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Research Article

Study of TCM Medication Rules against Aging based on Network Pharmacology and Data Mining

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Abstract

Background and Objective: Aging and age-related diseases have become a global concern. There may be a lot of room for the development of TRADITIONAL CHINESE MEDICINE (TCM) in the future. However, it has yet to fully form a system. Therefore, this study aims to explore the material basis and rules of TCM anti-aging based on network pharmacology and data mining.

Methods: In this study, potential targets were searched using the HAGR and Aging Atlas databases, followed by compounds and traditional Chinese herbs from the TCMSP database. On this basis, the target-compound network, compound-Chinese herb network and target-compound-herb network were constructed and visualized using Cytoscape 3.7.2. These networks were used to identify potential targets, compounds and herbs. Finally, the rules of Chinese herbs were summarized by the analysis of properties, flavors, and meridian tropism.

Results: A total of 25 potential targets, 210 candidate small compounds and 135 kinds of herbs were obtained. The top five targets included PTGS2, AR, ESR1, GSK3B and CCNA2, and diosgenin, formononetin, tanshinone IIA, phaseolin and phaseollidin were identified as the top 5 compounds. In addition, five core herbs (Huluba, Tiandong, Danshen, Kushen and Shandougen) were confirmed. Moreover, according to the frequency statistics, the Chinese herbs that interfere with aging were mainly bitter, acrid, and sweet, had both cold and warm properties, and belonged to the liver and lung meridians.

Conclusion: We explored the potential mechanisms of TCM anti-aging by using network pharmacology and summarized the general rules of traditional Chinese herbs medicine. TCM has great potential in the treatment of aging, and this study provides a new approach and idea for the clinical application of integrated Chinese and Western medicine in the treatment of aging.

Introduction

The proportion of people aged 65 and over has been rising steadily in both developed and developing countries. There is no doubt that the prevalence of the older populations has led to a global burden of age-related disorders, posing a serious threat to human health and reducing the quality of life for elderly people. As a result, health care costs have become a huge burden for both society and aging populations, and it is essential to explore the mechanisms of aging and counter the occurrence of aging-related diseases.

Aging, unlike sickness, is a progressive time-dependent process that can be divided into pathological and physiological aging. It carries from person to person and can be a complex biological process characterized by a decline in tissue and organ function, structural degradation, and reduced adaptability and resistance, all of which is closely contributed to most chronic diseases and increased morbidity and mortality [1,2], such as diabetes, hypertension, cardiovascular disease, cancer, and neurodegenerative disease. The search for effective strategies to improve normal lifespan has been an influential goal of aging research for many years. Until now, pharmacological interven-

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tions may have been an effective way to improve health span and delay the onset of age-related diseases, and numerous compounds with anti-aging activity have been found in yeast, worms, fruit flies and mice. While treatments for age-related diseases have been extensively studied and progress has been made, Traditional Chinese Medicine (TCM) is particularly well-suited for drug discovery for the long-term treatment of age-related diseases.

TCM is a treasure of natural compounds used in the treatment of a variety of diseases. It has a wide range of sources, a large number of effective compounds, stable compound structures and security. In addition, TCM has the combined advantages of multi-target and multi-effect for diseases with complex pathogenesis. Therefore, TCM has great significance in preventing and improving the clinical symptoms and severity of age-related diseases, such as Ginseng, Radix Astragali and Gynostemma pentaphyllum are recognized by the "nourishing of life" and their role as anti-aging psychotherapeutic is gaining attention increasingly [3].

Network pharmacology is a combination of systems pharmacology, multidirectional pharmacology, data mining and other multi-disciplines, which is used to analyze and predict the pharmacological mechanisms of drugs by constructing a "drug-target-disease" network, and it is suitable for the study of traditional Chinese medicine and compounds. Therefore, it is currently widely used in the mechanism study of the role of TCM and in the development of new drug compounds.

In this study, through the method of network pharmacology, aging-related targets were obtained as the breakthrough points and matched to the corresponding compounds in Chinese medicine, and further establish the "target-compound-herb" network, in order to analyze the relationship. In addition, we evaluated the mechanisms of action and general rules of TCM. Our findings provide a theoretical foundation for the follow-up exploration and provide ideas for clinical research on TCM, therapeutic strategies and the integration of TCM and Western medicine in aging management. A flow chart of this study is shown in (Figure 1).

