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To Investigate the Therapeutic Effect and Mechanism of "Ginger-Mume" Based on Bibliometrics and Network Pharmacology

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Abstract: In this study, bibliometrics and network pharmacology were used to explore the effect and mechanism of Ginger and Fructus Mume in the field of disease treatment. The research method is to construct a global distribution network of literatures related to "Ginger-Mume" by bibliometrix using the R package; the chemical composition and targets of "Ginger-Mume" are searched using TCMSP, BATMAN-TCM, Swiss, SEA, UniProt and other databases, and the disease targets are searched using the CTD database, followed by GO analysis and KEGG pathway enrichment analysis using the DAVID database. The results showed that a total of 34 eligible compounds, 525 targets, and 29 diseases were screened. GO analysis showed that biological function was extremely closely related to mitochondria. The most relevant pathway in KEGG analysis was the chemical carcinogenic risk factor-reactive oxygen species pathway. The results showed that "Ginger-Mume" through multi-component, multi-target, multi-way treatment of a variety of diseases, especially diabetes, cancer, genitourinary system, digestive system, cardiovascular system and other diseases have a significant effect, pointing out the direction for future drug research.

1. Introduction

Zingiber officinale Roscoe is a fresh rhizome of *Zingiber officinale* Rosc., which is lukewarm in nature, pungent in taste, and belongs to the lung meridian, spleen meridian, and stomach meridian, and has the effects of relieving exterior and dispersing cold, warming and stopping vomiting, and eliminating phlegm and relieving cough. "Famous Doctor Bie Lu": "Taste pungent, lukewarm... typhoid headache, nasal congestion, cough against the gas, stop vomiting... long service Xiaozhi Shaozhi, sad gas."; *Mume Fructus* is the dried nearly ripe fruit of *Prunus mume* (Sieb.) Sieb.etZucc.a member of the Rosaceae family, which is flat in nature, sour in taste, and belongs to the liver, spleen, lung, and large intestine meridians. It has the effects of converging lung, astringent

intestines, increasing body fluid, and ascaris. "Materia Medica Mengquan": "Convergent lung qi, thirst quencher in addition to annoyance. Because astringent large intestine, forbidden dysentery antidiarrheal … mole can be detached, insect pain can be safe." Ginger-Mume can make a total of decoction, "Experience Formula" records Ginger Fructus Mume Yin, with the stomach to stop vomiting, thirst quencher effect, attending to liver and stomach disharmony pregnancy vomiting. "Wan Shi from the radical cure": "Ginger Wu Mei Yin... This side and stomach stop vomiting, thirst quencher has a good effect."

Bibliometrics is a powerful tool to evaluate scientific development by quantitatively analyzing academic literature and revealing the regularity and development trend of scientific research activities[1]. Network pharmacology is based on the interaction between drugs, targets and diseases, using network analysis method, from the overall analysis of the basic characteristics of traditional Chinese medicine, the study of drug-disease interaction and mechanism of action, its research ideas are consistent with the concept of traditional Chinese medicine treatment[2]. In this paper, bibliometrics and network pharmacology will be used to systematically analyze and study the disease fields treated by "Ginger-Mume" and their pharmacological mechanisms, providing a direction for the future development of drugs.

2. Materials and Methods

2.1. Bibliometric Studies

The R package "bibliometrix" (version 4.3.0) was used (*https://www.bibliometrix.org*), bibliometric analysis was carried out to construct a global distribution network of literature related to "Ginger-Mume", and keywords and co-occurrence networks were selected for data mining and analysis, respectively. Biblioshiny command was used for co-occurrence network synthesis and thematic graph analysis.

2.2. Network Pharmacology Studies

2.2.1. Chemical composition screening

Through the TCMSP database (*https://tcmspw.com/tcmsp.php*) The chemical constituents of Ginger-Mume were searched, and the eligible chemical constituents were selected by using drug-like DL ≥ 0.18 as the screening condition for retrieval.

2.2.2. Network construction and analysis

Using the database of BATMAN-TCM (*http://bionet.ncpsb.org/batman-tcm/*), Swiss Target Prediction (*http://swisstargetprediction.ch/*), SEA (*https://sea.bkslab.org/*) searches the eligible chemical components retrieved from TCMSP for targets. Using the database of CTD (*http://ctdbase.org/*), the searches the retrieved targets for related diseases, and uses cytoscape 3.10.0 to construct "component-target network diagram" and "target-disease network diagram". The retrieved targets were imported into the String database to construct protein interaction networks (PPI), and the top 10 hub proteins scoring in the PPI network were calculated using the cytohubba plug-in of cytoscape 3.10.0.

