triangular arrows represent a positive regulation, T-shaped arrows indicate a negative regulation, and straight lines indicate that there is a correlation between two nodes. The number of edges node connected reflects its importance in the present network.

From Figure 1 we can see *Prunella* regulate blood pressure mainly through multi-step reactions of chemical compositions (oleanolic acid, esculetin, caffeic acid, kaempferol, luteolin, β-sitosterol, myristic acid, pyrone, scopoletol, delphinidin, malvidin, ursolic acid, rutin, oleic acid, palmitic acid, EIC, p-coumaric acid, stearic acid, quercetin) and targets (HMGCR, APOA1, CYP7A1, CYP4A11, PPARA, FYN, PTGS2, MAPK14, DECR1, IL-2, STAT1, CDK2, BCL2, ALOX5, CYP1A2, CYP3A4, CASP3, RELA, CDH1, ESR1, MAPK1, ALOX5AP, CYP2C8, CYP2D6, CYP2C9, CDK1, CYP1B1, SRC, JAK1, GJA1, ICAM1, RPS6KA3, JAK3, SLC2A1, CDKN1A, ERBB2, MAPK8, BAK1, CCND1, IGF1, BIRC2, CASP7, TLR5, CASP9, BIRC3, INS, ACADM, PTPN6, SULT1A1, ERN1, MMP9, SIRT1, HIF1A, HSPA1A, JUN), ultimately effect on the hypertensive-related targets CA1, C3, BDKRB2, PTGIS. CA1 is also the target of chemical compositions, that is to say, Prunella can regulate Hypertension directly through CA1. By the molecular network map we can find that *Prunella* regulates blood pressure in the way that various chemical constituents finally act on multiple associated proteins via multiple reaction pathways.

The hypertensive-related target CA1 is one of the Carbonic anhydrases. Carbonic anhydrases have a variety of physiological functions, such as keeping the equilibrium of acids and bases, participating in the transport of CO2 (Gilmour et al., 2009). The study of Jiang shows that acetazolamide (ACZ) could evaluate cerebrovascular reactivity of elderly hypertensive (Jiang et al., 2007). To sum up, we speculate CA1 may affect hypertensive indirectly. Previous study showed that complement 3 (C3) expresses in tunica in spontaneously hypertensive rats, and C3 plays a role in the regulation of APN in the perivascular adipose tissue (PVAT) via macrophage-derived TNFα, which contributes to perivascular inflammation and vascular injury in the DOCA-salt hypertensive mice (Ruan et al., 2015). Splicing mutation of the prostacyclin synthase gene in a family associated with hypertension (Nakayama et al., 2002) shows that PTGIS gene located on the 20th chromosome 20q13 is the candidate genes of human blood pressure regulation. Aniket Natekar (Nztekar et al., 2014) found that BDKRB2 has appeared in genetic and epigenetic research studies of hypertensive disease. The associated results of hypertensive-related targets and chemical compositions of *Prunella* can be seen in Table 1.

It is difficult to resolve the mechanism deeply from the total network, because the overall molecular network is complicated. So here we extract sub-networks to resolve the anti-hypertensive mechanism. As shown in Fig. 2.

FYN is a member of the Src protein-tyrosine kinase family. Fyn has been shown for the following signaling pathways: T and B cell receptor signaling (Palacios et al., 2004; Zamoyska et al., 2003), integrin-mediated signaling, growth factor and cytokine receptor signaling, platelet activation (Shi et al., 2014) and others. The protein associates with the p85 subunit of phosphatidylinositol 3-kinase and interacts with the Fyn-binding protein.

Table 1. The associated results of hypertensive-related targets and chemical compositions of *Prunella*

hypertensive-related target	chemical composition	hypertensive-related target	chemical composition
CA1	oleanolic acid	C3	EIC
	esculetin		myristic acid
	kaempferol		caffeic acid
	luteolin		oleanolic acid
	quercetin		β-sitosterol
BDKRB2	myristic acid		esculetin
	oleanolic acid		rutin
	esculetin		kaempferol
	Scopoletol		delphinidin
	kaempferol		ursolic acid
	delphinidin		luteolin
	malvidin		oleic acid
	ursolic acid		palmitic acid
	luteolin		morin
	palmitic acid		p-coumaric acid
	stearic acid		quercetin
	quercetin		
PTGIS	oleanolic acid		