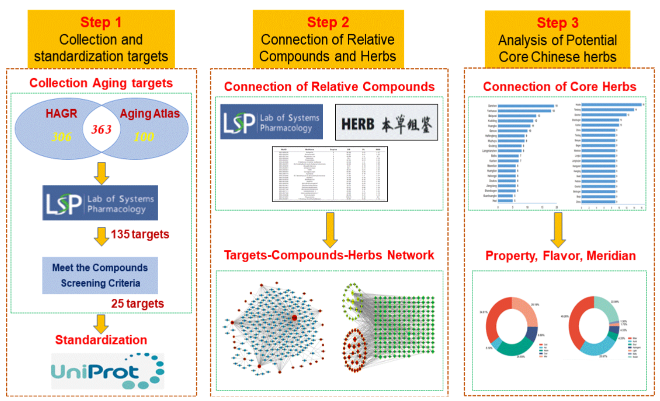

Figure 1: Research process.

Materials and Methods

Screening of Aging-Related Target Genes

The targets related to the mechanism of aging were obtained from HAGR [4] (https://www.genomics.senescence.info/) and Aging Atlas [5] (https://ngdc.cncb.ac.cn/databases) databases. The full name of each target is determined in the UniProt protein database [6] (https://www.uniprot.org/).

Screening Alternative Compounds and "Target-Compound" Network Construction

Compounds that have effects on age-related targets were obtained by using the Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMSP) [7] (https://tcmspw.com/). Candidate compounds were screened according to pharmacokinetic parameters (ADME) and Lipinski's rule [8]. Specific screening criteria were oral efficacy (OB) ≥ 30%, drug similarity (DL) ≥ 0.18 [9], drug half-life > 4 h, topological polar surface area < 140 angstroms [10], number of rotatable bonds ≤ 10 [11] and molecular weight ≤ 500 Da. Considering that the parameters provided by the TCMSP platform are predicted by the computer, some of the data may not be consistent with the actual situation. After the preliminary screening, the deleted compounds were checked one by one to complement the relevant active compounds. The modified compound was used as a candidate compound. Together with these compounds, potential targets were imported into Cytoscape 3.7.2 software [12] to build a "target-compound" network. The degrees of the network nodes were then calculated and based on core targets, compounds and herbs were identified.

Matching Herb and Target-Compound-Herb Network Construction

The herbs containing the candidate compounds were collected on TCMSP to construct a "compound-herb" network. Combine the "target-compound" network and "compound-herb" network through function module in Cytoscape 3.7.2 to build the "target-compound-herb" network. Then, the key nodes were determined according to the degree of each node in the network, and the efficacy intensity of the Chinese medicine and compound treatment for aging was evaluated.

Analyzing Characteristics of the Candidate Herbs

With the frequency analysis, the anti-aging rules of the candidate herbs were summarized. The features studied include properties, flavors, and meridional tropism. Considering the heterogeneity of characteristic information from different sources, the criteria adopted in this study were Chinese Pharmacopoeia (2015) [13], Chinese Pharmacy (the textbook of the 13th Five-Year Plan Period) [14] and Chinese Dictionary of Clinical Medicine [15]. Herbs were removed due to a lack of relevant information.

Results

Results of Target Acquisition

In this study, 306 and 100 age-related targets were obtained from HAGR and Aging Atlas databases, respectively. The targets were complemented with the Herb database, and a total of 363 targets were subsequently obtained after the duplicate values and 135 targets were successfully obtained in TCMSP database. Finally, 25 targets were matched to compounds that met both the ADME and Lipinski screening criteria. These targets were standardized in the Uni Prot database and defined as potential targets for herbs anti-aging, as shown in (Table 1).

Table 1: Information of potential aging targets.

