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Research status of network pharmacology of natural medicine for oral mucosal lesions

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Abstract: *Oral mucosal lesions is a common disease in human oral diseases. There are many kinds of oral mucosal diseases, and there are many treatment methods. Natural drugs are widely used in the treatment of oral mucosal diseases because of their good anti-inflammatory, analgesic, antioxidant, antibacterial and wound healing ability, easy to obtain and low cost. In this paper, the representative application of network pharmacology research in the treatment of common oral mucosal diseases by natural drugs is reviewed, and some representative articles on the potential pharmacological mechanism of natural drugs in the treatment of oral mucosal diseases are summarized and analyzed, providing reference ideas for the experimental research on the prevention and treatment of oral mucosal diseases by natural drugs.*

Keywords: *Network pharmacology; Natural medicine; Oral mucosal lesions*

1. Introduction

Oral mucosal Lesions (OML), also known as oral soft tissue diseases, are a series of diseases or conditions affecting the oral mucosa and soft tissue. It was rated as one of the major global public health problems by the World Health Organization (WHO) in 2003 and is the most common health problem faced by individuals worldwide [1].OML covers a wide variety of diseases, mainly including oral infectious diseases, such as oral candidiasis (OC);Oral mucous mottling diseases, such as oral lichen planus (OLP);Oral mucosal ulcerative lesions, such as recurrent aphthous ulcer (RAU);Oral precancerous lesions, such as oral Leukoplakia (OLK);Oral cancer or tumor, such as oral squamous cell carcinoma (OSCC), etc. The etiology of OML is very complex, with the in-depth study of scholars in recent years, it is found that genetic susceptibility, immune dysfunction, viral and bacterial infection, food allergy, vitamin and trace element deficiency and many other factors are closely related to the occurrence of OML[2].

In China, the use of natural medicine has a long history. With the vigorous research and promotion of Chinese medicine by scholars this year, the chemical components of Chinese medicine contained in Chinese medicine compound are also widely studied by scholars. So far, many natural products have been used in the treatment of oral mucosal diseases because of their good anti-inflammatory, analgesic, antioxidant, antibacterial and wound healing ability. A large number of studies have shown that bioactive substances derived from plants have great potential in the treatment of OML, and natural products may be the best and most valuable resources for multi-target drugs due to their multiple advantages of diverse structure, multi-target, high activity and low toxicity [1,3]. Natural medicine has great advantages in the treatment of oral mucosal diseases. However, unlike Western medicine, traditional Chinese medicine is not based on a single component of natural medicine. Therefore, it is difficult to systematically explain the mechanism of action of traditional Chinese medicine. It is the key to analyze the overall active ingredients and mechanism of action of natural medicines [4].

The concept of "network pharmacology" was first proposed by the British pharmacologist Hopkins in 2007, and it is defined as a branch of pharmacology, which uses the disease-gene-target-drug network method to analyze the relationship between drugs, diseases and targets, the characteristics of multi-level networks, and the huge data analysis system. It coincides with the characteristics of "multi-component, multi-target and multi-path" treatment of diseases in traditional Chinese medicine, so network pharmacology has certain advantages in discovering targets of natural drugs [5,6]. At present, the commonly used databases of network pharmacology include DrugBank, STITCH and TCM Chemical Information database, which cover drug molecular data. PubChem, ChEMBL, KEGG and

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Target databases related to active pharmaceutical ingredients; Gene related databases such as OMIM; Protein related databases such as HPRD, BioGRID and DIP; And a database of molecular interactions such as HPRD, BIND, DIP, HAPPI, MINT, STRING, and PDZBase. The aforementioned database can be used to find the necessary information, in addition to this, we also need appropriate analytical tools such as Cytoscape, Pajek, VisANT, GUESS, WIDAS, PA TIKA, PA TIKA web and CADLIVE, among which, in the field of TCM natural medicine research, Cytoscape, GUESS, Pajek and VisANT are currently the most widely used network analysis software [7].

