



Review Article



Biological, Functional and Network Pharmacological Exploration of Essential Oils in Treatment and Healthcare of Human Diseases

Yudong Zhang^{1#}, Jiawei Tang^{2#}, Qinghua Liu^{3#}, Jinming Ge⁴, Zhangwen Ma⁵, Jingyi Mou¹ and Liang Wang^{6*}

¹Department of Clinical Medicine, School of First Clinical Medicine, Xuzhou Medical University, Xuzhou, Jiangsu, China; ²Department of Intelligent Medical Engineering, School of Medical Informatics and Engineering, Xuzhou Medical University, Xuzhou, Jiangsu, China; ³State Key Laboratory of Quality Research in Chinese Medicines, Macau University of Science and Technology, Taipa, Macau, SAR, China; ⁴School of Anaesthesia, Xuzhou Medical University, Xuzhou, Jiangsu, China; ⁵School of Pharmacy, Xuzhou Medical University, Xuzhou, Jiangsu, China; ⁶Laboratory Medicine, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangzhou, Guangdong, China

Received: September 05, 2022 | Revised: September 23, 2022 | Accepted: November 16, 2022 | Published online: December 28, 2022

Abstract

Essential oils (EOs) are natural products with bioactive functions that are obtained from various plant species, including *Lavandula angustifolia* and plant parts, through extraction methods, such as hydro-distillation, steam distillation and cold pressing, which can be dated back to ancient Egyptian and Greek times. Although various EOs are effective for disease treatment, such as human infectious diseases and mental disorders, the specific pharmacological mechanisms remain unclear due to its complex composition. Previous studies have attempted to recruit pharmaceutical analysis techniques, such as HPLC and MALDI-TOF, in order to elucidate the compositions of EOs. However, these have provided limited information on the mechanism of the bioactive functions of EOs. In recent years, network pharmacology has emerged as a convenient and appropriate approach to study the molecular mechanism of traditional medicines. To date, there is a lack of updated reviews on the recent progress of network pharmacology in the field of interactions between EOs and human diseases. Therefore, the present study scrutinized recent and important literatures in the field of network pharmacology and EOs, aiming to provide a timely yet brief overview of EOs as a potential treatment for diseases via network pharmacology, and facilitating the application of EOs as a complementary medicine and therapy for human diseases.

Introduction

Essential oils (EOs), which are also known as volatile oils, are volatile aromatic compounds extracted from flowers, leaves, seeds, roots and other parts of plants,¹ which are biologically active natural products. The composition of EOs usually contain terpenes, aldehydes, esters, alcohols, polyphenols and other compounds.^{1–3}

Keywords: Essential oils; Network pharmacology; Infectious disease; Chronic Disease; Mental disorder.

Abbreviations: AD, alzheimer's disease; EOs, essential oils; GO, gene ontology; HS, herba siegesbeckiae; KEGG, kyoto encyclopedia of genes and genomes; RA, rheumatoid arthritis.

***Correspondence to:** Liang Wang, Laboratory Medicine, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangzhou, Guangdong 510062, China. ORCID: <https://orcid.org/0000-0001-5339-7484>. Tel.: +86 1392175 0542, E-mail: healthscience@foxmail.com

[#]These authors contributed equally to the study.

How to cite this article: Zhang Y, Tang J, Liu Q, Ge J, Ma Z, Mou J, et al. Biological, Functional and Network Pharmacological Exploration of Essential Oils in Treatment and Healthcare of Human Diseases. *Future Integr Med* 2023;2(1):23–31. doi: 10.14218/FIM.2022.00038.

Common EOs originate from medicinal plants in traditional medicine and aromatic plants in nature, such as lavender, lemon, tea tree, rose, orange, frankincense, myrrh and mint. EOs are usually added to various skin care products and ointments, and are widely used in perfumes and aromatherapy.^{4,5} Furthermore, various studies have reported that EOs have good effects in relieving stress,⁵ improving mental disorders,⁶ anti-viral infection,⁷ anti-inflammation,⁸ bacterial sterilization,⁹ anti-diabetes,¹⁰ anticancer,¹¹ and so on. However, the mechanism of action of EOs in the treatment of these diseases has not been fully elucidated, because EOs have complex compositions, and there may be synergistic or antagonistic effects among these components.⁷ Therefore, it remains difficult to fully dissect the mechanisms of EOs in the treatment or remission of a variety of human diseases using traditional techniques and methodologies.

Network pharmacology investigates the functions of multi-component drugs in an overall perspective, which systematically and comprehensively sheds light on the mechanism of the drug treatment of a particular disease.¹² Therefore, network pharmacology has been widely applied in the field of traditional Chinese



Fig. 1. Schematic illustration of the applications of essential oils in human diseases.

medicine,¹³ such as the research and development of new drugs, and the exploration of recipe mechanisms.^{14–16} In terms of the pharmacological functions of EOs, network pharmacology can provide novel insights and strategies for the in-depth understanding of EOs and its mechanism in treating or alleviating diseases, providing theoretical results for further experimental verifications. The present mini-review focused on the components and functions of EOs, the application of EOs for the alternative or adjuvant treatment of human diseases, and the exploration of EOs in the treatment of human diseases and its mechanisms via network pharmacology, in order to provide reference for further EO studies.

Applications of EOs in the treatment of human diseases

EOs are a class of complex plant secondary metabolites,¹ which contain a variety of bioactive components. Different components in EOs have versatile functions in plants, such as defense against various predators and the inhibition of infection of pathogenic microorganisms.¹ These components have the characteristics of small molecular weight, strong penetration, and easy absorption by the human body.³ Furthermore, these have important and effective roles in anti-infection, the alleviation of chronic diseases, and the improvement of poor mental disorders, and have a wide range of application prospects in the pharmaceutical industry for drug

discovery, design and development. The schematic illustration of the applications of EOs in human diseases is shown in Figure 1.

Anti-infection effects of EOs

Infectious diseases are usually caused by microbes, such as viruses, bacteria, fungi and nematodes. It has been reported that EOs exhibit the properties of significantly inhibiting various microbial pathogens. For example, *Origanum vulgare* (Oregano) EO has good inhibitory effects on common pathogens and fungi, such as *Candida albicans*, *Staphylococcus aureus*, *Escherichia coli* and *Salmonella*, based on the broth microdilution method.⁹ Furthermore, the results of *in vivo* and *in vitro* studies have revealed that EOs, such as *Artemisia annua*,¹⁷ *Vernonia polyanthes* Less (Asteraceae),¹⁸ *Chenopodium ambrosioides*¹⁹ and *Piper Species*,²⁰ can kill *Leishmania*, which is a single-celled parasitic organism that belongs to the genus trypanosomes, and is responsible for the disease, leishmaniasis. In addition, the EOs of *Piper Species*²⁰ and *Eucalyptus*²¹ can inhibit the growth and reproduction of tuberculosis-causing bacteria in *in vitro* antibacterial experiments. Moreover, *Eucalyptus* EO has antiviral activity,⁷ and *peppermint* EO has been shown to inhibit herpes simplex virus *in vitro*.²² The above-mentioned evidence confirms that EOs have potential clinical values in the prevention, control and treatment of infectious diseases.

In addition, *in silico* investigation has been adopted to explore

the potential functions of EO components in the treatment of emerging infectious diseases. A total of 171 EO components were selected for the computer-aided molecular docking analysis,²³ and the compound with the highest docking score with SARS-CoV-2 M^{pro} was sesquiterpene hydrocarbon (*E*)- β -farnesene.^{8,24,25} Therefore, the antiviral and anti-inflammatory properties of EOs and its components can be used as a reference for the prevention and treatment of COVID-19. With the emergence of resistance to antibiotics and antiviral drugs in clinical treatment, interests in the application of EOs in anti-infection is increasing in a fast pace. Since EOs are natural and relatively safe, these can act as good substitutes for chemically synthesized antibiotics in the future.

