Liuwei Dihuang Pills in the Treatment of Senile Dementia: A Review

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Abstract: Objective To elucidate the synergistic mechanism of Liuwei Dihuang Pills (LWDHP), with multi-components, multi-targets and multi-channels in the treatment of senile dementia. **Methods** We searched Chinese and English databases to obtain the blood components of LWDHP, its clinical and preclinical mechanism research progress in the treatment of senile dementia. Based on the network pharmacology of the key pathophysiological process of Alzheimer's disease (AD), we screened the anti-AD target of LWDHP and its blood components. **Results** The therapeutic effect of LWDHP on senile dementia is accurate, with few adverse reactions. Its mechanism includes regulation of cholinergic system, autophagy, cerebral microvascular function, neuron apoptosis, insulin signal transduction pathway, etc. In this review, 35 blood components of LWDHP based on HPLC were collected, and their drug toxicity and safety were evaluated. The network pharmacology analysis based on the pathophysiological process of AD shows that the key components of LWDHP in the treatment of AD are Alisol A monoacetate, Linoleic acid, Alisol F, Tumulosic acid, Methyl eugenol, Palmitic acid and Pachymic acid. **Conclusion** This article summarizes 35 blood components of LWDHP, summarizes the synergistic mechanism of LWDHP in the treatment of senile dementia, uses network pharmacology to provide a series of potential lead compounds for the development of senile dementia's drugs, and provides a theoretical basis for further expanding the clinical application of LWDHP.

1 INTRODUCTION

Senile dementia is a serious neurodegenerative disease with progressive loss of memory and mental ability and obvious personality changes as the main clinical manifestations. Alzheimer's disease includes Alzheimer's disease (AD), vascular dementia, Lewy bodies dementia, frontotemporal dementia, etc. AD is the most common subtype of Alzheimer's disease (accounting for 60-70%), followed by vascular dementia (accounting for 20%). According to the latest data from the World Health Organization, about 55 million people worldwide suffered from dementia in 2019, which is expected to increase to 139 million by 2050[1]. Currently, there are no effective treatments for Alzheimer's disease, Acetylcholinesterase inhibitor, N-methyl-D-aspartic acid (NMDA) receptor antagonist Memantine and Aducanumab targeting Amyloid-β (Aβ) play a certain therapeutic role[2, 3]. However, the above-mentioned drugs are often accompanied by side effects. Therefore, it is very important to develop effective, safe and non-toxic drugs or lead compounds for the prevention and treatment of Alzheimer's disease based on the single Chinese medicine and compound preparation of the effective ingredients of traditional Chinese medicine.

There is no record of senile dementia in ancient Chinese medicine books, and its clinical symptoms belong to the categories of "moronic disease", "dementia", "forgettability", "literary madness", "depression syndrome" and so on. Emphasize sufficient kidney qi, nourish the brain, marrow sea is insufficient, brain loss, divine machinery loss, and dementia. Therefore "kidney essence deficiency, marrow sea loss" is the occurrence and development of senile dementia fundamental pathogenesis [4]. Kidney tonifying prescription Liuwei Dihuang Pills (Liuwei Dihuang Pills, LWDHP) derived from the Song Dynasty medical scientist Qian Yi "children's medicine syndrome straight formula", composed of cooked rehmannia, cornus officinalis, yam, alisma, moutan bark, poria according to 8:4:4:3:3:3 ratio mixed. LWDHP formula has unique characteristics and positive curative effect, and its main clinical treatment syndroms are constantly expanding, including Alzheimer's disease, Parkinson's disease, female menopause syndrome, etc [5]. Although the main clinical treatment of LWDHP many, but can not blindly take, kidney Yang deficiency, spleen deficiency and stomach deficiency patients should not take LWDHP. This article aims to review the research progress and material basis of LWDHP in the treatment of Alzheimer's disease, in order to provide theoretical basis for the treatment of Alzheimer's disease and identify a series of potential lead compounds.

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2 CLINICAL AND MECHANISM RESEARCH PROGRESS OF LWDHP IN THE TREATMENT OF SENILE DEMENTIA

