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Original Article

Bioinformatics Based Therapeutic Effects of *Sinomenium Acutum**

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ABSTRACT **Objective**: To decipher the possible mechanisms of *Sinomenium Acutum* (SA) in treating diseases by a bioinformatics method. **Methods**: SA ingredients were searched according to Chinese Pharmacopoeia, Chinese Medicine Dictionary and Traditional Chinese Medicines Database (TCMD). Active compounds and target proteins of SA were acquired through the Pubchem platform. Pathway, network and function analyses of SA were performed with ingenuity pathway analysis (IPA), a bioinformatics analysis platform. Disease, biofunction-target networks were established with Cytoscape. **Results**: Eighteen ingredients from SA were obtained. Seven active ingredients with 31 active target proteins were acquired according to PubChem Bioassay test. By IPA analysis, 277 canonical pathways belonging to 17 function categories were collected, 23 kinds of diseases, 21 categories bio-functions were obtained. Based on *P* value, calculated by IPA, the top 5 significant pathway of SA targets include phosphatidylinositol 3 kinase/Akt (PI3K/Akt) signaling, prostate cancer signaling, macrophage migration inhibitory factor (MIF) regulation of innate immunity, Guanosine-binding protein coupled receptor (GPCR) signaling, and ataxia telangiectasia mutated protein (ATM) signaling. Disease and bio-function network analysis indicated that mitogen activated protein kinase 1 (MAPK1), MAPK3, p65 nuclear factor κB (RELA), nuclear factor of κB inhibitor alpha (NFκBIA), interleukin 1β (IL-1β), prostaglandin G/H synthase 2 (PTGS2) and tumor protein 53 (TP53) were the critical targets in various diseases treated by SA. **Conclusions**: In the different view of target, pathway, disease and bio-function, inflammation was found to be a central theme in many chronic conditions. SA could be used not only as an anti-inflammatory agent, but also for the treatment of cancers, neurological diseases, psychological disorders and metabolic diseases.

KEYWORDS *Sinomenium Acutum*, bioinformatics analysis, ingenuity pathway analysis, network pharmacology

Inflammation is a fundamental protective immune response mounted by the evolutionarily-conserved innate immune system to harmful stimuli and is tightly regulated by the host.[1] Inflammation has been linked to a variety of autoimmune and auto-inflammatory diseases, including neurodegenerative diseases (Alzheimer's disease, Parkinson's disease, and multiple sclerosis), metabolic disorders[2] and cancer.[3] Therefore, inflammation is a critical therapeutic point in many diseases. Safe and effective anti-inflammatory agents are indispensable in clinical practice. Non-steroidal anti-inflammatory agents (NSAIDs), such as ibuprofen and aspirin, with clear targets cyclooxygenase (COX)1 and COX2, are most widely prescribed drugs for the powerful anti-inflammation effect. However, NSAIDs have severe side effects, such as dyspepsia, gastroduodenal ulcer, hypertension, thrombosis and stroke.[4] Thus, more effective and safe agents are still a task.

Sinomenium Acutum (SA) has been successfully used for centuries in treatment of rheumatism, arthralgia and neuralgia with extremely low side effect in China and many areas of Far East.[5] Sinomenine, the main active chemical component of SA, could down-regulate interleukin (IL)-1β and IL-6 levels in serum, inhibit matrix metalloproteinase-2 (MMP-2) and matrix metalloproteinase-9 (MMP-9) expression, and up-regulate metallopeptidase inhibitor 1 (TIMP-1) and metallopeptidase inhibitor 3 (TIMP-3) expression

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in rat paw tissues.[6] Sinomenine could also inhibit the activation of macrophages through acting the nicotinic acetylcholine receptor α7.[7] Our previous studies showed that sinomenine had a similar anti-inflammatory effect with NSAIDs but less adverse events in treating rheumatoid arthritis.[8] Researchers reported sinomenine exhibitd a variety of biological activities including anti-arthritic, anti-proliferation, anti-angiogenic, anti-neoplastic, analgesic effects, immunosuppressive properties, suppression of osteoclast formation and bone loss.[5,9-11]

Bioinformatics analysis is an increasingly important approach in deciphering the mode of drug action, which has been well-illustrated in several articles.[12-14] The system-based network technology utilizes an integrated method to investigate the drug actions ranging from molecular and cellular levels to tissue and organism level. Network approach has proven to be useful for integrating abundant high-dimensional biological data, as well as deciphering the relationships among drugs, targets, diseases and pathways.[15] In this paper, we searched the ingredients and target proteins of SA and performed pathway, network and function analysis with ingenuity pathway analysis (IPA, http://www.ingenuity.com). With Cytoscape, we visualized the relationship among SA ingredients, target proteins, pathways and diseases.