Therefore, the use of network pharmacology system to comprehensively analyze the mechanism of action of multi-component drugs has been widely used in the study of natural medicine treatment of diseases. This paper reviewed the representative application of network pharmacology research in the treatment of common oral mucosal diseases by natural drugs. We summarized and analyzed the representative articles published on domestic and foreign websites that used network pharmacology to explain the potential pharmacological mechanism of natural drugs in the treatment of oral mucosal diseases. To provide a reference for the experimental study of natural medicine prevention and treatment of oral mucosal diseases.

2. Explore the treatment of mucosal diseases by natural medicine prescriptions based on network pharmacology

Oral lichen planus (OLP) is a chronic inflammatory disease of oral mucosa mediated by T lymphocytes, often manifested as white reticulate mucosa lesion. Li Yueyue [8] et al. combined TCMSP database, Genecards database and OMIM database to construct the "disease-active ingredients-target" diagram, and obtained 15 active ingredients in compound Gypenoside capsules, including gypenoside components, brevetin, quercetin and rhamnetin. It was found that these active ingredients could interact with 54 potential targets related to oral lichen planus. PPI network analysis, GO functional enrichment analysis, KEGG pathway enrichment analysis and molecular docking analysis were used. It was found that compound Gyantulan capsule may play a role in the treatment of OLP by regulating endocrine resistance, mitogen-activated protein kinase signaling pathway, hypoxia inducible factor 1 signaling pathway, cytokine - cytokine receptor interaction and other signaling pathways. Deng Qianlan et al[9]screened 169 active ingredients from Huashuixing Yuqingreet recipe through TCMSP, Batbat-TCM and UniProt databases, and obtained key ingredients such as quercetin, luteolin, han baicalin and kaempol after intersecting with OLP disease targets. By constructing PPI network, it was found that the treatment of OLP with Huashuxing Yuqingreai prescription involved many pathways such as inflammation, infection, metabolism and tumor, among which the interleukin-17 (IL-17) signaling pathway and TNF signaling pathway were closely related to the occurrence of oral lichen planus.

Some scholars[10] analyzed the treatment of OLP with Huoxue Huayu prescription based on network pharmacology. It was found that the main active components included quercetin, kaempferol, stigasterol, etc. It was found that the main active components included quercetin, kaempferol, stigasterol, etc. Core action targets include IL-1β,PTGS2(COX-2),MAO, etc. KEGG analysis showed that activating blood circulation to remove blood stasis could affect neurotransmitter metabolism, cytomegalovirus infection, AGE-RAGE and other pathways.

Oral ulcers are secondary lesions characterized by loss of oral mucosal tissue, often including local traumatic ulcers, recurrent aphthous ulcers (RAU), viral and bacterial infections, allergic reactions, adverse drug reactions, or systemic diseases. KouyanqingGranule,(KYQG) which was collected in the 2020 edition of Chinese Pharmacopoeia, is mainly used in the treatment of inflammatory diseases of mouth and throat, such as RAU, oral leukoplakia, OLP, etc. Some scholars[11] used network pharmacology to screen multiple targets of KYQG in the treatment of oral ulcer diseases, and a total of 47 key targets were selected through network analysis, mainly involving three functional modules of inhibiting inflammatory response, regulating immune response and inhibiting oxidative stress. The realization of these functions mainly depends on the TNF signaling pathway and HIF-1 signaling pathway. It was found that KYQG could significantly inhibit the levels of cycoperoxidase-2 (COX2), matrix metalloproteinase-9 (MMP9) and tumor necrosis factor-α (TNF-α) in serum of rats with oral ulcer. Li Xueli [12] explored the mechanism of action of Yatongting drip pill for treating oral ulcers based on ingredient-target interaction, and identified 19 ingredients of piperlongi and 13 ingredients of clove. Yatong Stop dropping pills in piperine, quercetin, kaempferol and other compounds, Through the expression of CDK2, CDK4, FOS, HIF-1, MAPK8 (JNK), TGF-β,It affects Cell cycle, P53, FOXO, MAPK, TOLL-LIKE, HIF-1, ERBB, Neurotrophin, TGF-beta, T cell, B cell, cAMP and other signaling pathways, and produces effects on regulating cell cycle, immune response, apoptosis, etc. Final