The role of EOs in alleviating chronic diseases

Chronic diseases usually cannot be completely cured, and the long course of the disease would cause irreversible damage to important organs, such as the brain, heart and kidney, which can seriously endanger human health. For example, chronic diseases, such as cerebrovascular diseases and malignant tumors, have become the main causes of death worldwide.^{26,27} In a series of studies, researchers have found that EOs and its corresponding components hold the potential in reducing blood pressure,^{28–32} regulating blood glucose^{10,33} and inhibiting tumor development,^{11,34–37} thereby imposing positive effects on the improvement of chronic diseases.

Anti-hypertensive effect of EOs

Various EOs have been reported to have the function of regulating blood pressure through different pharmacological mechanisms. In a clinical trial that recruited 83 pre-hypertensive and hypertensive subjects, it was revealed that inhaling an EO mixture of lavender, ylang-ylang, marjoram and neroli at a ratio of 20:15:10:2 can effectively relieve systolic blood pressure in patients.²⁸ In other studies, using the rat aortic ring model, it was revealed that EOs obtained from *Alpinia Zerumbet*²⁹ and *Trachyspermum ammi* Sprague³² can directly dilate blood vessels and lower blood pressure through the inhibition of calcium influx by acting on calcium channels with independence on endothelial cells. However, the EOs of *Ocimum gratissimum* L. and its main component, eugenol, were found to have vasodilation effects by inhibiting the influx of Ca²⁺ in the plasma membrane through the use of the aortic ring model of DO-CA-salt hypertensive rats, which depended on the integrity of the vascular endothelium.³⁰ Overall, although these above-mentioned EOs exhibit different mechanisms for reducing hypertension, these findings highlight the potential applications of EOs as an alternative therapy in anti-hypertensive treatment.

Anti-diabetes effect of EOs

A variety of EOs can improve and control diabetes by regulating blood sugar. Both *in vivo* and *in vitro* studies have reported that the EO of *Salvia officinalis* L. can significantly inhibit the activity of α -amylase and lipase, thereby reducing the blood glucose concentration and liver glycogen content in male rats with diabetes induced by Alloxan.¹⁰ The important chemical components contained in *Salvia officinalis* L. can be orally administered under the supervision of doctors, and may be a potentially valuable supplement for the treatment of diabetes in the future. Furthermore, the clinical-randomized controlled trial conducted by Shojaei *et al.*, and the results of the population study conducted by the Zabol Diabetes Center revealed that the EO of *Rhubarb* stem (shoot) can effectively reduce the HbA1c level and fasting blood glucose in patients with type-2 diabetes mellitus.³³ Interestingly, some EOs have good therapeutic and preventive effects on both hypertension

and diabetes. For example, Oboh *et al.* reported the mechanism by which black pepper EO controls and/or prevents type-2 diabetes mellitus and hypertension, which may be due to the inhibition of α -amylase, α -glucosidase and angiotensin converting enzyme activities through the phenolic content and antioxidant activity of the extract.^{38,39} Based on the above-mentioned studies, it can be implied that EOs hold a potential as a reservoir for the design and development for anti-diabetic drugs.

Anti-tumor effect of EOs

Some EOs have been reported to have biological activities in cancer treatment. For example, Greay *et al.* applied 10% of the topical melaleuca white (tea tree) oil abundant in terpenes to immunocompetent tumor-bearing mice. They found that tea tree oil can significantly inhibit the growth of invasive, subcutaneous and chemo-resistant tumors in mice, and has antitumor activity *in vivo*.³⁴ Frankincense EO³⁵ and Thymus vulgaris L. EO¹¹ were also identified to induce the apoptosis of tumor cells in *in vivo* and *in vitro* breast cancer models. Xing *et al.* reported that EOs obtained from the leaves of *Erythrina corallodendron* L. can inhibit the proliferation, migration and invasion of breast cancer cells in a dose-dependent manner.³⁶ Furthermore, a study reported that cinnamaldehyde can inhibit cell growth by inducing apoptosis and reversing the epithelial mesenchymal transition by terminating the Wnt/beta-catenin pathway.³⁷ All these findings suggest that certain types of EOs should deserve further investigation as adjuvant drugs for treating cancer migration and invasion.

The role of EOs in alleviating mental disorders

EOs usually contains a variety of small aromatic compounds. Some of these are liposoluble, and can easily cross the blood-brain barrier,⁴⁰ acting on the central nervous system.⁶ Furthermore, studies have revealed that EOs exhibit promising effects in the adjuvant treatment of emotional disorders, such as depression and anxiety, as well as insomnia. Hence, the proper and rational use of EOs can effectively relieve the discomfort caused by anxiety, and significantly improve psychological disorders, such as depression and anxiety (Table 1).^{6–8,10,17,18,20,21,30–32,34,36–38,40–53} Clinical trials have revealed that Lasea, the commercial product of lavender EO, can effectively relieve the anxiety level and insomnia disorder of patients with depression.⁶ Lasea is orally administered through 80 mg soft gelatin capsules, which is based on the extract of lavender, and mainly includes aloes and linalool acetate. In addition, Lehrner⁵⁴ and McCaffrey⁵⁵ reported that lavender, orange and rosemary EOs have good effects on anxiety in patients and volunteer participants. At present, the drugs used to treat insomnia usually have different degrees of side effects, as well as problems on drug dependence or resistance. The treatment of insomnia by EO aromatherapy can achieve the effect of improving sleep quality, and this can also be easily accepted by patients.^{56,57} A randomized cross-controlled clinical trial revealed that the inhalation of lavender EO can significantly improve the sleep quality, quality of daily life, and mood, of patients with insomnia and diabetes.⁵⁸

Other diseases

As reported by a variety of studies, EOs have anti-allergy, anti-asthma and anti-aging effects. For example, bronchial asthma is a chronic inflammatory disease of the airways, in which a variety of cells and cellular components are involved. The terpene contained in EOs can relax the bronchial smooth muscle,⁴¹ reduce airway inflammation,⁴² and inhibit airway remodeling. As a result, EOs have the potential to be used for relieving asthma symptoms