ID	Gene Symbol	Uniport ID	Protein Name
1	PTGS2	P35354	Prostaglandin G/H synthase 2
2	AR	P10275	Androgen receptor
3	ESR1	P03372	Estrogen receptor
4	GSK3B	P49841	Glycogen synthase kinase-3 beta
5	CCNA2	P20248	Cyclin-A2
6	MAPK14	Q16539	Mitogen-activated protein kinase 14
7	NR3C1	P04150	Glucocorticoid receptor
8	TNF	P01375	Tumor necrosis factor
9	IL6	P05231	Interleukin-6
10	TP53	P04637	Cellular tumor antigen p53
11	CDKN1A	P38936	Cyclin-dependent kinase inhibitor 1
12	MYC	P01106	Myc proto-oncogene protein
13	BCL2	P10415	Apoptosis regulator Bcl-2
14	BCL2L1	Q07817	Bcl-2-like protein 1
15	AKT1	P31749	RAC-alpha serine/threonine-protein kinase
16	HIF1A	Q16665	Hypoxia-inducible factor 1-alpha
17	VEGFA	P15692	Vascular endothelial growth factor A
18	CAT	P04040	Catalase
19	BAX	Q07812	Apoptosis regulator BAX
20	SOD1	P00441	Superoxide dismutase
21	CREB1	P16220	Cyclic AMP-responsive element-binding protein 1
22	NFKBIA	P25963	NF-kappa-B inhibitor alpha
23	MTOR	P42345	Serine/threonine-protein kinase mTOR
24	PPARG	P37231	Peroxisome proliferator-activated receptor gamma
25	TRPV1	8NER1	Transient receptor protential cation channel subfamily V member 1

Candidate Compound Acquisition and Target-Compound Network Construction

Twenty-five potential targets were matched with 7,501 small molecule compounds in the TCMSP database, among which 210 candidate compounds met the ADME and Lipinski criteria (Table 2). (Figure 2) shows the target-compound network constructed with 235 nodes and 455 edges of potential targets and candidate compounds. As shown in the figure, the red nodes represent the target points, the blue nodes represent the compounds, the edge represents the relationship between two adjacent nodes, and the degree represents the number of edges connected by the node. In addition, the size of the graph indicates the degree value of the node. The larger the graph, the more significant the effect on the network. The top 5 target proteins included PTGS2, AR, ESR1, GSK3B and CCNA2, and the top 5 compounds were diosgenin, formononetin, tanshinone IIA, phaseolin and phaseollidin. These findings suggest that the top 5 targets were involved in anti-aging therapies, and that these compounds may interact with related target proteins with high anti-aging activity.

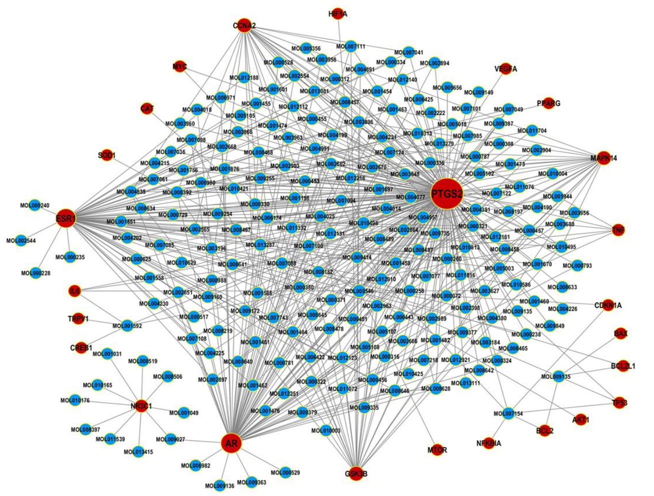

Figure 2: The target-compound network. The red nodes represent the target points; the blue nodes represent the compounds.

Table 2: Information of candidate core compounds (degree ≥ 5).

MolID	MolName	Degree	OB	DL	BBB
MOL000546	diosgenin	9	80.88	0.81	0.27
MOL000392	formononetin	7	69.67	0.21	0.02
MOL007154	tanshinone iia	6	49.89	0.4	0.7
MOL000456	Phaseolin	6	78.2	0.73	0.39
MOL000457	Phaseollidin	6	52.04	0.53	0.25
MOL003896	7-Methoxy-2-methyl isoflavone	6	42.56	0.2	0.56
MOL004391	8-(3-methylbut-2-enyl)-2-phenyl-chromone	6	48.54	0.25	0.99
MOL004835	Glypallichalcone	6	61.6	0.19	0.23
MOL004891	shinpterocarpin	6	80.3	0.73	0.68
MOL004957	HMO	6	38.37	0.21	0.25
MOL005003	Licoagrocarpin	6	58.81	0.58	0.61
MOL006174	Xyloidone	6	31.61	0.18	0.47
MOL010495	6,7-dimethoxy-2-(2-phenylethyl)chromone	6	31.93	0.3	0.37
MOL010496	DMPEC	6	32.38	0.39	0.18
MOL012910	Bianfugecine	6	36.08	0.42	0.29
MOL001592	piperine	5	42.52	0.23	0.62
MOL000258	dehydrodiisoeugenol	5	56.84	0.29	0.52