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treatment of mouth ulcers. Ma Xuan et al [13] explored the effect of Sipayi solid GIVA solution on recurrent Aphthous ulcer (RAU) through network pharmacology, and found that the core components contained in it, such as galic acid, can act on genes such as TNF and IFN-γ, and then regulate multiple signaling pathways such as NF-κB and HIF-1, thus playing a role in the treatment of RAU.

Oral submucous fibrosis (OSF) is a chronic inflammatory oral mucosal disease with insidious, progressive, and potential deterioration. The clinical manifestations of OSF are mainly cheek and soft palate whiteness and progressive mouth opening limitation. At present, the pathogenesis of OSF is not clear, mainly related to long-term chewing of betel nut, immune dysfunction, genetic susceptibility and dietary habits. Zhu Keke et al[14] explored the network and molecular mechanism of action of Taohong Siwu decoction in treating OSF based on the method of network pharmacology. The active components of Taohong Siwu decoction and its therapeutic targets for OSF were analyzed by combining multiple databases. According to Cytoscape and R software and bioinformatics analysis, 42 targets of Taohong Siwu decoction for treating OSF were obtained. quercetin, kaempferol, ferulicacid, paeoniflorin, luteolin and baicalein may be the main active components of Taohong Siwu decoction in the treatment of OSF. It can act on JUN, HMOX1, MAPK family, MMP family and other targets, and participate in biological processes such as cytokine activity, cytokine receptor binding, growth factor activity and DNA-binding transcriptional activation activity.HIF-1 signaling pathway, NF-κB signaling pathway, MAPK signaling pathway, Wnt signaling pathway and TGF-β signaling pathway are used to treat OSF. Compound salvia miltiorrhiza dropping pills also have certain clinical efficacy in treating OSF[15]. Through database analysis, the key active ingredients of compound salvia Miltiorrhiza dropping pills are luteolin, perillyl alcohol, salviol B, tanshinone IIA, ginsenoside Rh2, Xuexueoxalic acid, etc.Core targets include MAPK3, MAPK1, HRAS, JUN, VEGFA, PTPN11, EGFR, IL6, MAPK8, TNF and other key targets, which mainly act on cancer-related signaling pathways, PI3K-Akt signaling pathway, and microrNA-related pathways to exert biological activities.

Behcet syndrome (BD) is a systemic, chronic, progressive, and recurrent disease of the immune system that is closely associated with genetic factors (such as the HLA-B51 gene), bacterial or viral infections, and immune dysfunction. It often invades many organs including the mouth, eyes, skin and muscles and joints, mainly manifested by recurrent oral ulcers, genital ulcers, skin damage and ocular iritis. The main compounds of Sanwu Huangqin Decoction and their corresponding action targets were searched by TCMSOP and TCMID database. The target of Behset disease was searched by GeneCards database. Network visualization via String database and Cytoscape software; GO and KEGG sets were analyzed for intersection targets using DAVID database. Moreover, the regulation effect of Sanwu Huangqin Decoction on core target genes was verified by constructing BD mouse model[16].

Hand-foot and mouth disease (HFMD) has been the highest incidence of Class C infectious diseases since it was included in Class C infectious diseases in 2008.HFMD occurs mostly in school-age children under 5 years old, and its clinical symptoms are mainly fever, rash or herpes on the hands, feet, mouth and other parts, and severe cases can lead to death. Cao Zhiming et al[17]also found through network pharmacology that Coptis and Coptis can act on targets such as INS, TP53 and IL6 to regulate signaling pathways such as PI3K-Akt, P53, Apotosis and NF-κB to treat HFMD. Geranicin, ginkgo biflavone and isoginkgo biflavone may be the active components of EV71 resistance.