Table 1. Summary of bioactive functions of essential oils in human diseases

Category	Diseases	Essential oils	Plant information (plant parts)	Main compounds	Refs.
Infectious diseases	Virus infection: 1. Yellow fever virus; 2. Herpes simplex virus; 3. Zika; 4. COVID-19	1. <i>Lippia citriodora</i> ; 2. <i>Aloysia triphylla</i> ; 3. <i>Ayapana triplinervis</i> ; 4. <i>Eucalyptus</i>	1. <i>Verbenaceae</i> (not applicable); 2. <i>Verbenaceae</i> (leaves); 3. <i>Asteraceae</i> (aerial parts); 4. <i>Myrtaceae</i> (aerial parts)	1. Geranial, Neral, Limonene; 2. α-Tujone, cis-carveol, carvone, limonene; 3. Thymohydroquinone dimethyl ether; 4. 1,8-cineole, jensenone	1-44; 2-45; 3-46; 4-8
	Bacterial Infection: Tuberculosis	1. <i>Piper diospyrifolium</i> , <i>Piper aduncum</i> ; 2. Klonemax™ (<i>Eucalyptus</i>)	1. <i>Piperaceae</i> , <i>Piper</i> L. specie, (leaves); 2. <i>Myrtaceae</i> , (not applicable)	1. α-thujene, α-pinene, β-pinene, limonene, β-phellandrene, safrrole, δ-elemene, γ-elemene, α-humulene, dehydro-aromadendrene, trans-cadina-1(6), 4-diene, γ-gurjunene, bicyclogermacrene, (Z)-α-bisabolene, δ-cadinene, spathulenol, caryophyllene oxide, humulene epoxide II, epi-1-cubenol, epi-α-murolol and α-murolol; 2. 1,8-cineole	1-20; 2-21
Chronic diseases	Fungal Infection: 1. Dermatophytes; 2. Candidiasis; 3. Skin fungal infections	1. <i>Artemisia sieberi</i> Besser (Lotion 10%, twice daily for two weeks); 2. <i>Eucalyptus</i> ; 3. <i>Myrrh</i>	1. <i>Compositae</i> family (aerial parts); 2. <i>Myrtaceae</i> , <i>odorata</i> specie, (leaves); 3. <i>Burseraceae</i> family (aerial parts)	1. α-thujones, β-thujones; 2. 1,8-cineole; 3. Furanoidesma, 1,3-diene, menthofuran	1-47; 2-7; 3-48
	Protozoan Infection: Leishmaniasis	1. <i>Artemisia annua</i> leaves; 2. <i>Vernonia polyanthes</i> Less	1. <i>Asteraceae</i> (leaves); 2. <i>Asteraceae</i> (leaves)	1. Camphor; 2. Zerumbone	1-17; 2-18
Mental disorders	Diabetes	1. <i>Salvia officinalis</i> L.; 2. <i>Piper guineense</i> ; 3. <i>Clausena Harmandiana</i> , <i>Clausena Guillauminii</i> , <i>Clausena excavata</i>	1. <i>Lamiaceae</i> (leaves); 2. <i>Ashanti</i> black pepper (all); 3. <i>Citrus</i> family, <i>Clausena</i> specie (leaves)	1. Oxygenated monoterpenes, Hydrocarbon monoterpenes, Hydrocarbon sesquiterpenes; 2. α-Pinene, β-pinene, cis-ocimene, myrcene, Alloocimene, 1,8-cineole; 3. Seselin, terpinen-4-ol	1-10; 2-38; 3-49
	Hypertension	1. <i>Trachyspermum ammi</i> ; 2. <i>Ocimum gratissimum</i> L.; 3. <i>Alpinia zerumbet</i> ; 4. <i>Piper guineense</i> ; 5. <i>Aniba rosaeodora</i>	1. <i>Apiaceae</i> (seeds); 2. <i>Labiatae</i> (aerial parts); 3. <i>Zingiberaceae</i> (aerial parts); 4. <i>Ashanti</i> black pepper (all); 5. <i>Lauraceae</i> (trunk)	1. Thymol, gamma-terpinene, p-cymene; 2. Eugenol; 3. 1,8-Cineole; 4. α-Pinene, β-pinene, cis-ocimene, myrcene, alloocimene, 1,8-cineole; 5. Linalool	1-32; 2-30; 3-31; 4-38; 5-50
Mental disorders	Tumor: 1. AE17 mesotheliomas and B16-F10 melanomas; 2. Breast cancer; 3. Non-small cell lung cancer	1. <i>Melaleuca alternifolia</i> ; 2. <i>Erythrina corallodendron</i> L. leaves; 3. <i>Cinnamomum cassia</i>	1. <i>Myrtaceae</i> (leaves); 2. <i>Erythrina</i> genus (leaves); 3. <i>Lauraceae</i> (not applicable)	1. Terpenes; 2. Linalool; 3. Cinnamaldehyde	1-34; 2-36; 3-37
	Anxiety	1. Lasea™ (<i>Lavender</i>); 2. <i>Pelargonium roseum</i>	1. <i>Labiatae</i> family (flowers); 2. <i>Geraniaceae</i> family (leaves)	1. Linalool, linalyl acetate, 1,8-cineole, β-ocimene, terpinen-4-ol and camphor; 2. Monoterpene alcohols citronellol and geraniol	1-6; 2-40
Mental disorders	Depression	1. Lasea™ (<i>Lavender</i>); 2. <i>Reunion Geranium</i> ; 3. <i>Toona ciliata</i> Roem. var. <i>yunnanensis</i>	1. <i>Labiatae</i> family [flowers]; 2. <i>Geraniaceae</i> family [leaves]; 3. <i>Meliaceae</i> family [leaves]	1. Linalool, linalyl acetate, 1,8-cineole, β-ocimene, terpinen-4-ol, camphor; 2. Monoterpene alcohols citronellol, geraniol; 3. Estragole, β-elemene, β-cubebene, γ-elemene	1-6; 2-40; 3-51

(continued)

Table 1. (continued)

Category	Diseases	Essential oils	Plant information (plant parts)	Main compounds	Refs.
Other diseases	Insomnia	1. Lasea™ (Lavender); 2. Compound Anshen EO (Lavender, Sweet orange, Sandalwood, Frankincense, Orange blossom, Rose, Agarwood oil blend ratio 10:4:2:1.6:1.2:1:0.6)	1. <i>Labiatae</i> family (flowers); 2. (not applicable)	1. Linalool, linalyl acetate, 1,8-cineole, β-ocimene, terpinen-4-ol, Camphor; 2. D-limonene, Linalool, Linalyl acetate, α-Pinene, α-Santalol	1-6; 2-52
	Asthma	1. <i>Eucalyptus</i> oil; 2. <i>Nepeta cataria</i> L.; 3. Aromatic spices	1. <i>Myrtaceae</i> (not applicable); 2. <i>Limiaceae</i> (not applicable); 3. (not applicable)	1. 1,8-cineole; 2. 1,8-cineol, α-humulene, α-pinene and geranyl acetate; 3. Citronello, α-terpineol, carvacrol	1-21; 2-41; 3-42
	Aging	1. <i>Pluchea dioscoridis</i> ; 2. <i>Erigeron bonariensis</i> ; 3. <i>Coriander</i>	1. <i>Asteraceae</i> (above-ground parts); 2. <i>Asteraceae</i> (above-ground parts); 3. <i>Apiaceae</i> (fruits)	1. α-Maaliene, berkheyaradulen, dehydro-cycloolofolene oxide, aromadendrene oxide-2, β-murolene, and α-eudesmol; 2. Trans-α-farnesene, O-ocimene, isolongifolene-5-ol, α-maaliene, berkheyaradulen, and α-murolene; 3. Linalool	1-53; 2-53; 3-43

under the supervision of doctors. Furthermore, EOs have been shown to be rich in antioxidants, and have active effects in inhibiting elastase, tyrosinase and hyaluronidase. Therefore, these have potential biological activities in anti-wrinkle effects, and might have a good effect in improving exogenous aging.^{43,59} The EOs, main components, and related diseases reported in the literature are listed in Table 1.