2.2.3. GO functional enrichment and KEGG pathway enrichment analysis

In order to explore and analyze the biological effects of potential targets and the role of targets in signaling pathways, GO functional enrichment analysis as well as KEGG pathway enrichment

analysis of target proteins are required, specifically through the DAVID database for data analysis, and using Microletter (*http://www.bioinformatics.com.cn/*) tool drawing.

3. Results

3.1. Bibliometric Studies

Through co-occurrence and thematic analysis of the keywords "Ginger-Mume", it was found that the hotspots of drug research were diabetes, cancer, obesity, anti-inflammation, and anti-oxidation, as shown in Figure 1 and Figure 2.

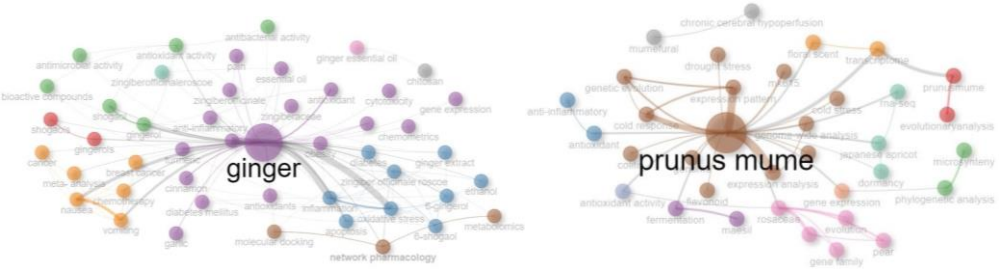

Figure 1: Network diagram of keyword co-occurrence analysis of "Ginger-Mume"

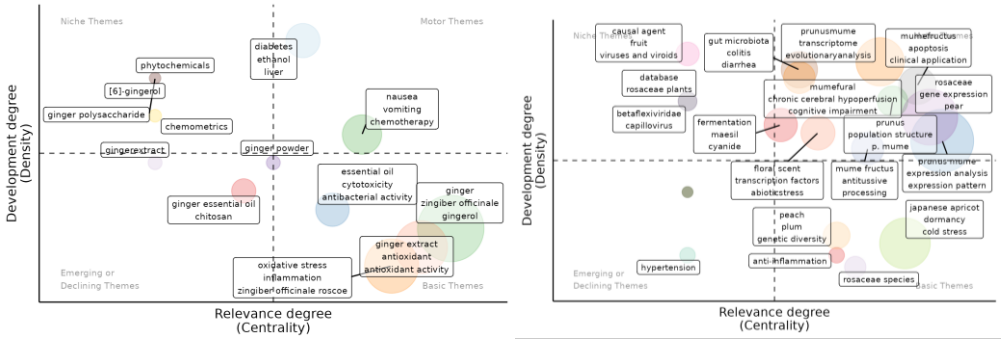

Figure 2: Thematic Analysis Diagram of Key Words of "Ginger-Mume"

3.2. Network Pharmacology Studies

3.2.1. Compound Acquisition and Screening

By TCMSP search, 265 compounds were obtained from medicinal Ginger and 40 compounds were obtained from Fructus Mume. Among them, there were 17 eligible active ingredients of Ginger and 19 active ingredients of Fructus Mume, which contained two identical active ingredients, β-sitosterol and stigmasterol.

3.2.2. Obtain target results and component-target relationship

Through searching and sorting, a total of 525 targets were obtained from 34 compounds, of which the degree values of 8-gingerdione, 8-shogaol, Methyl arachidonate, and Dihydrocapsaicin were 211, 200, 182, and 168, respectively, and the larger the degree value, the more interaction relationships, and in this study, the above four compounds played a central hub role in the network. Degree values of beta-sitosterol, a compound co-existing in the components of Ginger and Fructus Mume, add up to 273, indicating that these two compounds have a wide range of pharmacological effects in drug compatibility, and they may be compounds that play a key pharmacological role in "Ginger-Mume". There are a total of 525 targets intersected by Ginger and Fructus Mume, and the

combination of the two will produce synergistic effects.