MOL001461	Dihydrochelerythrine	5	32.73	0.81	0.61
MOL001463	Dihydrosanguinarine	5	59.31	0.86	0.49
MOL007100	dihydrotanshinlactone	5	38.68	0.32	0.81
MOL007111	Isotanshinone II	5	49.92	0.4	0.45
MOL007124	neocryptotanshinone ii	5	39.46	0.23	0.16
MOL010586	Formononetin	5	66.39	0.21	0.12
MOL013287	Physovenine	5	106.21	0.19	0.2
MOL004991	7-Acetoxy-2-methylisoflavone	5	38.92	0.26	0.16

Herb Acquisition and Target-Compound-Herb Network Construction

A total of 355 Chinese herbal medicines matching 210 candidate compounds were screened from TCMSP database, of which only 1 of which was not included in the Chinese Pharmacopoeia (2015), Chinese Pharmacy (“Thirteenth Five-Year Plan” textbook), and Chinese Dictionary of Clinical Medicine. After deleting duplicated values, 135 Chinese herbs were eventually obtained.

To further understand the relationship between the potential targets, compounds, and traditional Chinese medicine in aging treatment, Chinese herbs with degree greater than 3 were selected to generate the target-compound-herb network, as shown in (Figure 3). In the figure, green circle nodes represent compounds, yellow quadrilateral nodes represent potential targets, and red diamond nodes represent Chinese herbs. Moreover, the size of each node was positively correlated with the degree value, indicating that the effect is more significant in the network. As can be seen in Figure 4, the top 5 herb nodes with the highest degree were Danshen, Yanhusuo, Baiqucai, Kudiding and Huangbo containing 19, 18, 13, 12 and 11 candidate compounds, respectively. The herb targets were collected by bridging of candidate compounds. The results showed that Huluba, Tiandong, Danshen, Kushen and Shandougen contained the most targets, which were 16, 14, 12, 10 and 10, respectively). It can be inferred that these herbs had the strongest anti-aging regulation effect among the 135 herbs.

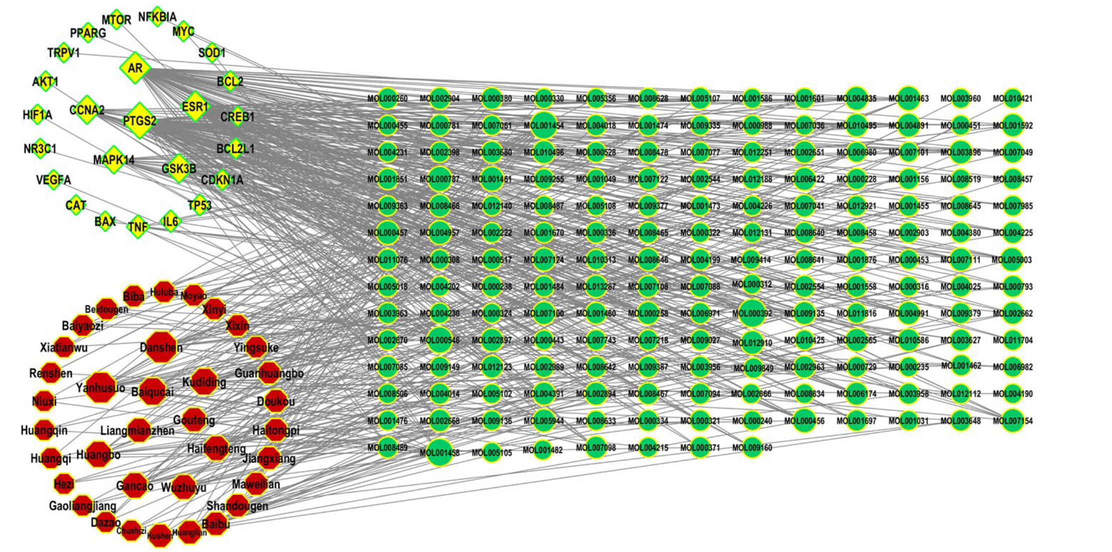

Figure 3: **The target-compound-traditional Chinese medicine network (degree ≥3)**. The green circle nodes represent the compounds, the yellow quadrilateral nodes represent the potential targets, and the red diamond nodes represent the traditional Chinese herbs, respectively.