2.1 Clinical research progress of LWDHP in the treatment of Alzheimer's disease

Clinical trials of drugs are necessary steps to confirm their effectiveness and safety. LWDHP, a representative prescription for nourishing Yin and tonifying kidney, has a long history of clinical use, and its safety and effectiveness in the treatment of Alzheimer's disease have been fully proved, which is also a significant advantage of drug development based on traditional Chinese medicine prescriptions. In recent ten years, a large number of clinical studies have paid attention to the clinical efficacy of LWDHP in the treatment of Alzheimer's disease. The total effective rate of LWDHP in the treatment of Alzheimer's disease is (89.56 ± 3.84) %[6-14]. For senile dementia with kidney-yin deficiency, LWDHP can significantly improve patients' cognitive ability, clinical symptoms (including mental disorders and TCM symptoms) and daily living ability[10, 11, 13]. Senile dementia is accompanied by mental symptoms in the middle and late stages, mainly manifested as irritability, irritability, eccentric personality, delusion, hallucination and other symptoms. LWDHP can improve the mental and behavioral symptoms of Alzheimer's disease, and its clinical efficacy is better than olanzapine (antipsychotic drug with significant efficacy), and its adverse reactions are lower than olanzapine[6, 7, 9, 12, 13]. The above clinical studies have proved that LWDHP has accurate and reliable therapeutic effect on Alzheimer's disease, significantly improving clinical symptoms and less adverse reactions than western medicine alone. A common reason for drug clinical trials to fail is the discrepancy between preclinical studies (in vitro and in vivo) and human trials, where a drug that has shown efficacy in animal trials cannot be confirmed clinically.

2.2 Preclinical research progress of LWDHP in the treatment of Alzheimer's disease

Preclinical research is the main means for researchers to explore the internal mechanism of disease occurrence and development, and also an important method to clarify the effect of drugs on disease prevention and treatment and its mechanism. Acetylcholine (Ach) is one of the most important neurotransmitters in the central cholinergic system. Acetylcholinesterase inhibitors are the most widely used drugs for treating AD. LWDHP can increase the activities of Ach, dopamine and norepinephrine in the brain of elderly mice, and reduce the activity of cholinesterase to improve the function of central nervous system[15]. Autophagy dysfunction is closely related to Alzheimer's disease and activation of autophagy is one of the strategies against neurodegenerative diseases. LWDHP can significantly improve the autophagy level of hippocampal neurons, reduce neuronal damage, and improve the learning and memory ability of Alzheimer's disease model mice[16-18]. Chronic cerebral hypoperfusion and microvascular changes are early clinical markers of AD [19, 20]. LWDHP regulate Aβ metabolism through RAGE/LRP1 receptor system, promote cerebral microangiogenesis by inhibiting von Willebrand factor (vWF) expression and increasing VEGF-A and CD34, and improve cerebral microvascular injury in SAMP8 mice. Improve spatial learning and memory [21]. The above-mentioned mechanism of LWDHP in the treatment of Alzheimer's disease involves symptomatic treatment and multiple links affecting the progression of the disease, suggesting that LWDHP can play a synergistic role in the treatment of Alzheimer's disease through multiple active ingredients and multiple targets and multiple ways. Research on the mechanism of LWDHP also has some defects, such as lack of application safety evaluation, high-quality basic research, and unclear relationship of "active ingredient-target-disease pathophysiological process". Therefore, it is of great significance to study the material basis and research progress of LWDHP targeting Alzheimer's disease pathological process.

3 EVALUATION OF SUBSTANCE BASIS AND DRUG PROPERTIES OF LWDHP

3.1 Material basis of LWDHP

Through the action of various active components on multiple targets of different organs, the compound exerts clinical efficacy through synergistic action on pathophysiological processes of diseases. The overall drug effect of the compound is significantly greater than that of any drug or a group of drugs in the compound. The pharmacodynamic material basis of the compound cannot be clarified by focusing only on the components of traditional Chinese medicine contained in the compound or the ingredients with pharmacological activity in vitro. Therefore, there are serious methodological defects in the material basis research of LWDHP based on TCM database (such as TCM systematic pharmacology database and analysis platform TCMSP), which usually results in highly homogeneous research results[22-24].The pharmacochemistry of TCM serum is an effective method to study the pharmacochemistry and compatibility of the compound. The prototype components of LWDHP in serum and cerebrospinal fluid of SD rats were detected after intragastric administration of 3 mL LWDHP solution (6.75 g/kg). Wang Di et al[25] identified 21 components (paeonol, eugenic acid, ellagic acid and isocarcinolactone) of LWDHP into blood and 4 components (paeonol, eugenic acid, ellagic acid and isocarcinolactone) into brain based on UPLC-LTQ-Orbitrap-MS technology combined with ultra-high performance liquid chromatography, linear ion trap/electrostatic field orbital trap). In order to comprehensively collect the blood entry components of LWDHP, further literature retrieval [25-35], obtained 35 main blood entry components of LWDHP (Table 1). These

blood entry components are the basis of pharmacodynamic substances of LWDHP.

3.2 Evaluation of medicinal properties of LWDHP

Lipinski's rule of five (RO5) is an empirical rule for medicinal compounds and an accepted standard for oral drugs [36]. This article USES ADMETlab 2.0 (https://admetmesh.scbdd.com/)[37] to evaluate 35 of LWDHP into the blood and into the components of the brain RO5 (table 1), it shows that the majority of LWDHP into the composition of blood in the body has good bioavailability. The efficacy and mechanism of LWDHP with poor drug properties and low oral bioavailability against Alzheimer's disease need to be explored in future studies. For example, Yu Lei [38] found that cornus officinarin improved cognitive impairment in AD mice through anti-oxidative damage, anti-neuroinflammation and anti-apoptosis.