3.2.3. Build target-disease network diagram

After retrieval, there were 11 categories of diseases related to the obtained targets, including 29 diseases, of which 524 targets were related to genitourinary system diseases and 518 targets were related to digestive system diseases, of which 524 targets were related to renal diseases in genitourinary system diseases, 517 targets were related to liver tumors in digestive system diseases, and 449 targets were related to liver injury, suggesting that the component targets of "Ginger-Mume" are closely related to liver and kidney diseases. Among the disease-related targets, Degree values of TNF (tumor necrosis factor), MAPK14 (mitogen-activated protein kinase 14), TP53 (tumor protein p53), and PTGS2 (prostaglandin-endoperoxide synthase 2) ranked top, 29, 28, 27, and 27, respectively; the target-disease network diagram is shown in Figure 3, and the purple quadrangle in the figure represents the disease and the green ellipse represents the target.

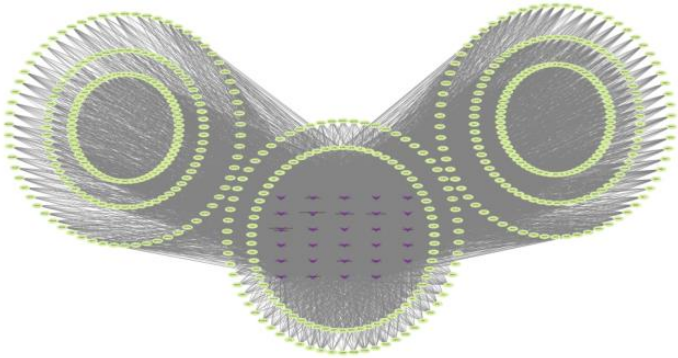

Figure 3: Target-Disease Network Diagram

3.2.4. Construction of protein interaction network and extraction of hub protein

Target-corresponding genes were entered into the String database, and a total of 520 nodes and 8958 edges were obtained. The interaction score ≥ 0.9 was selected to obtain the PPI network. The hub protein was obtained using the cytohubba plug-in in cytoscape 3.10.0 and the top ten hub proteins were taken, as detailed in Figure 4.

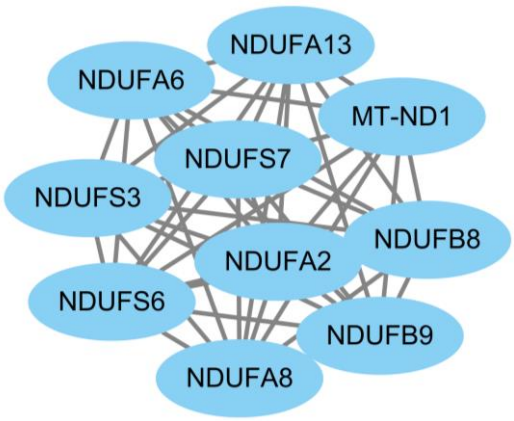

Figure 4: Hub protein in PPI network

3.2.5. GO functional enrichment analysis and KEGG pathway enrichment analysis

GO enrichment analysis showed that biological processes (BP) was closely related to mitochondrial ATP synthesis coupled transport complex I, cellular components (CC) was most

closely related to mitochondrial respiratory chain complex I, and molecular functions (MF) was most closely related to NADH dehydrogenase (ubiquinone) activity. KEGG pathway analysis involved 177 pathways, of which the highest correlation was Chemical carcinogenesis-reacive orygen species, followed by Retrograde endocannabinoid signaling, and Diabetic cardiomyopathy ranked third. See Figure 5 and Figure 6.