Application of network pharmacology in essential oil researches

Network pharmacology was first proposed by Andrew L Hopkins in 2007,⁶⁰ which integrates large amounts of information to obtain new discoveries by combining computational and experimental methods. In contrast to the classical “one target, one drug” view, network pharmacology has transformed the previous research framework into a “network target, multi-component therapy” model, in order to study the mechanisms of medicinal herbs and its complex components from a holistic perspective.⁶¹ This is completely consistent with the holistic view of herb-centered complementary therapy.⁶² This would allow for the exploration of complex active molecular components and potential molecular targets in herbal formulations, and enable researchers to understand the molecular relationship between different components in a compound, and between components and complex diseases.⁶³ Pharmacological efficacy benefits from its internally integrated multimolecular systems, resulting in clinically meaningful collective effects. In network pharmacology, a network is a combination of various connections between herbal formulations and diseases. Networks mainly comprise of nodes and edges, in which the nodes represent the genes or any biological entity in a biomolecular network, and the edges represent the association, interaction, or any other well-defined relationship. In practice, the construction, analysis and verification of this network is the general path of network pharmacology research. A complex biological network on top of the vast array of existing databases is initially built. Then, the key nodes in the network are identified, and the key biological processes are predicted through network analysis. Finally, further verification through experiments, molecular docking and other operations is performed to ensure the reliability of the predicted results. At present, various modern tools are used for network pharmacology research, such as disease-target databases: TCMSP and OMIM.^{64,65} Active compound databases, such as PubChem⁶⁶ and ChEMBL,⁶⁷ can also be routinely and interactively used. Biomolecular interaction databases, such as HAPPI⁶⁸ and STRING,⁶⁹ are essential for the analysis. In addition to these databases, suitable analysis tools, such as CytoScape⁷⁰ and GUESS, are required. These tools can more effectively and accurately screen out the active ingredients and targets from EOs, and predict the mechanism of action.⁷¹ In recent years, the mechanisms of traditional herbal medicines, including EOs, in the treatment of various serious diseases have been successfully predicted, including depression,⁷² arthritis,⁷³ diabetes⁷⁴ and other diseases,^{75,76} and achieved certain results.

EOs are widely used in the form of aromatherapy or phytotherapy. Some of these are used to treat insomnia, depression, Alzheimer's disease (AD), inflammation, asthma, and various other health conditions.^{77,78} Although various molecular mechanisms of actions have been proposed for EOs, most studies have only tested purified molecules, and the complex mixtures of compounds in herbal medicines have not been investigated, to date, although these have been shown to have more potent effects, when compared to a single isolated compound.^{79,80} Therefore, there is a need

to develop new methods for assessing the effects of complex mixtures of compounds obtained from Eos. Network pharmacology, as a powerful strategy that considers all potential active ingredients, has unprecedented potential for the holistic study of Eos.⁸¹ This method constructs a plant complex target disease network based on the known molecular targets of experimental bioactive molecules in EOs. Through the characterization of disease-related target networks, the multiple roles of EO components can be rationalized, maintaining the integrity of the active molecular properties of plant complexes, and its use in the treatment or prevention of specific medical conditions.⁸¹ In the analysis of the main components of EOs by network pharmacology, the more a disease targets a certain EO, the more these targets are enriched in the main pathogenic pathways of the disease. This indicates that the component may have a more important role in the treatment of the disease. If different EO components act on a common target or signaling pathway, this indicates that these EO components have synergistic effects in the treatment of the disease.⁸²

Various studies have explored the mechanisms by which EOs and its components are used to treat diseases via network pharmacology. For mental disorders, Wang *et al.* used network pharmacology to study the effective components, target proteins and molecular pathways of lavender in the treatment of insomnia. The ingredients of volatile oil obtained from lavender were analyzed by gas chromatography-mass spectrometry, and 906 target proteins of lavender and 182 target proteins of insomnia were predicted by different databases. Furthermore, Kyoto Encyclopedia of Genes and Genomes (KEGG) and Gene Ontology (GO) enrichments were conducted based on the shared parts of the target proteins of lavender, and the target proteins of insomnia. By drawing network diagrams and performing an enrichment analysis, it was found that acetic acid and hexyl ester regulates key target proteins ADRB1 and HLA-DRB1, and interferes with the 5-hydroxytryptamine signaling pathway and GABAergic synapses signaling pathway, playing key roles in the treatment of insomnia.⁸² This study expounds the mechanism of lavender in regulating insomnia through multi-target and multi-channel, and provides a scientific basis for further research on the effect of lavender on insomnia. Another study was carried out by Li *et al.* to investigate the mechanism of volatile oil obtained from *Alpinia oxyphylla* for treating AD based on network pharmacology.⁸³ Six effective components of *Alpinia oxyphylla* were identified by gas chromatography-mass spectrometry, and four potential active ingredients in the treatment of AD and four core targets were screened through the protein-protein interaction network. The GO and KEGG enrichment analysis results revealed that this included nerve ligand receptor interaction, the calcium signaling pathway, cholinergic synapse, and 5-hydroxytryptaminergic synapse. Furthermore, the results indicated that EOs obtained from *Alpinia oxyphylla* can synergistically treat AD by regulating calcium balance, cholinergic balance and phosphorylation.

In addition, Herb Siegesbeckiae (HS) has been widely used to treat inflammatory joint diseases, such as rheumatoid arthritis (RA) and arthritis. However, its molecular mechanisms and active ingredients have not been completely elucidated. Yang *et al.* investigated the multi-target action mechanism and main active components of HS EO in anti-RA, and screened out 31 HS core targets and 16 main active components by network pharmacology. The binding degree of most active components that refer to CSF2 and IL1 β exceeded 10 (degree=16), indicating that the prevention and treatment of RA by HS may play a role through the combination of multiple components and multiple targets.⁸⁴ It is noteworthy

that aromatherapy does not appear to have the side effects of various traditional psychotropic drugs, which clearly deserves further clinical and scientific research.⁸⁵

In recent years, network pharmacology prediction technology has been widely used in the field of herbal medicine due to its systematic and holistic advantages.^{13,86,87} It is very important to validate the results of the network pharmacology method.⁶³ Molecular docking, which is a drug design method based on receptor properties, and interactions between receptors and drug molecules,⁸⁸ can confirm the validity of predicted targets based on the docking scores, and binding between the receptor and ligand molecules.⁸⁹ As an important technology in the field of computer-assisted drug research, a large number of software and computational web servers have been developed and applied, including DOCK,⁹⁰ AutoDock,⁹¹ AutoDock Vina,⁹² PyMOL,⁹³ Protein Database and PubChem (<https://pubchem.ncbi.nlm.nih.gov/>). Xiao *et al.* investigated the mechanism of turmeric EOs in the treatment of insomnia. They used AutoDock Vina and PyMOL to conduct the molecular docking and visualization of 17 targets, and active components related to sedation and hypnosis, providing useful insights into the mechanism of action of active ingredients.⁹⁴ Lu *et al.* used molecular docking to verify the affinity of active compounds in *Artemisia argyi* essential oil for the treatment of pressure injury with core targets by downloading the top 10 core targets and top seven ligand files from the Protein Database and PubChem databases. Then, they used the AutoDock Vina software for molecular docking.⁹⁵ The results revealed that the top seven active compounds of *Artemisia argyi* essential oil had good affinity for key targets, and that the root mean square deviation of each docking target and compound was <2 angstroms.⁹⁵ In summary, the application of network pharmacology and molecular docking technology can effectively clarify the pharmacodynamic material basis of complex chemical substance systems, and improve the efficiency in drug discovery and development via the EO screening process.^{71,96}

Conclusions

Network pharmacology is an integrated approach to efficiently elucidate the molecular mechanisms of EOs in the treatment of various human diseases, such as infectious diseases, chronic diseases, and mental disorders. The present study conducted a review of EOs, from the extraction of plant EOs to the functional application of EOs in human diseases, and subsequently to the network pharmacology of EOs. This provides a timely and brief updated overview of recent studies that involve EOs and human diseases, leading to insights in the potential applications of EOs as a natural reservoir for novel drug development. Overall, it can be concluded that network pharmacology offers a comprehensive and accurate understanding of molecular mechanisms for EOs in the complementary therapy processes of human diseases. This could significantly promote cost-effective natural drug development, and facilitate the popularity of EOs as a complementary medicine.

Acknowledgments

None.

Funding

We are grateful for the support provided by the University Philosophy and Social Science Research Foundation of Jiangsu Education Department (2022SJYB1185), and the Collaboration and Innova-

tion Project of Xuzhou Medical University (XYRHXC2021008).