METHODS

Searching for Ingredients and Target Proteins of SA

The major ingredients were determined according to Chinese Pharmacopoeia, Chinese Medicine Dictionaries and Traditional Chinese Medicine Database (TCMD). All of the ingredients names were used as keywords in PubChem (http://pubchem.ncbi.nlm.nih.gov) searches. Target proteins of SA were searched in the PubChem Compound. The active ingredients were collected according to PubChem Compound target proteins searching. The target proteins of active compounds were tested in bioassays that could be collected in PubChem.[16] A detailed search process is shown in Figure 1.

Pathway, Network and Function Analysis by IPA

The relevant pathways, functions, networks were ranked by the scores or *P* values. IPA performs pattern recognition analyses to characterize the biomarkers, so as to evaluate the biomarkers in canonical pathways and biological networks. The calculation was either based on the ratio (number of SA targets that map to the canonical pathway/the total number of proteins that map to the same canonical pathway) or significance (Fisher's exact test was used to calculate *P* value indicating the probability that the association between the SA targets and the canonical pathway). In this study, the score was -10 logarithms of Fisher's exact test *P* values in canonical pathway analysis by IPA. Significances for biological functions were assigned to each network by determining a *P* value for the enrichment of the targets in the network for such functions compared with the whole Ingenuity Pathway Knowledge Base (IPKB). The *P* values were adjusted using a Benjamini and Hochberg false discovery rate (FDR) of 1%. We chose the shared pathways via score [-log (*P* value), 2.0] (*P* value of pathway, 0.01). All the networks were constructed by the Cytoscape 2.8 software, an open software for biological data integration and validation.

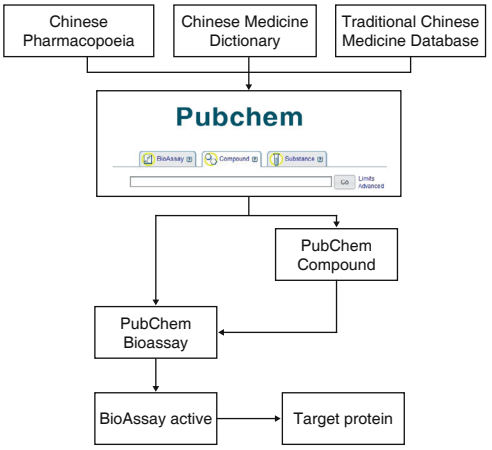

Figure 1. Process of Searching Protein Targets in PubChem Platform

RESULTS

Active Ingredients Identification

In our study, 18 ingredients of SA were extracted with their names: sinomenine, stigmasterol, isosinomenine, disinomenine, beta-sitosterol, syringaresinol, salutaridine, autumidine, acutumine, magnoflorine, methyl hexadecanate, michelalbine, sinacutine, stepharine, tuduranine, ainomendine, bianfugenine and dihydrosalutaridine. According to PubChem Bioassay test, 9 ingredients with 31 active compounds (active compounds rate 31/117) were screened out. The biology information of 9 ingredients is list in Appendix 1. A total of 110 bioassay test results were extracted from PubChem database. Twenty four tests (22%) indicated the active anti-

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inflammation property of SA in anti-inflammatory assay. In the other activity assessments, 15 (14%) are relevant with cancer, 9 (8%) with psychological disorder and 7 (6%) with diabetes.