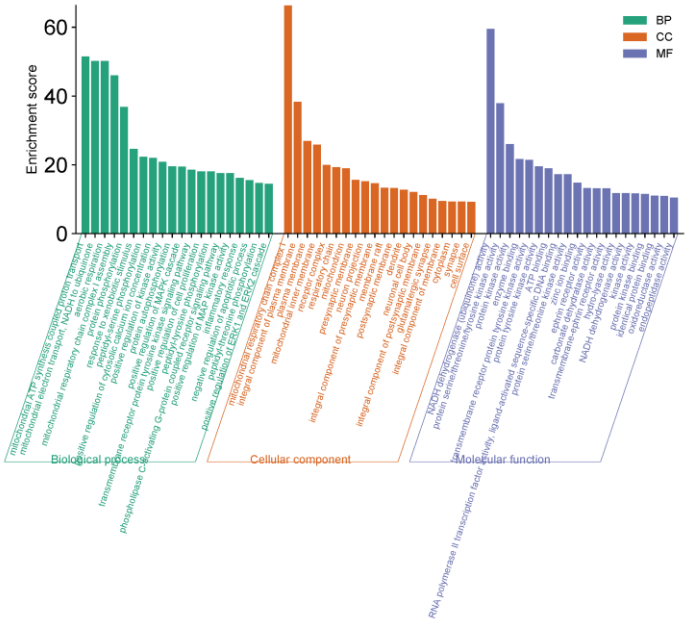

Figure 5: GO Enrichment Analysis 3-in-1 Histogram

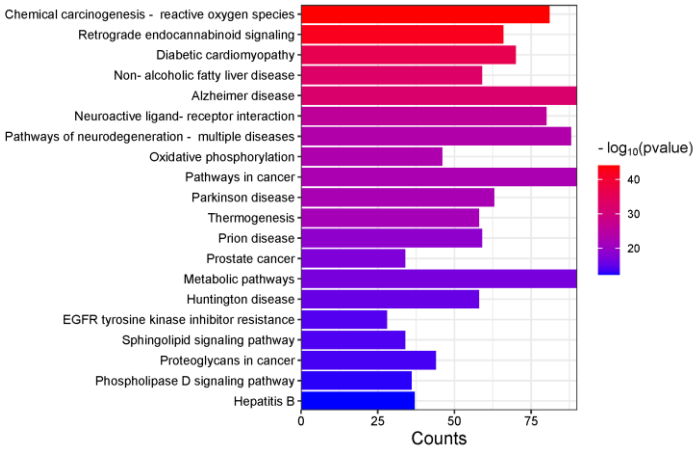

Figure 6: KEGG enrichment analysis plot

4. Conclusions

In this study, network pharmacology was used to investigate the diseases associated with "Ginger-Mume" and its pharmacological mechanism of action. Through the study, a total of 34 compounds with good medicinal properties were obtained, which were associated with 525 target genes and involved 29 diseases, of which they were most closely related to genitourinary system diseases, digestive system diseases, cancer, and cardiovascular diseases.Among the active ingredients of "Ginger-Mume", 8-curcumin, the most important active compound, has been demonstrated to have good anti-inflammatory and anticancer properties[3].In this study, β-sitosterol and stigmasterol were found to be the common active components of "Ginger-Mume".

Phytosteroids are bioactive compounds naturally present in the plasma membrane of herbaceous plants, and their chemical composition is similar to that of animal plasma membrane cholesterol[4], which can be found in almost all fat-rich plant diets. β-Sitosterol is one of the important plant sterols and has a variety of biological activities, and has been shown to have a variety of physiological activities in various in vivo and in vitro studies, such as antioxidant, central nervous system activities, lipid-lowering effects, anti-diabetic, anti-inflammatory and analgesic effects, anti-cancer and immunomodulation, protective effects of pulmonary fibrosis, wound healing effects, and antiviral and COVID-19 activities[5]. Stigmasterol is a common dietary phytosterol with high nutritional value and physiological activity. Stigmasterol can not only prevent hyperlipidemia, atherosclerosis and coronary heart disease[6], but also has a significant effect on preventing diabetes with hyperlipidemia and coronary heart disease. In addition, stigmasterol can improve airway remodeling and significantly reduce asthma attack symptoms[7]. Fructus mume has the effects of converging lung, astringent intestines, generating fluid, and ascaris, and modern studies have found that it also has the effects of preventing and treating insomnia[8], preventing cancer[9], anti-inflammation[10], and anti-depression[11]. Ginger has the effects of evacuating wind cold, warming spleen and stomach to stop vomiting, eliminating phlegm and relieving cough, and is used for wind cold cold cold, stomach cold vomiting, and cold phlegm cough. In clinical practice, it is commonly used to treat low back and leg pain, rheumatic pain[12], gastric ulcer, duodenal ulcer[13],chemotherapy-related diarrhea[14], acute bacillary dysentery, malaria, and acute orchitis, in addition to ginger has the effects of anti-tumor[15], antibacterial, antiemetic, antioxidant, anti-inflammatory, anti-allergic, and regulating the immune system[16].