Conflict of interest

Liang Wang serves as an editorial board member of *Future Integrative Medicine*. The authors have no other commercial or financial relationships that could be construed as a potential conflict of interest to disclose.

Author contributions

LW conceived the core ideas of the manuscript, planned the structure of the manuscript, and was responsible for the student supervision and project administration. YDZ, JWT, QHL MG, ZWM and JYM performed the literature review. JWT visualized the literature data. All authors wrote and revised the manuscript. All authors read and approved the final manuscript.

Reference

- Hoffmann KH. Essential oils. *Z Naturforsch C J Biosci* 2020;75(7-8):177. doi:10.1515/znc-2020-0124, PMID:32609657.
- Karrar E, Ahmed IAM, Wei W, Sarpong F, Proestos C, Amarowicz R, *et al*. Characterization of Volatile Flavor Compounds in Supercritical Fluid Separated and Identified in Gurum (Citrullus lanatus Var. colocynthis) Seed Oil Using HSME and GC-MS. *Molecules* 2022;27(12):3905. doi:10.3390/molecules27123905, PMID:35745026.
- Aziz ZAA, Ahmad A, Setapar SHM, Karakucuk A, Azim MM, Lokhat D, *et al*. Essential Oils: Extraction Techniques, Pharmaceutical And Therapeutic Potential - A Review. *Curr Drug Metab* 2018;19(13):1100–1110. doi:10.2174/1389200219666180723144850, PMID:30039757.
- Vigan M. Essential oils: renewal of interest and toxicity. *Eur J Dermatol* 2010;20(6):685–692. doi:10.1684/ejd.2010.1066, PMID:20840911.
- Ramsey JT, Shropshire BC, Nagy TR, Chambers KD, Li Y, Korach KS. Essential Oils and Health. *Yale J Biol Med* 2020;93(2):291–305. PMID:32607090.
- Fissler M, Quante A. A case series on the use of lavendula oil capsules in patients suffering from major depressive disorder and symptoms of psychomotor agitation, insomnia and anxiety. *Complement Ther Med* 2014;22(1):63–69. doi:10.1016/j.ctim.2013.11.008, PMID:24559818.
- Elaissi A, Rouis Z, Salem NA, Mabrouk S, ben Salem Y, Salah KB, *et al*. Chemical composition of 8 eucalyptus species' essential oils and the evaluation of their antibacterial, antifungal and antiviral activities. *BMC Complement Altern Med* 2012;12:81. doi:10.1186/1472-6882-12-81, PMID:22742534.
- Asif M, Saleem M, Saadullah M, Yaseen HS, Al Zarzour R. COVID-19 and therapy with essential oils having antiviral, anti-inflammatory, and immunomodulatory properties. *Inflammopharmacology* 2020;28(5):1153–1161. doi:10.1007/s10787-020-00744-0, PMID:32803479.
- Hammer KA, Carson CF, Riley TV. Antimicrobial activity of essential oils and other plant extracts. *J Appl Microbiol* 1999;86(6):985–990. doi:10.1046/j.1365-2672.1999.00780.x, PMID:10438227.
- Belhadj S, Hentati O, Hammami M, Ben Hadj A, Boudawara T, Dammak M, *et al*. Metabolic impairments and tissue disorders in alloxan-induced diabetic rats are alleviated by Salvia officinalis L. essential oil. *Biomed Pharmacother* 2018;108:985–995. doi:10.1016/j.biopha.2018.09.108, PMID:30372910.
- Kubatka P, Uramova S, Kello M, Kajo K, Samec M, Jasek K, *et al*. Anticancer Activities of Thymus vulgaris L. in Experimental Breast Carcinoma *in Vivo* and *in Vitro*. *Int J Mol Sci* 2019;20(7):1749. doi:10.3390/ijms20071749, PMID:30970626.
- Hopkins AL. Network pharmacology: the next paradigm in drug discovery. *Nat Chem Biol* 2008;4(11):682–690. doi:10.1038/nchembio.118, PMID:18936753.
- Li S, Zhang B. Traditional Chinese medicine network pharmacology: theory, methodology and application. *Chin J Nat Med* 2013;11(2):110–120. doi:10.1016/S1875-5364(13)60037-0, PMID:23787177.
- Li R, Li Y, Liang X, Yang L, Su M, Lai KP. Network Pharmacology and bioinformatics analyses identify intersection genes of niacin and COVID-19 as potential therapeutic targets. *Brief Bioinform* 2021;22(2):1279–1290. doi:10.1093/bib/bbaa300, PMID:33169132.
- Xia QD, Xun Y, Lu JL, Lu YC, Yang YY, Zhou P, *et al*. Network pharmacology and molecular docking analyses on Lianhua Qingwen capsule indicate Akt1 is a potential target to treat and prevent COVID-19. *Cell Prolif* 2020;53(12):e12949. doi:10.1111/cpr.12949, PMID:33140889.
- Cai Y, Zeng M, Chen YZ. The pharmacological mechanism of Huashi Baidu Formula for the treatment of COVID-19 by combined network pharmacology and molecular docking. *Ann Palliat Med* 2021;10(4):3864–3895. doi:10.21037/apm-20-1759, PMID:33691446.
- Islamuddin M, Chouhan G, Tyagi M, Abdin MZ, Sahal D, Afrin F. Leishmanicidal activities of Artemisia annua leaf essential oil against Visceral Leishmaniasis. *Front Microbiol* 2014;5:626. doi:10.3389/fmicb.2014.00626, PMID:25505453.
- Moreira RRD, Martins GZ, Varandas R, Cogo J, Perego CH, Roncoli G, *et al*. Composition and leishmanicidal activity of the essential oil of Vernonia polyanthes Less (Asteraceae). *Nat Prod Res* 2017;31(24):2905–2908. doi:10.1080/14786419.2017.1299723, PMID:28368666.
- Monzote L, Pastor J, Scull R, Gille L. Antileishmanial activity of essential oil from Chenopodium ambrosioides and its main components against experimental cutaneous leishmaniasis in BALB/c mice. *Phytomedicine* 2014;21(8-9):1048–1052. doi:10.1016/j.phymed.2014.03.002, PMID:24768411.
- Bernuci KZ, Iwanaga CC, Fernandez-Andrade CM, Lorenzetti FB, Torres-Santos EC, Faioes VD, *et al*. Evaluation of Chemical Composition and Antileishmanial and Antituberculosis Activities of Essential Oils of Piper Species. *Molecules* 2016;21(12):1698. doi:10.3390/molecules21121698, PMID:27973453.
- Sadlon AE, Lamson DW. Immune-modifying and antimicrobial effects of Eucalyptus oil and simple inhalation devices. *Altern Med Rev* 2010;15(1):33–47. PMID:20359267.
- Civitelli L, Panella S, Marrocchi ME, De Petris A, Garzoli S, Pepi F, *et al*. *In vitro* inhibition of herpes simplex virus type 1 replication by Mentha suaveolens essential oil and its main component piperitenone oxide. *Phytomedicine* 2014;21(6):857–865. doi:10.1016/j.phymed.2014.01.013, PMID:24629600.
- Silva J, Figueiredo PLB, Byler KG, Setzer WN. Essential Oils as Antiviral Agents. Potential of Essential Oils to Treat SARS-CoV-2 Infection: An In-Silico Investigation. *Int J Mol Sci* 2020;21(10):3426. doi:10.3390/ijms21103426, PMID:32408699.
- Panikar S, Shoba G, Arun M, Sahayarayan JJ, Usha Raja Nanthini A, Chinnathambi A, *et al*. Essential oils as an effective alternative for the treatment of COVID-19: Molecular interaction analysis of protease (M(pro)) with pharmacokinetics and toxicological properties. *J Infect Public Health* 2021;14(5):601–610. doi:10.1016/j.jiph.2020.12.037, PMID:33848890.
- Wilkin PJ, Al-Yozbaki M, George A, Gupta GK, Wilson CM. The Undiscovered Potential of Essential Oils for Treating SARS-CoV-2 (COVID-19). *Curr Pharm Des* 2020;26(41):5261–5277. doi:10.2174/138161282666201015154611, PMID:33059564.
- GBD 2016 Causes of Death Collaborators. Global, regional, and national age-sex specific mortality for 264 causes of death, 1980–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet* 2017;390(10100):1151–1210. doi:10.1016/S0140-6736(17)32152-9, PMID:28919116.
- GBD 2016 Stroke Collaborators. Global, regional, and national burden of stroke, 1990–2016: A systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol* 2019;18(5):439–458. doi:10.1016/S1474-4422(19)30034-1, PMID:30871944.
- Kim IH, Kim C, Seong K, Hur MH, Lim HM, Lee MS. Essential oil inhalation on blood pressure and salivary cortisol levels in prehypertensive and hypertensive subjects. *Evid Based Complement Alternat Med* 2012;2012:984203. doi:10.1155/2012/984203, PMID:23259002.
- da Cunha GH, de Moraes MO, Fecine FV, Frota Bezerra FA, Silveira ER, Canuto KM, *et al*. Vasorelaxant and antihypertensive effects of methanolic fraction of the essential oil of Alpinia zerumbet. *Vascul Pharmacol* 2013;58(5-6):337–345. doi:10.1016/j.vph.2013.04.001, PMID:23603277.
- Interaminense LF, Juca DM, Magalhaes PJ, Leal-Cardoso JH, Duarte