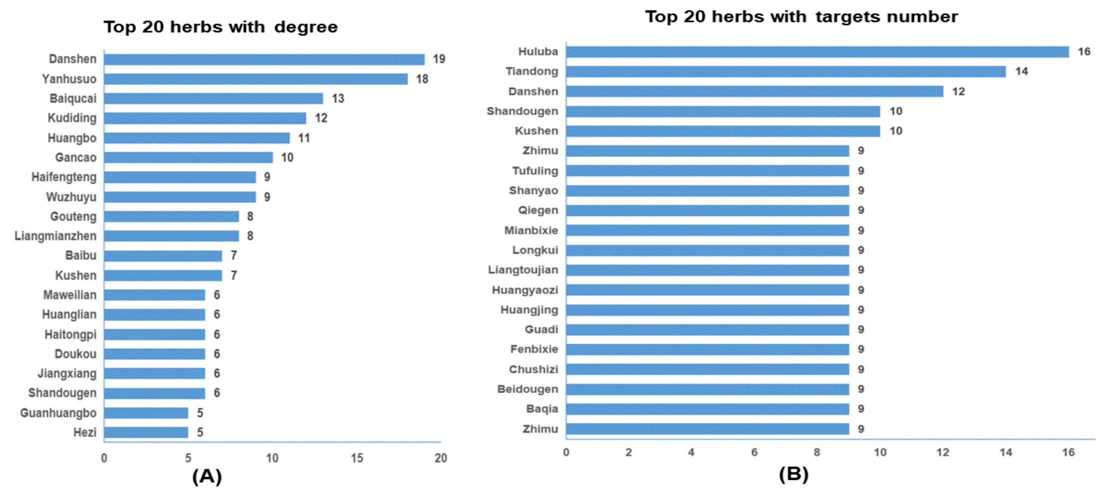

Figure 4: Distribution of candidate compounds and targets in herbs.

Properties, Tastes, and Meridian Tropism of Herbs

To analyze the information of properties, tastes, and meridian tropism of the 135 traditional Chinese herbs, a statistical analysis of frequency using the Excel program showed that bitter (93), acrid (60) and sweet (51) ranked highest in terms of nature. In addition, the proportion of cold (34.81%) and warm (25.93%) herbs was the highest. The results of frequency statistical analysis were shown in (Figure 5 (A-B)).

In terms of meridian tropism, among the 135 Chinese herbal medicines, the liver meridian accounted for 19.42%, the lung meridian accounted for 17.97%, the spleen meridian accounted for 14.78%, the kidney meridian accounted for 13.62%, and the stomach meridian accounted for 11.30%. It can be seen that anti-aging treatment may be closely related to liver, lung, spleen, kidney and stomach meridian, as shown in (Figure 5 (C)).

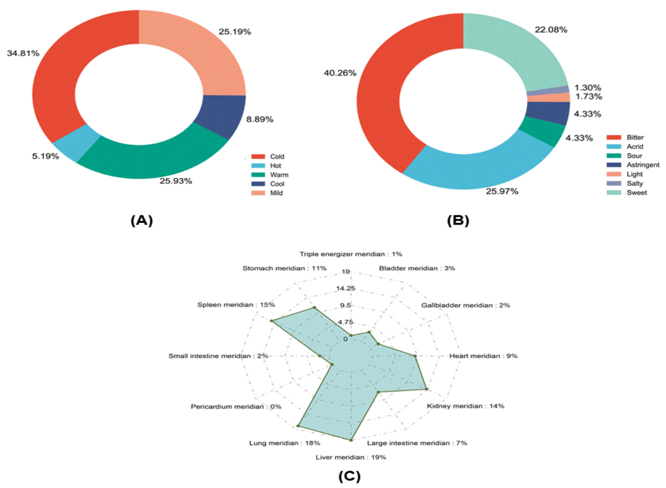

Figure 5: Information on Chinese medicine herbs. (A) nature; **(B)** flavour; **(C)** meridian.

Discussion

Aging is an irreversible biological process that manifests itself mainly through functional decline. With the development of the economy, aging and age-related diseases, including cardiovascular and cerebrovascular diseases, have become crucial health problems [16]. After thousands of years of clinical practice in China, Traditional Chinese Medicine (TCM) has accumulated a large number of valuable experiences. With its multi-component, multi-target and multi-functionality, TCM has demonstrated unique advantages in the prevention and treatment of age-related diseases. As a result, TCM is used as a complementary therapy to delay aging. However, systematic studies of TCM interventions in aging have been inadequate. It is of great clinical importance to study the mechanisms of TCM intervention in aging and develop related drug preparations based on this.