Active Target Identification

In this study, 31 active target proteins were screened out with an active target rate of 31/449, Appendix 2). A network of ingredients and target proteins was also constructed with Cytoscape. As presented in Figure 2, the ingredient-target protein network embodies 40 nodes (9 ingredients and 31 target proteins) and 38 edges. In this network, 22 (71%) target proteins are correlated with sinomenine. Sinomenine and disinomenine share 4 common target proteins, P65 nuclear factor κ B (RELA), nuclear factor of κ B inhibitor alpha (NF κ BIA), mitogen activated protein kinase 1 (MAPK1) and MAPK3. Tyrosyl-DNA phosphodiesterase 1 (TDP1) is a shared target of isosinomenine and sinomenine. In PubChem database, 3 bioassay tests showed the TDP1 inhibition effects of sinomenine and disinomenine (PubChem BioAssay AID 686979, 686978, 49946). Beta-sitosterol and stigmasterol get 2 common target proteins, serine/threonine kinase glycogen synthase kinase-3 beta (GSK3B) and the enzyme dipeptidyl peptidase 4 (DPPⅣ).

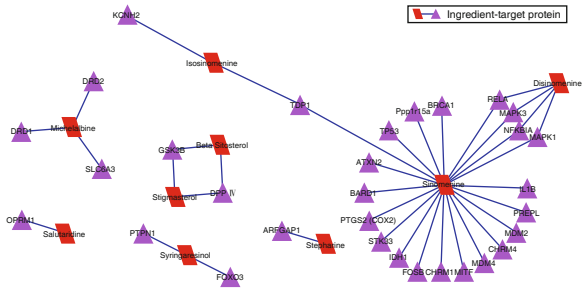

Figure 2. Ingredients and Target Proteins of SA

Notes: The purple triangle indicates target proteins of SA and the red parallelogram means the ingredients of SA. The edge shows the interaction between ingredients and targets proteins

IPA Canonical Pathway Analysis of SA

In our study, 277 canonical pathways belonging to 17 function categories were obtained according to the SA target proteins with IPA analysis (Table 1). Pathways about cancer, intracellular and second messenger, cytokine, cellular stress and injury as well as cell cycle regulation have higher *P* value than other categories. Based on *P* value, the top 5 signaling include phosphatidylinositol 3 kinase/Akt (PI3K/Akt) signaling, prostate cancer signaling, macrophage migration inhibitory factor (MIF) regulation of innate immunity, guanosine-binding protein coupled receptor (GPCR) signaling and ataxia telangiectasia mutated protein (ATM) signaling. Pathway-target network of SA was also constructed in Appendix 3. The pathway-target network embodies 302 nodes (277 pathways and 25 target proteins) and 773 edges. MAPK1, MAPK3, RELA and NF κ BIA, which links with 187, 175, 106 and 67 pathways, respectively, become the major therapeutic targets of SA due to their dominant positions. Besides, another 2 targets, IL1 β and PTGS2 (prostaglandin endoperoxide synthase-2, COX2) also present highly interconnected pathways, with degree of 30, 24 respectively. In Appendix 3, PI3K/Akt signaling and GPCR signaling both get 9 targets, molecular mechanisms of cancer with 8 targets and CAMP-mediated signaling, prostate cancer signaling, glucocorticoid receptor signaling each with 7 targets (Table 2). Pathways about cancer and neurotransmitters are listed in Figure 3.

Table 1. Signaling Categories of SA Target Protein

	Category	*P* range	No.
1	Cancer	8.96×10^{-12}–3.81×10^{-2}	35
2	Intracellular and second messenger signaling	1.99×10^{-11}–4.27×10^{-2}	28
3	Cytokine signaling	7.62×10^{-10}–4.43×10^{-2}	43
4	Cellular stress and injury	1.08×10^{-10}–1.80×10^{-2}	17
5	Cell cycle regulation	1.08×10^{-10}–4.78×10^{-3}	12
6	Cellular growth, proliferation and development	1.62×10^{-10}–3.31×10^{-2}	43
7	Cellular immune response	1.75×10^{-9}–4.31×10^{-2}	45
8	Pathogen-influenced signaling	2.04×10^{-8}–3.48×10^{-3}	10
9	Apotosis	2.11×10^{-8}–4.31×10^{-2}	21
10	Transcriptional regulation xenobiotic metabolism	2.11×10^{-8}–4.00×10^{-3}	5
11	Nuclear receptor	2.11×10^{-8}–2.16×10^{-2}	9
12	Ingenuity toxicity list pathways	2.11×10^{-8}–2.66×10^{-2}	16
13	Humoral immune response	1.41×10^{-6}–9.97×10^{-3}	9
14	Growth factor signaling	1.60×10^{-6}–8.10×10^{-3}	22
15	Organismal growth and development	6.47×10^{-6}–3.81×10^{-2}	17
16	Cardiovascular	8.58×10^{-6}–2.05×10^{-2}	13
17	Neurotransmitters and other nervous system signaling	1.04×10^{-5}–2.11×10^{-2}	27