Cheilitis, similar to the "lip wind" and "tight lips" documented in Chinese medicine literature. Clinical symptoms can be divided into allergic contact cheilitis, photolinear cheilitis, exfoliative cheilitis, glandular cheilitis, granulomatous cheilitis and so on. The specific manifestations are dry desquamation, itching, burning pain, swelling, exudation and scab on the lip mucosa. Ren Xuewen et al[18] used TCMSP and TCMID to screen the effective compounds and targets of compound comfrey oil. The disease target of cheilitis was selected by searching GeneCards and OMIM database, and the intersection of disease and drug target was selected by R language. The drug-compound - target-disease interaction network was constructed by Cytoscape software. The PPI network was built using STRING platform, and the Bioconductor software package was used to perform GO function enrichment and KEGG pathway analysis. Among them, the 21 active ingredients screened play a key role in targeting IL-6, STAT3 and TNF, and are mainly enriched in several signaling pathways such as AGE-RAGE, FssAs and TNF, playing anti-inflammatory and regulating cell proliferation and apoptosis.

3. Explore the treatment of mucosal diseases by single medicinal plants based on network pharmacology

Dictinum skin has the efficacy of clearing heat and detoxifying, dewetting and relieving itch, etc.,

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which can be used in the treatment of skin mucosal diseases. Liu Shiwei et al. [19] selected the pharmacodynamic components and target of dictinum skin through TCMSP database and Swiss Target Prediction database, and predicted the target related to OLP disease through Gene Cards database. The intersection of drugs and disease targets was established, and a "drug-ingredient-target-disease" network was constructed, and it was found that dichotoma can play a role in the treatment of OLP through multiple targets and pathways such as IL-4 and IL-17.

Oral squamous cell carcinoma (OSCC) is one of the most common cancer types in the world, accounting for more than 90% of oral malignancies. OSCC usually presents as a persistent hemorrhagic ulcer or ulcer, often developed from precancerous lesions such as white spots and erythema. Liu [20] studied the treatment of oral squamous cell carcinoma (OSCC) with tripterygium vine through network pharmacology combined with molecular docking model, and analyzed the key targets of Tripterygium vine in the treatment of OSCC as STAT3, TNF, JUN, TP53 and AKT1 through PPI network topology. Topological analysis of the "drug component-target-disease" network showed that kaverol, triptolide, triptolide, tangerine and epicatecin were the core active components, which mainly affected the proliferation, apoptosis, invasion and migration of OSCC, and the PI3K-Akt signaling pathway was the key signaling pathway. Through the network pharmacological analysis of tripterygium in the treatment of OLP, Wu et al. [21] found that the core active components of tripterygium included tripterygium lactone, kauniol, and cephalotin, and the key targets included tumor necrosis factor, serine/threonine protein kinase 1, and the major pathways involved were TNF signaling pathway and IL-17 signaling pathway. In addition, based on the effects of tripterygium wilfordii on pain, swelling, detoxification, blood circulation and circulation, the research group also used network pharmacological means to predict the main active ingredients of Tripterygium wilfordii and their pharmacological properties and mechanism of action in the treatment of recurrent aphthous ulcer (RAU), and found that the main ingredients that play a role in the treatment of RAU still include kauniol and tangerine.In addition, triptolide is also included, and the main signaling pathways are TNF signaling pathway, Toll-like receptor pathway, and T cell receptor signaling pathway. From this we can see that network pharmacology can reveal the mechanism of "different diseases of the same treatment" in the study of oral mucosal diseases in traditional Chinese medicine. In other words, network pharmacology can elucidate the mechanisms of the same strategy to treat different diseases through the target-pathway-organ network of the same drug.