Targets

In this study, 6 core targets (PTGS2, AR, ESR1, GSK3B, CCNA2 and MAPK14) were identified from the target-compound-herb network. It is worth mentioning that PTGS2 is the most remarkable with a degree of 190. PTGS2, is also known as COX-2, an enzyme inhibited by nonsteroidal anti-inflammatory drugs such as aspirin, which is associated with prognosis in patients with colorectal cancer [17]. Besides, activated PTGS2 can produce Prostaglandin E2 (PGE2), which acts on a number of cell signaling pathways involving cell proliferation, angiogenesis, apoptosis and immunosuppression which could increase tumor progression.

Compound

The core compounds obtained in this study included diosgenin, formononetin, tanshinone IIA and phaseolinz. Diosgenin is a naturally occurring steroidal saponin found in a variety of plants, including dioscorea species, fenugreek and costus speciosus. Diosgenin has many biological activities such as anticancer [18-21], antiviral [22] and anti-inflammatory [23]. Diosgenin has been recognized as the most potent component of yam, and according to traditional Chinese medicine theories, it is believed to improve ovarian function in women. Researchers have investigated that diosgenin could counteract age-associated ovarian dysfunction in a natural aging mice model [24], and provide neuroprotective effects for prevention of the D-galactose-induced aging brain by suppressing neuronal Fas-dependent and mitochondria-dependent apoptotic pathways and enhancing the Bcl-2 family associated pro-survival and IGF-1-PI3K-AKT survival pathways.

Formonetin, the principal ingredient in Radix Astragali, has long been used in traditional Chinese medicine to treat age-related diseases. Several studies have reported that formononetin has numerous pharmacological properties [25-26], including anti-tumor, anti-inflammatory, anti-atherosclerosis, anti-oxidant, and selective neuroprotective effects. Huang et al. demonstrated formononetin was able to alleviate I/R (ischemia/reperfusion)-induced cellular apoptosis in aged cells by facilitating autophagy [27], Fei et al. found formononetin could significantly improve learning and memory ability. Moreover, FMN treatment alleviated ultra structural changes in hippocampal vascular endothelial cells [28].

Tanshinone IIA (Tan IIA) is one of the major therapeutic components of Salvia miltiorrhiza Bunge, which is popularly known as Danshen and widely used in China and Southeast Asian countries for many centuries. Modern pharmacological research showed that Tan IIA had many effective activities such as cardioprotective, neuroprotective, renoprotective, hepatoprotective and it has been widely used to treat aging-related diseases such as Myocardial Infarction (MI), stroke, Alzheimer's disease, Parkinson's disease and other conditions. Some reports have shown that Tan IIA can inhibit ROS-induced oxidative stress and attenuate vascular inflammation [29]. Furthermore, a few clinical trials have been perused to evaluate the beneficial effects of tanshinone in humans. The above effects lead us to speculate that Tanshinone may play an influential role in anti-aging and cardiovascular and cerebrovascular diseases.

Herbs

The core herbs obtained in this study include Huluba, Tiandong, Danshen, Kushen and Shandougen. Fenugreek has been a traditionally well-used medicinal plant in Asian countries for centuries. According to traditional Chinese medicine theory, fenugreek, which is bitter in taste and warm in nature, belongs to the meridian of the kidney, and it has the effect of warming and toning the kidney, dissipating cold and relieving pain. Modern pharmacological studies have shown that it has antioxidant, antidiabetic, anticarcinogenic, hypocholesterolemic and immunological activities [30]. In recent decades, many of the health benefits of fenugreek have been clinically and preclinically validated. Trigonelline is the main alkaloid with bioactivity presented in fenugreek, which is reported to have neuroprotective [31], anti-inflammatory [32], anti-oxidant [33], anti-degranulation [34], and anti-carcinogenic effects [35]. A previous study has reported that trigonelline at different concentrations could prolong the healthy lifespan, enhance the locomotor ability and reduce the accumulation of lipofuscin in the body in C. elegans. Moreover, trigonelline was also able to delay the progression of age-related diseases in C. elegans models of AD, PD, and HD [36].

