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A molecular docking study of Rhizoma Atractylodis and Rhizoma Atractylodis Macrocephalae herbal pair with respect to type 2 diabetes mellitus

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Abstract *Objective:* To investigate the action mechanism of Rhizoma Atractylodis (*Atractylodes lancea (Thunb.) Dc.*) and Rhizoma Atractylodis Macrocephalae (*Atractylodes macrocephala Koidz.*), a two-herb ancient traditional Chinese medicine used to treat type 2 diabetes mellitus, using molecular docking.
Methods: The Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform was searched for compounds in the two herbs and oral bioavailability and drug-likeness values were used to select compounds. The target proteins were selected based on a survey of the literature and related databases, and three receptors closely related to type 2 diabetes were chosen: insulin receptor, peroxisome proliferator activated receptor and dipeptidyl peptidase-IV. Molecular docking was performed using the CDocker module in Discovery Studio software. The interactions between targets and ligands were observed and analyzed, including the mode of action.
Results: Nineteen compounds from the herbal pair interacted with the insulin receptor, the peroxisome proliferator activated receptor and dipeptidyl peptidase-IV. Among them, 10 compounds bound successfully with all three targets, one compound bound with two targets, and eight compounds bound with one target. According to CDocker Interaction Energy, most compounds from the herbal pair had good binding activities with receptors and nine compounds had even higher scores than those of the original ligands. These data indicate that these compounds may be active in reducing blood glucose levels for the treatment of type 2 diabetes.

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Conclusion: Multiple compounds in the Rhizoma Atractylodis-Rhizoma Atractylodis Macrocephalae herbal pair can affect multiple human targets related to type 2 diabetes.

Introduction

Diabetes is a chronic metabolic disorder that occurs when the body cannot produce enough insulin or cannot use insulin. It is currently one of the largest global health emergencies; according to the International Diabetes Federation (IDF), in 2017 there were 425 million adults estimated to have diabetes, and the number is likely to reach 629 million by 2045.[1] Type 2 diabetes mellitus (T2DM) is the most common type of diabetes, and the causes of the T2DM are various.

In traditional Chinese medicine (TCM) theory, there are six main functional systems within the human body: liver-gall bladder, heart-small intestine, pericardium-sanjiao, spleen-stomach, lung-large intestine, and kidney-bladder, with each system possessing two meridians. These six functional systems along with the 12 meridians maintain the normal function of a human being, and any disorder within those systems may lead to different kinds of disease. The spleen-stomach functional system is mainly in charge of activities related to digestion, absorption, distribution and metabolism. Disorders of the spleen-stomach functional system may cause a number of digestive diseases and metabolic diseases including T2DM.

Rhizoma Atractylodis (*Atractylodes lancea* (*Thunb.*) *Dc.*) and Rhizoma Atractylodis Macrocephalae (*Atractylodes macrocephala Koidz.*) are commonly used TCM herbs that are both believed to be able to adjust the spleen-stomach functional system. Rhizoma Atractylodis accelerates spleen functions and Rhizoma Atractylodis Macrocephalae restores stomach functions; the herbal pair has a long history in treating spleen-stomach functional system diseases. Rhizoma Atractylodis can motivate qi in the spleen to accelerate spleen functions and disperse dampness caused by spleen qi deficiency, while Rhizoma Atractylodis Macrocephalae can restore qi in the stomach and can ease nausea and improve appetite by recovering stomach functions.[2] By using the two herbs as a pair, TCM practitioners can restore balance of spleen-stomach system and therefore enhance functions of this system to treat related diseases. Many TCM practitioners now add this herbal pair to their formulas when treating T2DM with spleen-stomach functional system disorders.

By reviewing previous studies,[3,4] we found that Rhizoma Atractylodis extract inhibits small intestine sucrase, which would reduce the hydrolysis of sucrose. This can be used to reduce the absorption of glucose in diabetic patients. Rhizoma Atractylodis can also reduce blood glucose levels in alloxan-induced hyperglycemia mice.[5] Rhizoma Atractylodis Macrocephalae can accelerate the body's glucose metabolism and prevent glycogen breakdown. This significantly reduces fasting and postprandial blood glucose, improves glucose tolerance, and increases the insulin sensitivity index. This suggests that Rhizoma Atractylodis Macrocephalae may act by increasing the insulin sensitivity of peripheral target organs, improving insulin resistance and inducing a hypoglycemic effect.[6,7] Pharmacological tests show that Rhizoma Atractylodis and Rhizoma Atractylodis Macrocephalae are effective in treating diabetes.

Although the Rhizoma Atractylodis-Rhizoma Atractylodis Macrocephalae herbal pair is commonly used in TCM formulas to treat T2DM, its pharmacological mechanism is still unclear. Therefore, this study used molecular docking to try to reveal the pharmacological mechanism of the Rhizoma Atractylodis-Rhizoma Atractylodis Macrocephalae herbal pair in treating T2DM.

Materials and methods

Data preparation

Preparation of small molecules (ligands)

Compounds from Rhizoma Atractylodis and Rhizoma Atractylodis Macrocephalae were identified in the Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMSP) (http://ibts.hkbu.edu.hk/LSP/tcmsp.php, updated on 2014-05-31). The TCMSP is a platform for integrating drug pharmacokinetics, drug chemistry, and drug-target protein-disease networks, and consists of the 499 Chinese herbs with 29,384 ingredients registered in the Chinese pharmacopoeia. Twelve important properties, including human oral bioavailability, half-life, drug-likeness and Lipinski's rule of five are provided in the TCMSP for drug screening and evaluation.[8] TCMSP provides a new rationale to discover active components in Chinese medicines and to study their mechanisms of action.[9] Using "Cangzhu" and "Baizhu" as keywords, the TCMSP was searched for all related chemical compounds.

Most TCM herbs are oral preparations and their compounds usually reach targets in the human body by absorption, distribution, metabolism and excretion (ADME). Oral bioavailability (OB) means the extent to which a drug or other substance is taken up by a specific tissue or organ after administration, and the higher the value the better the drug or substance is absorbed (OB $\geq$ 30% indicates the drug or substance is absorbed well).[10] Drug-likeness (DL) means the similarity of compounds to known drugs, and the DL standard is usually set as 0.18.[11] Compound selection is usually made according to that standard (DL $\geq$ 0.18). These two parameters are the key parameters of ADME in Chinese medicine.[12] The chemical structures of compounds were downloaded from TCMSP and the PubChem database and saved as mol2 format files. The small molecules were pretreated with the Discovery Studio software package (Accelrys, San Diego, CA). "Prepare Ligands" was selected

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