Oral leukoplakia (OLK) is a kind of white plaque occurring in the oral mucosa. It is the most common potential malignant oral lesion. The pathological feature of Oral leukoplakia is abnormal proliferation of epithelioid cells, which is a precancerous lesion with a cancer risk of about 0.6% to 20%. The clinical classification of OLK can be divided into homogeneous and heterogeneous lesions. The selection of effective ingredients for OLK treatment from natural medicines is currently a hot topic in disease prevention research [22].By means of network pharmacology, molecular docking and experimental evaluation, Hou Fanfan et al. found that the main active component of anti-OLK in radix flax was radix flax glycoside; KEGG pathway analysis revealed that PI3K/Akt was the key pathway for its action; PPI analysis showed that Akt1, VEGFA, EGFR, HIF1A and PTGS2 were the main target genes. Based on the above predicted results, in vitro experiments were conducted to further prove that baicalin can inhibit the proliferation of DOK cells, induce apoptosis, block cell cycle, and inhibit the mRNA expression level of central genes by inhibiting PI3K/Akt pathway [23].

Compound salvia miltiorrhiza dripping pills have a certain effect in the treatment of oral submucous fibrosis, in which Salvia miltiorrhiza, as the main active component of the prescription, plays a great role, but its mechanism has not been fully clarified. Therefore, Cai et al[24]found through network pharmacology that active components of Salvia miltiorrhizae may inhibit OSF by targeting cytokine-mediated signaling pathways, apoptosis and IL-17 signaling pathways.

4. Explore the effective components of monomer for the treatment of mucosal diseases based on network pharmacology

Quercetin, as a natural flavonoid, has a variety of biological activities and is widely distributed in nature. Quercetin often exists in the flowers, fruits, roots and leaves of many common plants. Quercetin is mainly stored in the form of quercetin and hypericin, and has many pharmacological effects such as antioxidant, anti-inflammatory, anti-tumor and immune regulation [25]. The above-mentioned compound Gantulan capsule, Huashui Xingyu Qingrefang, Huoxue Huayu Decoction, Yatong Stopping Tiao Pill and Taohong Siwu decoction all contain quercetin, which has good effects on various diseases. Zhao et al [26] combined network pharmacology with experimental verification to predict and verify the key

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anti-OLP targets of quercetin.66 quercetin -OLP common targets were analyzed from different databases, PPI networks were constructed, topology analysis and MCODE cluster analysis were performed for common targets, and key targets such as TP53, IL-6 and IFN-γ were identified. The key signaling pathways of active oxygen metabolism, IL-17 and AGE-RAGE were enriched by GO and KEGG analysis. In vitro experiments have also confirmed that quercetin interferes with Th1/Th2 balance by acting on IL-6 and IFN-γ, regulates the immune system, and then treats OLP, laying a foundation for the clinical application of quercetin.

Total paeoniflorin is extracted from the dried root of Paeoniflorin. It is a general name of a group of glycosides including paeoniflorin, paeoniflorin, benzoyl paeoniflorin, hydroxy paeoniflorin and Paeoniflorin. It has anti-inflammatory, analgesic and immunomodulatory effects. Lou et al[27]obtained five major chemical components of total glucosides of Paeony through network pharmacological screening. The biological processes in GO enrichment analysis mainly involved the positive regulation of RNA polymerase II promoter transcription, the positive regulation of NF-κB transcription factor activity, inflammatory response, and apoptosis process. The molecular functions are mainly involved in metal endopeptidase activity, lipopolysaccharide binding, zinc ion binding, etc. The cellular components mainly involve nuclear, extracellular space and plasma membrane. The target of KEGG pathway enrichment analysis plays a role in the treatment of oral lichen planus by regulating signaling pathways such as TLR, TNF, Proteoglycans, PI3K-Akt and NOD-like receptors.

5. Discussion

Based on the published literature, this paper reviews the application of network pharmacology in the treatment of oral mucosal diseases with natural drugs. Through the interdisciplinary application of holistic biological network analysis and integration, network pharmacology reveals the correlation between drugs and targets, and elucidates the synergistic mechanism of the active ingredients of natural medicines in traditional Chinese medicine formulations. Network pharmacology optimizes known Chinese medicine compounds or effective ingredients for diseases, and evaluates their clinical efficacy and functions, providing theoretical basis for the development of multi-target therapies and providing a good condition for promoting the development of Chinese medicine.

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