Diseases and Bio-Functions Analysis of SA

Corresponding diseases and bio-function of SA targets were acquired according to IPKB. As displayed in Table 3 and Appendix 4, 30 target proteins were connected with 23 diseases, such as

Table 2. Top 10 Signaling of SA Target Proteins

Signaling	*P*-value	Overlap
PI3K/AKT	1.17×10^{-13}	7.3% (9/123)
Prostate cancer	2.74×10^{-11}	8.5% (7/82)
MIF regulation of innate immunity	2.81×10^{-11}	14.6% (6/41)
G-protein coupled receptor	8.81×10^{-11}	3.5% (9/256)
ATM	2.76×10^{-10}	10.2% (6/59)
IL-17A in fibroblasts	7.62×10^{-10}	17.1% (6/35)
Melanoma	1.99×10^{-9}	11.9% (5/42)
CAMP-mediated	9.15×10^{-9}	3.2% (7/219)
Molecular mechanisms of cancer	1.29×10^{-8}	2.2% (8/563)
IL-17Ag in airway cells	1.75×10^{-8}	7.8% (5/64)

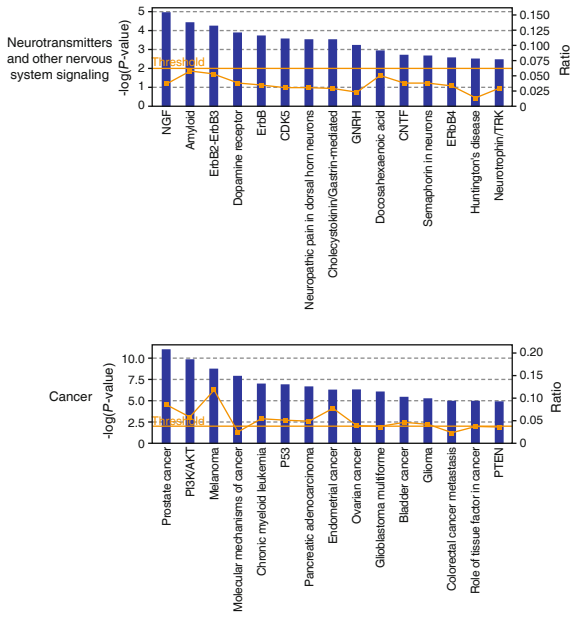

Figure 3. Canonical Pathway Analysis of SA

Notes: NGF: nerve growth factor; CDK5:cyclin-dependent kinase 5

inflammation diseases, cancer, neurological diseases and psychological disorders (432 edges were included). PTGS2, IL1 β , dopamine receptor D2 (DRD2), NF κ BIA were the crucial targets as their high degree in disease-target network (Appendix 5). Based on *P* value, we found SA targets mainly regulated neurological diseases, psychological disorders, skeletal and muscular disorders, inflammatory disease, and cancer (Table 4). Bio-function and target network is composed of 52 nodes (21 bio-functions and 31 target proteins) and 386 interactions (Table 5 and Appendix 6). TP53 is a core target for it participating in all the 21 bio-functions. The following IL1 β , PTGS2, NF κ BIA, MAPK1, RELA and FOXO3, which were significantly relevant with inflammation, also had higher degree (Table 6). Functions like organisml injury and abnormalities, cellular growth, proliferation and cell death and survival show more relative targets than other bio-functions. Based on *P* value calculated by IPA, gene expression, cell cycle, cell death and survival, lipid metabolism and small molecule biochemistry indicated higher significance with SA targets (Table 7).