- GP, Lahlou S. Pharmacological evidence of calcium-channel blockade by essential oil of *Ocimum gratissimum* and its main constituent, eugenol, in isolated aortic rings from DOCA-salt hypertensive rats. *Fundam Clin Pharmacol* 2007;21(5):497–506. doi:10.1111/j.1472-8206.2007.00514.x, PMID:17868202.
- [31] Pinto NV, Assreuy AM, Coelho-de-Souza AN, Ceccatto VM, Magalhaes PJ, Lahlou S, *et al.* Endothelium-dependent vasorelaxant effects of the essential oil from aerial parts of *Alpinia zerumbet* and its main constituent 1,8-cineole in rats. *Phytomedicine* 2009;16(12):1151–1155. doi:10.1016/j.phymed.2009.04.007, PMID:19524416.
- [32] Sargazi Zadeh G, Panahi N. Endothelium-independent vasorelaxant activity of *Trachyspermum ammi* essential oil on rat aorta. *Clin Exp Hypertens* 2017;39(2):133–138. doi:10.1080/10641963.2016.1235178, PMID:28287882.
- [33] Shojaei Shad F, Haghighi MJ. Study of the effect of the essential oil (extract) of rhubarb stem (shoot) on glycosylated hemoglobin and fasting blood glucose levels in patients with type II diabetes. *Biomedicine (Taipei)* 2018;8(4):24. doi:10.1051/bmdcn/2018080424, PMID:30474605.
- [34] Greay SJ, Ireland DJ, Kissick HT, Heenan PJ, Carson CF, Riley TV, *et al.* Inhibition of established subcutaneous murine tumour growth with topical *Melaleuca alternifolia* (tea tree) oil. *Cancer Chemother Pharmacol* 2010;66(6):1095–1102. doi:10.1007/s00280-010-1267-3, PMID:20577741.
- [35] Ren P, Ren X, Cheng L, Xu L. Frankincense, pine needle and geranium essential oils suppress tumor progression through the regulation of the AMPK/mTOR pathway in breast cancer. *Oncol Rep* 2018;39(1):129–137. doi:10.3892/or.2017.6067, PMID:29115548.
- [36] Xing X, Ma JH, Fu Y, Zhao H, Ye XX, Han Z, *et al.* Essential oil extracted from *Erythrina corallodendron* L. leaves inhibits the proliferation, migration, and invasion of breast cancer cells. *Medicine (Baltimore)* 2019;98(36):e17009. doi:10.1097/MD.00000000000017009, PMID:31490383.
- [37] Wu C, Zhuang Y, Jiang S, Tian F, Teng Y, Chen X, *et al.* Cinnamaldehyde induces apoptosis and reverses epithelial-mesenchymal transition through inhibition of Wnt/beta-catenin pathway in non-small cell lung cancer. *Int J Biochem Cell Biol* 2017;84:58–74. doi:10.1016/j.biocel.2017.01.005, PMID:28093328.
- [38] Oboh G, Ademosen AO, Odubanjo OV, Akinbola IA. Antioxidative properties and inhibition of key enzymes relevant to type-2 diabetes and hypertension by essential oils from black pepper. *Adv Pharmacol Sci* 2013;2013:926047. doi:10.1155/2013/926047, PMID:24348547.
- [39] Mnafigui K, Kchaou M, Ben Salah H, Hajji R, Khabbabi G, Elfeki A, *et al.* Essential oil of *Zygophyllum album* inhibits key-digestive enzymes related to diabetes and hypertension and attenuates symptoms of diarrhea in alloxan-induced diabetic rats. *Pharm Biol* 2016;54(8):1326–1333. doi:10.3109/13880209.2015.1075049, PMID:26439719.
- [40] Abouhosseini Tabari M, Hajizadeh Moghaddam A, Maggi F, Benelli G. Anxiolytic and antidepressant activities of *Pelargonium roseum* essential oil on Swiss albino mice: Possible involvement of serotonergic transmission. *Phytother Res* 2018;32(6):1014–1022. doi:10.1002/ptr.6038, PMID:29468757.
- [41] Gilani AH, Shah AJ, Zubair A, Khalid S, Kiani J, Ahmed A, *et al.* Chemical composition and mechanisms underlying the spasmolytic and bronchodilatory properties of the essential oil of *Nepeta cataria* L. *J Ethnopharmacol* 2009;121(3):405–411. doi:10.1016/j.jep.2008.11.004, PMID:19041706.
- [42] Pina LTS, Ferro JNS, Rabelo TK, Oliveira MA, Scotti L, Scotti MT, *et al.* Alcoholic monoterpenes found in essential oil of aromatic spices reduce allergic inflammation by the modulation of inflammatory cytokines. *Nat Prod Res* 2019;33(12):1773–1777. doi:10.1080/14786419.2018.1434634, PMID:29394874.
- [43] Salem MA, Manaa EG, Osama N, Aborehab NM, Ragab MF, Haggag YA, *et al.* *Coriander* (*Coriandrum sativum* L.) essential oil and oil-loaded nano-formulations as an anti-aging potentiality via TGFbeta/SMAD pathway. *Sci Rep* 2022;12(1):6578. doi:10.1038/s41598-022-10494-4, PMID:35449437.
- [44] Gomez LA, Stashenko E, Ocazone RE. Comparative study on *in vitro* activities of citral, limonene and essential oils from *Lippia citriodora* and *L. alba* on yellow fever virus. *Nat Prod Commun* 2013;8(2):249–252. PMID:23513741.