3.3 Safety evaluation of chemical constituents of LWDHP

The mechanism of compound toxicity is more complex than that of monomer. Understanding the basis of compound toxicity is very important to improve the safety of compound clinical application. One of the advantages of the compound is that the bias and toxicity of the prescription can be reduced through the organic compatibility of the drugs. Although LWDHP is less than Western medicine alone in the treatment of senile dementia, its safety material basis has not been clearly reported. In this paper, ProTox-II (https://tox-new.charite.de/protox_II/)[39] was used to evaluate the safety of 35 blood entry components of LWDHP. Toxicological parameters included hepatotoxicity, acute oral toxicity (Median lethal dose, LD50, mg/kg), and multiple toxicological endpoints including carcinogenicity, immunotoxicity, mutagenicity, and cytotoxicity. ProTox-II classifies the acute toxicity of each compound from 1 to 6, corresponding to lethal, lethal, toxic, harmful, possibly harmful, and non-toxic. According to literature[40, 41], compounds with acute toxicity levels below grade 3 and greater than three positive toxicity endpoints are considered toxic. Therefore, 35 components of LWDHP were non-toxic, among which 15 components had no positive toxicological end points, 6 components had 2 positive toxicological end points, and 14 components had 1 positive toxicological end point (Figure 1). Alismol F has immunosuppressive and antiviral functions, and has inhibitory activity on the secretion of hepatitis B virus surface antigen in vitro, with IC50 of 0.6 μM [42]. The acute oral toxicity of alismol F was the highest among the 35 LWDHP (LD50: 34 mg/kg). Whether the content of alismol F in the daily oral dose of LWDHP is related to the common side effects in the treatment of senile dementia needs further study.

4 SCREENING OF ANTI-AD TARGETS OF 4 LWDHP AND ITS COMPONENTS INTO BLOOD

AD is the most common subtype of Alzheimer's disease (60-70%), Major pathological features were Senile plaques (SPs) formed by extracellular Aβ peptide plaques, neuroillary tangles formed by intracellular hyperphosphorylated tau, NFTs), neuroinflammation and loss of neuronal and synaptic plasticity[43, 44]。 In order to clarify the synergistic anti-AD mechanism of LWDHP with multiple components and multiple targets, the author conducted network pharmacological analysis based on the important pathophysiological processes of AD based on 35 components of LWDHP into blood (Table 1) [45]. Firstly, based on AlzData database (http://www.alzdata.org/)[46] the author screened targets related to AD pathology of LWDHP. Among 580 LWDHP targets, 154 were significantly correlated with the main pathological features of AD, among which 52 were significantly correlated with Aβ pathology, 33 were correlated with tau pathology, and 69 were correlated with both Aβ and tau pathology (Figure 2A). Secondly, based on 384 targets of Alzheimer's disease pathway (hsa05010) in the Kyoto Encyclopedia of Genes and Genomes (KEGG) database, 51 anti-AD targets of LWDHP were obtained (Figure 2B), and AD (DOID:10652) was most significantly enriched (Adjust p value = 7.05E-30). In addition, 102 targets of LWDHP were involved. After summarizing the above three screening strategies, 246 targets of LWDHP for AD treatment were obtained (Figure 2C). These results are consistent with the exact and reliable clinical therapeutic effect of LWDHP on Alzheimer's disease, which further suggests that AD is the main disease specifically targeted by LWDHP.

The 246 anti-AD targets of LWDHP correspond to 32 entry components, and the frequency distribution of the number of anti-AD targets of these entry components is shown in Figure 2E. LWDHP with more than 10 anti-AD targets had a total of 21 components into the blood (Figure 2D). The PPI network generated by 246 targets of LWDHP against AD contained 244 nodes and 2841 edges, among which the AKT1 isodegree value was in the top 20 (Figure 2E). Screening of anti-AD targets and blood entry components of LWDHP is helpful to further understand the material basis and mechanism of LWDHP in the treatment of Alzheimer's disease, and provide a series of potential lead compounds for the follow-up research and development of Alzheimer's disease drugs.

5 CONCLUSION

The effect of LWDHP in the treatment of senile dementia is reliable and has few adverse reactions, so it has a good development prospect. However, there are still some key problems to be solved in the treatment of Alzheimer's disease by LWDHP. In the future, multi-disciplinary theories should be integrated in the study of compound ingredients, metabolic process and pharmacological mechanism, so as to enrich the modern connotation of

compound ingredients and promote the modernization and internationalization of TCM.

Table 1: Main blood chemical constituents of LWDHP.