Network pharmacology provides a powerful framework for the development of multi-target drugs based on systems biology principles by precisely identifying specific signal transduction nodes. This approach can comprehensively elucidate the intricate interactions between drugs and biological systems, including organs, diseases, metabolic pathways, and target proteins[17]. Thus, pharmacological effects can be more fully understood using network pharmacology. In this study, we found that among the active compound targets of Ginger-Mume, there were the most renal disease-related targets in genitourinary diseases, up to 524. This was followed by liver tumors in digestive system diseases, with 517 related targets. The highest degree value among disease-related targets is TNF, a pleiotropic inflammatory cytokine[18], which, in combination with other excess pro-inflammatory cytokines, produces macrophages and is one of the important drivers of systemic inflammation, not only directly inducing inflammatory gene expression, but also triggering apoptotic and necrotic cell death, leading to tissue damage and indirectly exacerbating the inflammatory response. Thus, identification of inhibitors of TNF-induced cell death has broad therapeutic implications for TNF-related inflammatory diseases. Inflammation causes oxidative stress in vivo, which in turn leads to apoptosis and activates inflammatory cells, which can lead to or aggravate kidney injury[19]. At the same time, TNF, as a tumor necrosis factor, has been shown to kill some tumor cells, or inhibit their proliferation, and can be performed in vivo and in vitro.It has been shown that TNF-α has a close correlation with liver tumors[20], TNF-α is able to stimulate effector T cells to drive inflammatory responses and cause liver injury[21], and liver inflammation is a major risk factor for hepatocellular carcinoma[22]. MAPK14, mitogen-activated protein kinase 14, is a serine/threonine protein kinase that orchestrates cellular responses to stress and inflammation. Aberrant expression of MAPK14 triggers proapoptotic and pro-inflammatory mechanisms in a variety of human diseases, including cancer[23]. The above data indicate that the effective active components of "Ginger-Mume" have good anti-inflammatory effects, especially for kidney injury caused by kidney and liver inflammation and liver tumors induced by hepatitis. In GO enrichment analysis, mitochondrial ATP coupled proton transport, mitochondrial electron synthesis transport, NADH to ubiquinone, and aerobic respiratory chain I were most enriched in the cellular

fraction, and NADH dehydrogenase (ubiquinone) activity was most enriched in molecular function, indicating that the biological function of "Ginger-Mume" was most closely related to mitochondria. Mitochondria are key organelles that coordinate countless cellular functions and, in addition to providing energy to cells, participate in immune-inflammatory responses by regulating processes such as cell death and inflammasome activation, and this result suggests that "Ginger-Mume" may have an effective role in reducing inflammation. NADH dehydrogenase, present in the inner mitochondrial membrane, can catalyze electrons to transmit from NADH to coenzyme Q. This enzyme plays an important role in cellular anabolism and maintaining intracellular redox balance. It is fully demonstrated that NDUFS7, NDUFA2, NDUFS3, NDUFB8, NDUFA6, NDUFB9, NDUFA8, MT-ND1, NDUFS6 and NDUFA13, which obtain the top ten protein scores by the cytohub hubba plugin String database combined with cytoscape 3.10.0, play an important role in the regulation of biological processes. In KEGG pathway analysis, the chemical carcinogenesis-reactive oxygen species pathway had the highest correlation, demonstrating that this pathway plays an important role in the treatment of related diseases by "Ginger-Mume". It has been shown that acute kidney injury is closely related to the overproduction of reactive oxygen species and may also cause multiple organ failure[24], and pathological analysis suggests that reactive oxygen species can trigger oxidative stress and inflammation and cause damage to lipids, nucleic acids, and proteins[25]. Early analyses showed that human cancer cells produce more reactive oxygen species than normal cells. Because reactive oxygen species destroy DNA, proteins, and lipids, it is thought that elevated levels of reactive oxygen species increase genomic instability to promote tumorigenesis [26].

In summary, through the network pharmacology method to "Ginger-Mume" related diseases and its pharmacological mechanism of action, it is suggested that the combination of the two has a certain therapeutic effect in the prevention and treatment of diabetes, cancer, genitourinary system diseases, digestive system diseases, cardiovascular system diseases and other fields, and its mechanism of action may be related to reactive oxygen species levels and mitochondrial function, providing a new direction for clinical application.

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