- [45] Duschatzky CB, Possetto ML, Talarico LB, Garcia CC, Michis F, Almeida NV, *et al.* Evaluation of chemical and antiviral properties of essential oils from South American plants. *Antivir Chem Chemother* 2005;16(4):247–251. doi:10.1177/095632020501600404, PMID:16130522.
- [46] Haddad JG, Picard M, Benard S, Desvignes C, Despres P, Diotel N, *et al.* Ayapana triplinervis Essential Oil and Its Main Component Thymohydroquinone Dimethyl Ether Inhibit Zika Virus at Doses Devoid of Toxicity in Zebrafish. *Molecules* 2019;24(19):3447. doi:10.3390/molecules24193447, PMID:31547527.
- [47] Mahboubi M. *Artemisia sieberi* Besser essential oil and treatment of fungal infections. *Biomed Pharmacother* 2017;89:1422–1430. doi:10.1016/j.biopha.2017.03.036, PMID:28346993.
- [48] Mahboubi M, Kashani LM. The anti-dermatophyte activity of *Commiphora molmol*. *Pharm Biol* 2016;54(4):720–725. doi:10.3109/13880209.2015.1072831, PMID:26427766.
- [49] Athipornchai A, Kumpang R, Semsri S. Potential Biological Activities of *Clausena* Essential Oils for the Treatment of Diabetes. *J Oleo Sci* 2021;70(11):1669–1676. doi:10.5650/jos.ess19294, PMID:34732637.
- [50] de Siqueira RJ, Rodrigues KM, da Silva MT, Correia Junior CA, Duarte GP, Magalhaes PJ, *et al.* Linalool-rich rosewood oil induces vago-vagal bradycardic and depressor reflex in rats. *Phytother Res* 2014;28(1):42–48. doi:10.1002/ptr.4953, PMID:23447129.
- [51] Duan D, Chen L, Yang X, Tu Y, Jiao S. Antidepressant-like effect of essential oil isolated from *Toona ciliata* Roem. var. *yunnanensis*. *J Nat Med* 2015;69(2):191–197. doi:10.1007/s11418-014-0878-0, PMID:25465853.
- [52] Zhong Y, Zheng Q, Hu P, Huang X, Yang M, Ren G, *et al.* Sedative and hypnotic effects of compound Anshen essential oil inhalation for insomnia. *BMC Complement Altern Med* 2019;19(1):306. doi:10.1186/s12906-019-2732-0, PMID:31711477.
- [53] Elgamal AM, Ahmed RF, Abd-ElGawad AM, El Gendy AEG, Elshamy AI, Nassar MI. Chemical Profiles, Anticancer, and Anti-Aging Activities of Essential Oils of *Pluchea dioscoridis* (L.) DC. and *Erigeron bonariensis* L. *Plants (Basel)* 2021;10(4):667. doi:10.3390/plants10040667, PMID:33807147.
- [54] Lehrner J, Marwinski G, Lehr S, Johren P, Deecke L. Ambient odors of orange and lavender reduce anxiety and improve mood in a dental office. *Physiol Behav* 2005;86(1-2):92–95. doi:10.1016/j.physbeh.2005.06.031, PMID:16095639.
- [55] McCaffrey R, Thomas DJ, Kinzelman AO. The effects of lavender and rosemary essential oils on test-taking anxiety among graduate nursing students. *Holist Nurs Pract* 2009;23(2):88–93. doi:10.1097/HNP.0b013e3181a110aa, PMID:19258850.
- [56] Lewith GT, Godfrey AD, Prescott P. A single-blinded, randomized pilot study evaluating the aroma of *Lavandula angustifolia* as a treatment for mild insomnia. *J Altern Complement Med* 2005;11(4):631–637. doi:10.1089/acm.2005.11.631, PMID:16131287.
- [57] Johannessen B. Nurses experience of aromatherapy use with dementia patients experiencing disturbed sleep patterns. An action research project. *Complement Ther Clin Pract* 2013;19(4):209–213. doi:10.1016/j.ctcp.2013.01.003, PMID:24199975.
- [58] Nasiri Lari Z, Hajimonfarednejad M, Riasatian M, Abolhassanzadeh Z, Raji A, Vojoud M, *et al.* Efficacy of inhaled *Lavandula angustifolia* Mill. Essential oil on sleep quality, quality of life and metabolic control in patients with diabetes mellitus type II and insomnia. *J Ethnopharmacol* 2020;251:112560. doi:10.1016/j.jep.2020.112560, PMID:31931160.
- [59] Lohani A, Verma A, Hema G, Pathak K. Topical Delivery of Geranium/Calendula Essential Oil-Entrapped Ethanol Lipid Vesicular Cream to Combat Skin Aging. *Biomed Res Int* 2021;2021:4593759. doi:10.1155/2021/4593759, PMID:34552986.
- [60] Hopkins AL. Network pharmacology. *Nat Biotechnol* 2007;25(10):1110–1111. doi:10.1038/nbt1007-1110, PMID:17921993.
- [61] Moodley D, Yoshida H, Mostafavi S, Asinowski N, Ortiz-Lopez A, Symanowicz P, *et al.* Network pharmacology of JAK inhibitors. *Proc Natl Acad Sci USA* 2016;113(35):9852–9857. doi:10.1073/pnas.1610253113, PMID:27516546.
- [62] Dong R, Huang R, Shi X, Xu Z, Mang J. Exploration of the mechanism of luteolin against ischemic stroke based on network pharmacol-