Ingredient	Literature	Formula	RO5
(-)-Hydroxycitric acid lactone	[25]	$C_6H_6O_7$	◯
5-(Methoxymethyl) -2-furoic acid	[31, 32, 35]	$C_7H_8O_4$	◯
6-O-methylcatalpol	[30]	$C_{16}H_{24}O_{10}$	◯
Alisol A monoacetate	[30]	$C_{32}H_{52}O_6$	▲
Alisol F	[30]	$C_{30}H_{48}O_5$	◯
Caffeic acid	[25]	$C_9H_8O_4$	◯
Caftaric acid	[25]	$C_{13}H_{12}O_9$	◯
Catalpol	[25, 30]	$C_{15}H_{22}O_{10}$	▲
Cornuside	[25]	$C_{24}H_{30}O_{14}$	▲
DehydropachyMic acid	[26]	$C_{33}H_{50}O_5$	▲
Ellagic acid #	[25]	$C_{14}H_6O_8$	◯
Ferulic acid	[25]	$C_{10}H_{10}O_4$	◯
Forsythoside A	[25]	$C_{29}H_{36}O_{15}$	▲
Gallic acid	[25]	$C_7H_6O_5$	◯
Geniposidic acid	[25]	$C_{16}H_{22}O_{10}$	▲
Isoalantolactone #	[25]	$C_{15}H_{20}O_2$	◯
Kaurane	[30]	$C_{20}H_{34}$	▲
Linoleic acid	[30]	$C_{18}H_{32}O_2$	▲
Loganic acid	[25]	$C_{16}H_{24}O_{10}$	▲
Loganin	[25-29, 31-33, 35]	$C_{17}H_{26}O_{10}$	◯
Manninotriose	[25]	$C_{18}H_{32}O_{16}$	▲
Methyl eugenol	[30]	$C_{11}H_{14}O_2$	◯
Morroniside	[26, 28, 30-35]	$C_{17}H_{26}O_{11}$	▲
Oxypaeoniflorin	[25]	$C_{23}H_{28}O_{12}$	▲
Pachymic acid	[26]	$C_{33}H_{52}O_5$	▲
Paeoniflorin	[25, 29, 33]	$C_{23}H_{28}O_{11}$	▲
Paeonol #	[25-27, 29, 31-33, 35]	$C_9H_{10}O_3$	◯
Paeonolide	[25, 30]]	$C_{20}H_{28}O_{12}$	▲
Palmitic acid	[30]	$C_{16}H_{32}O_2$	▲
Sarracenin	[25, 30]	$C_{11}H_{14}O_5$	◯
Stigmasterol	[30]	$C_{29}H_{48}O$	▲
Sweroside	[25, 26, 31, 32, 35]	$C_{16}H_{22}O_9$	◯
Syringic acid #	[25]	$C_9H_{10}O_5$	◯
Tumulosic acid	[30]	$C_{31}H_{50}O_4$	▲
Verbascoside	[30]	$C_{29}H_{36}O_{15}$	▲

Note: # represents the prototype component of LWDHP into brain. The contents of the table that do not meet RO5 are marked with ▲. The contents of the table that meet RO5 are marked with ◯.

Note: Toxicological endpoint is Active if present, Inactive if not present. # represents LWDHP into the brain prototype component.

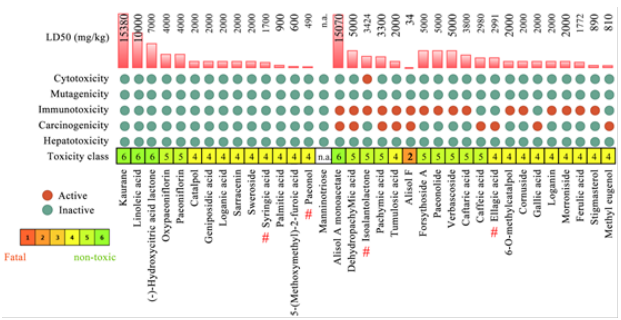

Figure 1: Components of LWDHP into the blood and brain and their toxicological parameters

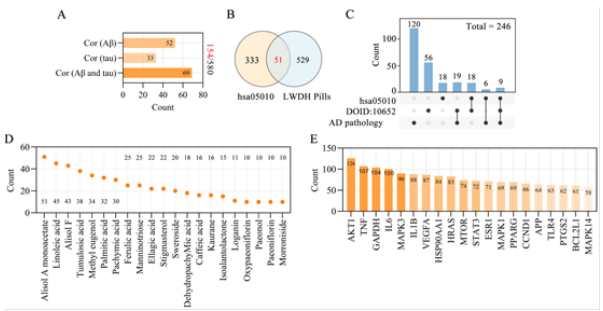

Figure 2: Screening of anti-AD targets of LWDHP and its chemical constituents

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