GAB2 is GRB2-associated binding protein 2. It is a member of the GAB/DOS family localized on the intracellular membranes of the cell. It mediates the interaction between receptor tyrosine kinases (RTKs) and non-RTK receptors serving as the gateway into the cell for activation of SHP2, Phosphatidylinositol 3-kinase (PI3K), Grb2, ERK, AKT and acting as one of the first steps in these signaling pathways. The C-terminal tail of GAB2 acts as a site for multiple-phosphorylation of tyrosine kinases (Simister et al., 2012).

STAT5B is a member of the STAT family of transcription factors. It has been shown involved in diverse biological processes, such as TCR signaling, apoptosis, adult mammary gland development. Christian Kosan shows that the cytokine-inducible transcription factors signal transducer and activator of transcription 5A and 5B (STAT5A and STAT5B) are important for the normal development of multicellular eukaryotes (Kosan et al., 2013). STAT5A and STAT5B regulate the quiescence of hematopoietic stem cells (Wang et al., 2009). The activation mechanism of STAT is binding ligands (cytokines or growth factors) to cognate receptors and activating the associated Janus kinases, JAK1–3 and TYK2 (Kosan et al., 2013). The activation of STAT5 has been reported in CLL cells after exposing IL-15, resulting in malignant cell proliferation and inhibition of apoptosis (de Totero et al., 2008).

AKT1 is RAC-alpha serine/threonine-protein kinase. GAB2 transits the PI3K signaling pathway, and PI3K activates the serine/threonine protein kinase (AKT), then inactivates GSK3 by phosphorylation (Ding et al., 2013). Which will causes the phosphorylation of tau and the production of amyloid (Lynch and Daly, 2002; Pan et al., 2010). And some results suggested that OPN expression in the hypertensive vasculature was increased via signaling pathways that involve Akt1/AP-1, leading to vascular remodeling by increasing the production of MMP-2 (Seo et al, 2015).

Lu found that Man B suppresses the activation of Fyn kinase and the consequent signaling processes, involved to Syk, Gab2, and Akt. So, we can suppose that FYN, GAB, and Akt have some correlation (Lu et al., 2013).

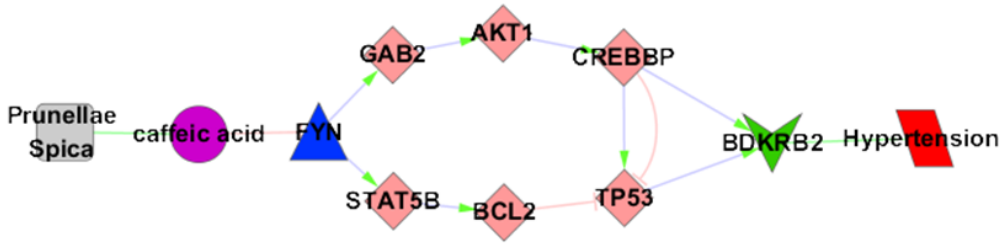

Fig.2 The pathway network of caffeic acid of *Prunella vulgaris* to therapeutic target BDKRB2

BCL-2 is a type of apoptosis-related genes, its expression and regulation is one of the key factors affecting apoptosis, and plays an important role in apoptotic signal transduction pathway. Bcl-2 family have two categories, anti-apoptosis and promoting cell death. Bcl-2 is a negative regulatory factor for cell death in many cell types, and it can protect cells from death when external stimulus exists. Many tissues and organs exert relatively higher or lower level of apoptosis in patients with hypertension, so the balance between apoptosis and proliferation is broken. Previous study showed that Bcl-2 expression was directly correlated with systolic pressure, and smooth muscle cell apoptosis might be inhibited in small arteries of adult SHR as a consequence of an excess of the protein Bcl-2 (Díez, 1997). And the expression levels of Bcl-2 were decreased in DOCA-salt hypertensive rats (Ma et al, 2012).