Table 3. Disease-Target Protein Network of SA

Disease	Degree	Target protein	Degree	Target protein	Degree
Skeletal and muscular disorders	27	PIGS2	23	PREPL	10
Cancer	26	IL1 β	23	MDM4	7
Hepatic system disease	24	DRD2	21	MAPK1	7
Immunological disease	24	NFKBIA	21	ARFGAP1	6
Gastrointestinal disease	24	SLC6A3	21	MITF	5
Reproductive system disease	23	OPRM1	20	STK33	2
Neurological disease	23	CHRM1	20	TDP1	1
Psychological disorders	20	TP53	20	—	—
Hematological disease	20	CHRM4	20	—	—
Respiratory disease	19	FOXO3	19	—	—
Hereditary disorder	19	DPP4	19	—	—
Inflammatory disease	19	BRCA1	17	—	—
Infectious diseases	19	RELA	17	—	—
Inflammatory response	19	GSK3B	17	—	—
Cardiovascular disease	19	MDM2	16	—	—
Connective tissue disorders	18	DRD1	15	—	—
Metabolic disease	18	PIPN1	15	—	—
Endocrine system disorders	16	MAPK3	14	—	—
Developmental disorder	15	KCNH2	12	—	—
Nutritional disease	14	IDH1	12	—	—
Renal and urological disease	13	ATXN2	12	—	—
Dermatological diseases	8	FOSB	10	—	—
Ophthalmic disease	5	BARD1	10	—	—

Table 4. Disease or Disorders of SA Target Proteins

Name	*P* value	Molecules (kD)
Neurological disease	3.09×10^{-6}–3.00×10^{-13}	23
Psychological disorders	2.40×10^{-6}–3.00×10^{-13}	20
Skeletal and muscular disorders	2.40×10^{-6}–3.00×10^{-13}	27
Inflammatory disease	4.09×10^{-6}–5.84×10^{-13}	19
Cancer	4.55×10^{-6}–7.81×10^{-13}	26

DISSCUSION

In the present study, a bioinformatics analysis approach was adopted to provide new insights into the therapeutic targets of SA. The results indicated that the anti-inflammatory herb SA had plenty of therapeutic effects in treating cancers, neurological diseases, psychological disorders and metabolic diseases.

The mechanisms of SA exhibiting anti-inflammation effect may be through the targets like RELA, NF κ BIA, MAPK1, MAPK3, DRD2, TP53, IL1 β and PTGS2. RELA is a member of the mammalian

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Table 5. Bio-Function-Target Protein Network of SA

Bio-function	Degree	Target	Degree	Target	Degree
Organismal injury and abnormalities	29	TP53	21	CHRM4	9
Cellular growth and proliferation	25	IL1B	20	BARD1	8
Cell death and survival	25	PIGS2	20	FOSB	8
Cellular development	23	NFKBIA	19	KCNH2	7
Molecular transport	23	MAPK1	19	SLC6A3	6
Organismal survival	22	RELA	19	Ppplr15a	3
Cellular movement	21	FOXO3	19	ARFGAP1	2
Small molecule biochemistry	21	DRD2	18	PREPL	1
Cell-co-cell signaling and interaction	20	GSK3B	18	STK33	1
Lipid metabolism	19	MAPK3	18	TDP1	1
Gene expression	19	MITF	17	—	—
Cell cycle	19	BRCA1	16	—	—
Cell morphology	19	OPRM1	15	—	—
Protein synthesis	16	DPP4	15	—	—
Cellular assembly and organization	15	MDM2	14	—	—
DNA replication, recombination, and repair	15	PIPN1	14	—	—
Cell signaling	15	ATXN2	13	—	—
Tumor morphology	14	DRD1	13	—	—
Immune cell trafficking	11	MDM4	11	—	—
Cell mediated immune response	9	IDH1	11	—	—
Post-translational modification	8	CHRM1	10	—	—

Table 6. Degree of Relevant Bio-functions and Targets of SA

Bio-function	Degree	Target	Degree	Target	Degree
Organismal injury and abnormalities	29	TP53	21	CHRM4	9
Cellular growth and proliferation	25	IL1B	20	BARD1	8
Cell death and survival	25	PTGS2	20	FOSB	8
Cellular development	23	NFκBIA	19	KCNH2	7
Molecular transport	23	MAPK1	19	SLC6A3	6
Organismal survival	22	RELA	19	Ppp1r15a	3
Cellular movement	21	FOXO3	19	ARFGAP1	2
Small molecule biochemistry	21	DRD2	18	PREPL	1
Cell-to-cell signaling and interaction	20	GSK3B	18	STK33	1
Lipid metabolism	19	MAPK3	18	TDP1	1
Gene expression	19	MITF	17	——	——
Cell cycle	19	BRCA1	16	——	——
Cell morphology	19	OPRM1	15	——	——
Protein synthesis	16	DPP4	15	——	——
Cellular assembly and organization	15	MDM2	14	——	——
DNA replication, recombination, and repair	15	PTPN1	14	——	——
Cell signaling	15	ATXN2	13	——	——
Tumor morphology	14	DRD1	13	——	——
Immune cell trafficking	11	MDM4	11	——	——
Cell-mediated immune response	9	IDH1	11	——	——
Post-translational modification	6	CHRM1	10	——	——