Tiandong, a popular traditional Chinese medicine, is sweet in taste and cold in nature. It belongs to the lung and stomach meridian and mainly treats the syndrome of lung and stomach yin deficiency and kidney yin deficiency. Modern pharmacological studies have confirmed that tiandong can be used to treat a variety of diseases, including age-related conditions. Therefore, Xiong et al. [37] investigated the biochemical indicators related to aging in mouse brains and livers. Similarly, Lei and colleagues [38] explained the anti-aging proprieties in the D-galactose-induced mouse aging model.

Danshen is regarded as an important herb for “activating circulation and dispersing stasis or sludging of blood” with light smell, lightly bitter and astringent taste in traditional Chinese medicine. A total of 201 compounds from Danshen have been reported, which have proved various pharmacological activities, including anti-inflammation, anti-oxidation, anti-tumor, anti-atherogenesis, and anti-diabetes. In recent years, Danshen has been widely applied in studies and clinics. The different dosage forms of Danshen such as tablets, capsules, granules, oral liquid and injections have become effective methods for treating various human diseases. Meanwhile, Fufang Danshen tablet and dripping pill have been officially listed in Chinese Pharmacopoeia (2020). In the anti-aging aspect, Hou et al. [39] selected 24-month-old guinea pigs as the aging model and fed them with different doses (75, 100, 150 mg/kg/day) of Danshen extract for 28 days continuously, the study was surprised to find that the blood viscosity and viscoelasticity were significantly improved at the 150 mg/kg/day dose and the aging phenotype was reduced to a certain extent.

Actual Property, Flavor, and Meridian

Traditional Chinese medicine for anti-aging is mainly bitter, acrid and sweet, and its medicinal properties are mainly cold and warm, belonging to the liver, lung, spleen and kidney meridians. Pharmacological studies have shown that most of the bitter and warm herbs contain volatile oil, while the bitter and cold drugs contain more alkaloids and glycosides, which have anti-inflammatory and anti-oxidant effects. Chen et al. [40] detected the distribution of TCM active components in body and confirmed that was basically in line with the theory of traditional Chinese. For example, heart meridian drugs contain terpenoids, flavonoids and volatile oils, which have the effect of dilating coronary arteries and anti-arrhythmia, while lung meridian herbs have anti-inflammatory and anti-viral effects. Therefore, in exploring the relationship between TCM and anti-aging effects, we should fully integrate taste and meridian tropism to explore the potential value of TCM.

In summary, the aforementioned herbs may have anti-aging potential, which would provide an alternative to related trials of TCM for the treatment of aging. Moreover, information on herbal flavors and meridians can serve as a foundation for future theoretical discussions and research on TCM on aging. At the same time, the obtained core compounds and targets can provide evidence for prescription exploration in integrating traditional Chinese and Western medicine for the treatment of aging, which may be an alternative strategy in future studies.

In this study, network pharmacology was used to obtain herbs and compounds with the potential to treat aging from a large number of TCM practitioners, and then data mining was performed according to TCM theory, which not only saves time and economic costs, but also improves the efficiency of research. Despite the insightful findings, there are still some limitations: Firstly, we focus on the relationship between the targets, the ingredients and the drugs, but the content of the ingredients and the efficacy of TCM have not been thoroughly discussed. Secondly, drugs were selected from existing databases or literature, and new drugs on the market are not sufficiently included. Thirdly, the study is limited to a single TCM, except for TCM compounds that have been clinically applied. Thus, further research is needed and we will continue to follow up related advances in the future.

Conclusion

In conclusion, based on a network pharmacology approach, we constructed a target-compound-herb network using aging-related targets from multiple databases and matched compounds and herbs from the TCMSP platform. The core compounds (diosgenin, formononetin, tanshinone IIA, phaseolinz) and potential Chinese herbs (Huluba, Tiandong, Danshen, Kushen) were identified from the network. In addition, most of the candidate herbs were bitter, acrid, and warm, and belonged to the liver, lung, and spleen meridians. Therefore, these conclusions provide a reference for the prescription of combining TCM and Western medicine to treat aging in an advanced manner, and their mechanism of action should be further explored.

Author Contributions

Data curation: Li Dong, Li Wang, Bo Li.

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Investigation: Wei Meng.

Methodology: Mengnan Liu, Fei Wang.

Validation: Huairong Luo.

Writing- original draft: Fei Wang.

Writing-review & editing: Li Dong, Li Wang, Bo Li.

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