- ogy, molecular docking and experimental verification. *Bioengineered* 2021;12(2):12274–12293. doi:10.1080/21655979.2021.2006966, PMID:34898370.
- [63] Jiao X, Jin X, Ma Y, Yang Y, Li J, Liang L, *et al.* A comprehensive application: Molecular docking and network pharmacology for the prediction of bioactive constituents and elucidation of mechanisms of action in component-based Chinese medicine. *Comput Biol Chem* 2021;90:107402. doi:10.1016/j.compbiolchem.2020.107402, PMID:33338839.
- [64] Ru J, Li P, Wang J, Zhou W, Li B, Huang C, *et al.* TCMSP: a database of systems pharmacology for drug discovery from herbal medicines. *J Cheminform* 2014;6:13. doi:10.1186/1758-2946-6-13, PMID:24735618.
- [65] Hamosh A, Scott AF, Amberger JS, Bocchini CA, McKusick VA. Online Mendelian Inheritance in Man (OMIM), a knowledgebase of human genes and genetic disorders. *Nucleic Acids Res* 2005;33(suppl 1):D514–517. doi:10.1093/nar/gki033, PMID:15608251.
- [66] Cheng T, Pan Y, Hao M, Wang Y, Bryant SH. PubChem applications in drug discovery: a bibliometric analysis. *Drug Discov Today* 2014;19(11):1751–1756. doi:10.1016/j.drudis.2014.08.008, PMID:25168772.
- [67] Papadatos G, Overington JP. The ChEMBL database: a taster for medicinal chemists. *Future Med Chem* 2014;6(4):361–364. doi:10.4155/fmc.14.8, PMID:24635517.
- [68] Chen JY, Mamidipalli S, Huan T. HAPPI: an online database of comprehensive human annotated and predicted protein interactions. *BMC Genomics* 2009;10(Suppl 1):S16. doi:10.1186/1471-2164-10-S1-S16, PMID:19594875.
- [69] Szklarczyk D, Franceschini A, Wyder S, Forslund K, Heller D, Huerta-Cepas J, *et al.* STRING v10: protein-protein interaction networks, integrated over the tree of life. *Nucleic Acids Res* 2015;43(D1):D447–452. doi:10.1093/nar/gku1003, PMID:25352553.
- [70] Shannon P, Markiel A, Ozier O, Baliga NS, Wang JT, Ramage D, *et al.* Cytoscape: a software environment for integrated models of biomolecular interaction networks. *Genome Res* 2003;13(11):2498–2504. doi:10.1101/gr.1239303, PMID:14597658.
- [71] Han K, Zhang L, Wang M, Zhang R, Wang C, Zhang C. Prediction Methods of Herbal Compounds in Chinese Medicinal Herbs. *Molecules* 2018;23(9):2303. doi:10.3390/molecules23092303, PMID:30201875.
- [72] Pan HT, Xi ZQ, Wei XQ, Wang K. A network pharmacology approach to predict potential targets and mechanisms of “*Ramulus Cinnamomi* (cassiae) - *Paeonia lactiflora*” herb pair in the treatment of chronic pain with comorbid anxiety and depression. *Ann Med* 2022;54(1):413–425. doi:10.1080/07853890.2022.2031268, PMID:35098831.
- [73] Xie B, Lu H, Xu J, Luo H, Hu Y, Chen Y, *et al.* Targets of hydroxychloroquine in the treatment of rheumatoid arthritis. A network pharmacology study. *Joint Bone Spine* 2021;88(2):105099. doi:10.1016/j.jbspin.2020.105099, PMID:33160044.
- [74] Xu F, Zhang M, Wu H, Wang Y, Yang Y, Wang X. Study on the mechanism of lupenone for treating type 2 diabetes by integrating pharmacological evaluation and network pharmacology. *Pharm Biol* 2022;60(1):997–1010. doi:10.1080/13880209.2022.2067568, PMID:35635284.
- [75] Zhou J, Wang Q, Xiang Z, Tong Q, Pan J, Wan L, *et al.* Network Pharmacology Analysis of Traditional Chinese Medicine Formula Xiao Ke Yin Shui Treating Type 2 Diabetes Mellitus. *Evid Based Complement Alternat Med* 2019;2019:4202563. doi:10.1155/2019/4202563, PMID:31583009.
- [76] Hu RF, Sun XB. Design of new traditional Chinese medicine herbal formulae for treatment of type 2 diabetes mellitus based on network pharmacology. *Chin J Nat Med* 2017;15(6):436–441. doi:10.1016/S1875-5364(17)30065-1, PMID:28629533.
- [77] Lillehei AS, Halcon LL. A systematic review of the effect of inhaled essential oils on sleep. *J Altern Complement Med* 2014;20(6):441–451. doi:10.1089/acm.2013.0311, PMID:24720812.
- [78] Ali B, Al-Wabel NA, Shams S, Ahamad A, Khan SA, Anwar F. Essential oils used in aromatherapy: A systematic review. *Asian Pac J Trop Biomed* 2015;5(8):601–611. doi:10.1016/j.apjtb.2015.05.007.
- [79] Raut JS, Karuppayil SM. A status review on the medicinal properties of essential oils. *Industrial Crops and Products* 2014;62:250–264. doi:10.1016/j.indcrop.2014.05.055.
- [80] Cravotto G, Boffa L, Genzini L, Garella D. Phytotherapeutics: an evaluation of the potential of 1000 plants. *J Clin Pharm Ther* 2010;35(1):11–48. doi:10.1111/j.1365-2710.2009.01096.x, PMID:20175810.
- [81] Buriani A, Fortinguerra S, Sorrenti V, Caudullo G, Carrara M. Essential Oil Phytocomplex Activity, a Review with a Focus on Multivariate Analysis for a Network Pharmacology-Informed Phytogenomic Approach. *Molecules* 2020;25(8):1833. doi:10.3390/molecules25081833, PMID:32316274.
- [82] Wang Y, Zou J, Jia Y, Liang Y, Zhang X, Wang CL, *et al.* A Study on the Mechanism of Lavender in the Treatment of Insomnia Based on Network Pharmacology. *Comb Chem High Throughput Screen* 2020;23(5):419–432. doi:10.2174/1386207323666200401095008, PMID:32233997.
- [83] Li WJ, Xiao S, Zheng Q, Zhu LY, Zhang MX, Yang M, *et al.* Mechanism of volatile oil from *Alpinia oxyphylla* in treating Alzheimer's disease based on GC-MS and network pharmacology. *Zhongguo Zhong Yao Zhi* 2021;46(12):3052–3057. doi:10.19540/j.cnki.cjcmm.20210301.401, PMID:34467695.
- [84] Yang X, Li Y, Lv R, Qian H, Chen X, Yang CF. Study on the Multitarget Mechanism and Key Active Ingredients of Herba Siegesbeckiae and Volatile Oil against Rheumatoid Arthritis Based on Network Pharmacology. *Evid Based Complement Alternat Med* 2019;2019:8957245. doi:10.1155/2019/8957245, PMID:31885670.
- [85] Perry N, Perry E. Aromatherapy in the management of psychiatric disorders: clinical and neuropharmacological perspectives. *CNS Drugs* 2006;20(4):257–280. doi:10.2165/00023210-200620040-00001, PMID:16599645.
- [86] Zhang W, Huai Y, Miao Z, Qian A, Wang Y. Systems Pharmacology for Investigation of the Mechanisms of Action of Traditional Chinese Medicine in Drug Discovery. *Front Pharmacol* 2019;10:743. doi:10.3389/fphar.2019.00743, PMID:31379563.
- [87] Luo TT, Lu Y, Yan SK, Xiao X, Rong XL, Guo J. Network Pharmacology in Research of Chinese Medicine Formula: Methodology, Application and Prospective. *Chin J Integr Med* 2020;26(1):72–80. doi:10.1007/s11655-019-3064-0, PMID:30941682.
- [88] Pinzi L, Rastelli G. Molecular Docking: Shifting Paradigms in Drug Discovery. *Int J Mol Sci* 2019;20(18):4331. doi:10.3390/ijms20184331, PMID:31487867.
- [89] Lee WY, Lee CY, Kim YS, Kim CE. The Methodological Trends of Traditional Herbal Medicine Employing Network Pharmacology. *Biomolecules* 2019;9(8):362. doi:10.3390/biom9080362, PMID:31412658.
- [90] Allen WJ, Balius TE, Mukherjee S, Brozell SR, Moustakas DT, Lang PT, *et al.* DOCK 6: Impact of new features and current docking performance. *J Comput Chem* 2015;36(15):1132–1156. doi:10.1002/jcc.23905, PMID:25914306.
- [91] Wojciechowski M. Simplified AutoDock force field for hydrated binding sites. *J Mol Graph Model* 2017;78:74–80. doi:10.1016/j.jmgm.2017.09.016, PMID:29054096.
- [92] Rentzsch R, Renard BY. Docking small peptides remains a great challenge: an assessment using AutoDock Vina. *Brief Bioinform* 2015;16(6):1045–1056. doi:10.1093/bib/bbv008, PMID:25900849.
- [93] Lill MA, Danielson ML. Computer-aided drug design platform using PyMOL. *J Comput Aided Mol Des* 2011;25(1):13–19. doi:10.1007/s10822-010-9395-8, PMID:21053052.
- [94] Xiao S, Liu S, Yu H, Xie Y, Guo Y, Fan J, *et al.* A Study on the Mechanism of the Sedative-hypnotic Effect of Cinnamomum camphora char. Borneol Essential Oil Based on Network Pharmacology. *J Oleo Sci* 2022;71(7):1063–1073. doi:10.5650/jos.ess21278, PMID:35691835.
- [95] Lu ST, Tang LL, Zhou LH, Lai YT, Liu LX, Duan Y. Study on the Multitarget Mechanism and Active Compounds of Essential Oil from *Artemisia argyi* Treating Pressure Injuries Based on Network Pharmacology. *Evid Based Complement Alternat Med* 2022;2022:1019289. doi:10.1155/2022/1019289, PMID:35096100.
- [96] Yu L, Wei F, Liang J, Ren G, Liu X, Wang CZ, *et al.* Target Molecular-Based Neuroactivity Screening and Analysis of Panax ginseng by Affinity Ultrafiltration, UPLC-QTOF-MS and Molecular Docking. *Am J Chin Med* 2019;47(6):1345–1363. doi:10.1142/S0192415X19500691, PMID:31495181.