Table 7. Molecular and Cellular Functions

Name	*P*-value	Molecules (kD)
Gene expression	2.00×10^{-6}–1.44×10^{-17}	19
Cell cycle	3.89×10^{-6}–2.52×10^{-13}	19
Cell death and survival	4.52×10^{-6}–1.64×10^{-12}	25
Lipid metabolism	2.52×10^{-6}–8.45×10^{-12}	19
Small molecule biochemistry	4.52×10^{-6}–8.45×10^{-12}	21

NF-κB family,[17] which contribute to human disease processes, like angiogenesis, notably inflammatory diseases and cancer.[18,19] IκBα inhibitor protein, encoded by NFκBIA, is responsible for nuclear localization of NF-κB in mammalian cells.[20] IκBα could suppress the activation of inflammation by binding to NF-κB and play a major role in circumventing oncogenesis and other diseases due to its missing inhibitory function.[21,22] P38MAPK, ERK, encode by MAPK1, MAPK3 separately, are member of the MAPK super family that can mediate cell proliferation and apoptosis.[23] Abnormal regulation of the MAPK pathways have been reported for a wide range of diseases including cancers,[24] obesity,[25] diabetes,[25] cardiovascular diseases[26,27] and Alzheimer's diseases.[28] TP53 is a tumor suppressor protein[29,30] that has been dubbed the "guardian of the genome" because of its ability to induce senescence, cell cycle arrest or apoptosis when cells are exposed to various forms of stress, including DNA damage.[31,32] DRD2 is an important component of neural network controlling innate immunity in the central nervous system. By influencing alpha-crystallin B expression, DRD2 may modulate inflammatory response and maintain balance of immune state. PTGS2, also colloquially referred to as COX-2 represents a key enzyme in arachidonic acid metabolism. PTGS2 plays a key role in generation of inflammation. High levels of PTGS2 have been detected in many cancers. IL1β is a member of IL 1 family of cytokines. This cytokine is an important mediator of the inflammatory response, and is involved in a variety of cellular activities, including cell proliferation, differentiation, and apoptosis. The induction of PTGS2 by IL1β in the central nervous system is found to contribute to inflammatory pain hypersensitivity. Deep analysis of inflammation relevant targets showed us an important relationship among inflammation, cancer and metabolic diseases.

Besides, cancer and metabolism targets also

indicate the plentiful effects of SA. For example, sinomenine and isosinomenine have a shared target TDP1. TDP1 has been reported to relate to cancer,[33] neuropathy,[34] oxidative stress response and longevity.[35] Inhibition of TDP1 was expected to have broad clinical utility as a single-agent treatment in tumor disease.[36] GSK3B and DPPⅣ are two common target proteins of beta-sitosterol and stigmasterol. GSK3B is a known master regulator for several pathways including neurotrophic factor signaling, neurotransmitter signaling, Wnt signaling, insulin signaling and glycogen synthesis and microtubule dynamics.[37] It is critical in development, metabolism, transcription, cell survival and neuronal functions. GSK3B has been implicated in multiple disorders including Alzheimer's disease, bipolar disorder, cancer, diabetes mellitus and cardiac hypertrophy.[38-40] Inhibitors of DPPⅣ, a key determinant of incretin bioactivity, are used in treating type 2 diabetes mellitus (T2DM). Besides the action on glycemia, DPPⅣ also participates in the regulation of blood pressure[41], development of atherosclerosis,[41] acute myocardial infarction (AMI)[42] and heart failure.[43] DPPⅣ also has interaction with mannose 6-phosphate receptor and promotes endothelial cell transmigration of T cells.[44]

Pathways relevant cancer, intracellular and second messenger, cytokine, cellular stress and injury and cell cycle regulation had higher significance than other categories during our enrichment analysis of SA targets. The top 5 signaling included PI3K/Akt signaling, prostate cancer signaling, MIF regulation of innate immunity, GPCR signaling and ATM signaling.