CREBBP is CREB-binding protein, also known as CREBBP or CBP. Recent results suggest that post-translational activity of N-glycosylation mediated by novel CBP can alter the conformation of CBP-interacting proteins, and lead to the regulation of gene expression, cell growth and differentiation (Siddique et al., 2009). Liu discovered that Akt phosphorylates CBP at threonine 1871 and it can suppresses the activity of acetyltransferase by impeding the binding of CBP and histone H3 (Liu et al., 2013).

TP53 is a tumor suppressor protein, and plays an important role in regulating cell cycle, apoptosis and maintaining the stability of genome. Also, it regulates growth and apoptosis according to different physiological condition and cell types and induces apoptosis by expressing BAX and FAS antigen or inhibiting expression of Bcl-2. In addition, the histone acetyl transferase (HAT) proteins p300 and CBP (CREB-binding protein) could stabilize p53 by acetylation, and the result can be abrogated by the formation of a ternary complex of Mdm2, p53 and p300 or CBP (Ito et al., 2001; Kobet et al., 2000).

BDKRB2 is a bradykinin beta 2 receptor gene, and it is also a gene of G protein-coupled related to angiogenesis, and it can form a complex with angiotensin converting enzyme (ACE), which is considered to work interactively between renin-angiotensin system (RAS) and kinin-kallikrein system (KKS). Heptapeptide angiotensin 1-7 (A1-7) also causes the behavior of B2 receptor bradykinin (Fernandes et al., 2001). Li found that the BDKRB2-58T/C gene polymorphism is associated with increased EH risk, and the results of this study suggest that carriers of the -58C allele are susceptible to EH (Li, 2012). Wang examined whether a genetic variant (-58T/C) in the promoter region of the human beta2 bradykinin receptor gene was genetically involved in essential hypertension, and found significant differences between hypertensive and normotensive subjects were seen in the genotypes distribution (p = 0.045) and allelic frequencies (p = 0.033) (Wang et al., 2001). And Aniket Natekar found that BDKRB2 has appeared in genetic and epigenetic research of hypertensive disease (Natekar et al., 2014). Therefore, we make use of the sub-networks of *Prunella* to hypertension can find that caffeic acid could activate some genes and inhibit TP53, then play a role in anti-hypertensive by regulating apoptosis, cell growth and cell differentiation.

According to the complete biological process: traditional Chinese medicine - Chinese medicine chemical compositions - targets of the chemical compositions - proteins or small molecules - disease-related target proteins – disease, we constructed molecules biology network and analyzed the anti-hypertensive mechanism of *Prunella* systematically. *Prunella* can maintain the balance of gene function in the molecular interaction network, and based on the comprehensive analysis of the network we obtained, we could find the anti-hypertensive mechanism of *Prunella* mainly contains: regulation of apoptosis and cell death, regulation of cell proliferation; cell migration and cell differentiation, regulation of cell cycle, regulation of immune system process, regulation of inflammatory response, regulation of blood vessel development and vasoconstriction, regulation of nitric oxide biosynthetic process , regulation of blood pressure stability, regulation of metabolic process stability and others. Hence, *Prunella* is able to improve or lower blood pressure by many paths.

CONCLUSIONS

The study shows that *Prunella* regulates blood pressure through multiple targets and multiple ways, and overall regulation of traditional Chinese medicine treatment of diseases also can be further illustrated. The compositions of *Prunella* linolenic acid, myristic acid, caffeic acid, hydroxyl coumarin, oleanolic acid, β-sitosterol, esculin yuan, hydroxy methicillin and pyrone, kaempferol, larkspur pigment, malvidin, ursolic acid, luteolin, oleic acid, palmitic acid, morin, coumaric acid, stearic acid, quercetin can affect the hypertensive-related targets CA1, C3, BDKRB2, PTGIS by multiple pathways, so *Prunella* can regulate, improve or lower blood pressure. Finally we found the built network of action mechanism includes 262 nodes and 802 edges, and explained it systematically in some degree. The study gives guidance for studying on pharmacology of *Prunella*, provides a scientific basis for clinical and routine health applications, and lays a foundation for drug development and drug compatibility. But the result is limited by data integrity. However, we trust data quality will be improved continuously in the post-genomic era, and related technologies will continue to develop, so it will be increasingly significant that the result of systematic research will be improved.

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CONFLICT OF INTEREST

There are no competing financial interests existing.

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