The PI3K-AKT pathway generates signals regulating a wide range of reactions, in particular events involved in cell survival, cell cycle progression, DNA repair, protein synthesis, glucose metabolism, differentiation, angiogenesis, and cellular migration.[45] Defect regulation of the PI3K-AKT pathway is linked to diseases including cancer, diabetes, and atherosclerosis.[46] The PI3K catalytic isoform, p110β, is activated by a majority of GPCRs.[47]

GPCRs are cell surface proteins of sensory nerves for sensing noxious, irritating, and inflammatory stimulants. GPCRs could also result in MAPK pathway activation, P38MAPK has been shown as vital for GPCR-induced AKT phosphorylation in different cancer cell lines.[48] MAPK pathways are critical to many diseases for which inflammation play an important role, including diabetes, cancer, autoimmune disorders, and atherosclerosis.

MIF, a mediator of innate immunity, promotes host inflammatory responses through induction of pro-inflammatory cytokines, IL-6 and TNF-α. MIF can regulate cellular processes such as T-cell proliferation, counter regulation of the immunosuppressive actions of glucocorticoids (GCs) and suppression of p53-dependent apoptosis.[49,50] MIF activates Src-family tyrosine kinases downstream of extracellular signal regulated kinase (ERK1/2) and p38MAPK,[51] and activates cPLA2 and COX-2, blocking p53-induced apoptosis.[52]

ATM, a member of PI3K-like protein kinases family, is a master regulator of the DNA damage response and it coordinates checkpoint activation, DNA repair, and metabolic changes in response to DNA double-strand breaks and oxidative stress.[53] ATM could activate the transcription factor nuclear factor-κB, which promoted the expression of several anti-apoptotic genes.[54] ATM could also activate and stabilize p53 in response to DNA damage.[55,56]

Through our analysis, all the 5 signaling pathways could be connected and form a complicated network. MAPK pathway is vital for GPCR-induced AKT phosphorylation, coordinating GPCRs and PI3K-AKT pathway. MIF activates MAPK pathway and COX-2 blocking p53-induced apoptosis. ATM, a member of PI3K-like protein kinases family, could also activate and stabilize p53 in response to DNA damage. All the 5 pathways could regulate inflammation, immune and be relevant with cancer and metabolic diseases.

According to disease and bio-function network analysis, core targets and major diseases of SA targets were screened out. There were 23 relevant diseases sharing the common inflammation factor, PTGS2 and IL1β. Considering the fact that critical targets are implicated in inflammation, we speculated that inflammation may be the critical point of all the 23 diseases. Recent study found inflammation was emerging as a central theme not only in diseases caused by microbial pathogens, but also in many chronic conditions including neurological diseases, psychological diseases, metabolic diseases, endocrine diseases and cancer. An increasing number of genetic studies suggested that the

pathogenesis of Parkinson's disease and cancer shared common genes, pathways, and mechanisms. Chronic inflammation is an important link between cancer and Parkinson's disease.[57] The compromised MAPK signaling pathways contribute to the pathology of diverse human diseases including cancer and neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis.[58] Research on psychological disorders also showed a similar result.[59] PI3Ks have pivotal roles in diseases such as cancer, diabetes, primary immune disorders, and inflammation. These enzymes are activated downstream of numerous activating stimuli including G protein-coupled receptors.[60] PI3K/Akt and MAPK signaling may be the shared pathway. According to our study and previous research, we assume that SA could treat inflammation, cancer, neurological, psychological and metablomic diseases through regulating PI3K/Akt, MAPK and GPCR pathways.

In the different view of target, pathway, disease and bio-function, we found inflammation was a central theme in many of the chronic conditions including neurological diseases, psychological diseases, metabolic diseases and cancer. SA could be used not only as an anti-inflammatory agent, but also for the treatment of cancers, neurological diseases, psychological disorders and metabolic diseases.

Conflict of Interest

The authors declare that they have no conflict of interests.

Author Contributions

All authors participated in the review of the manuscript. Liu L and Zheng G conceived, designed and performed the study; LI YY performed the study; Li YY and Zheng G analyzed the data; Li YY and Zheng G wrote the paper.

Electronic Supplementary Material: Supplementary materials (Appendixes 1–6) are available in the online version of this article at http://dx.doi.org/10.1007/s11655-017-2796-y.

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