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Effect of Liuwei Dihuang decoction, a traditional Chinese medicinal prescription, on the neuroendocrine immunomodulation network

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ABSTRACT

Liuwei Dihuang decoction (LW) has been used in traditional Chinese medicine (TCM) for more than 900 years to prevent and treat various diseases with characteristic features of kidney yin deficiency. To date, LW has been commonly prescribed in TCM as therapy or adjuvant therapy against various diseases. To elucidate the pharmacological characteristics and mechanism of action of this formula, studies have been conducted on the pharmacological effects and chemical profiles (including bioactive ingredients) to investigate the role of LW in the neuroendocrine immunomodulation (NIM) network. In this review, we provide an overview of the pharmacological effects of LW on the NIM network, particularly on learning and memory, immunomodulation, and neuroendocrine–immune interactions, including the effects of LW on the central nervous system, endocrine system, and immune system. We also discuss advances in related chemical studies, especially those identifying the bioactive components of LW and their unique combinational effects on the immune system. Our experimental results indicate that LW exerts a broad spectrum of pharmacological effects, by modulating and restoring the balance of the NIM network disturbed by several pathological factors.

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1. Introduction

Traditional Chinese medicine (TCM) has been practiced for thousands of years, and many of the herbal drugs and formulae, particularly classical TCM formulae, are still being used in modern Chinese medicine. Formulae or prescriptions are composed of different kinds and quantities of Chinese medicinal herbs with optimal therapeutic efficacy for a comprehensive regimen, according to the principles of TCM. TCM adopts a holistic view of the prevention and treatment of diseases, wherein the human body is an organic entirety, composed of viscera, tissues, and many other organs. The viscera, organs, and superficial structures are closely interrelated physiologically and pathologically. "Treatment with syndrome differentiation" is the basic underlying principle of a TCM formula, implying that the composition of a formula is based on the symptoms and signs analyzed, which are summarized to identify the etiology, location of lesion, pathologic changes, and body conditions. Thus, TCM formulae are the main form of therapy in TCM.

Liuwei Dihuang decoction (LW) is a classic TCM formula consisting of six herbs: *Radix Rehmanniae* (Dihuang; prepared root of *Rehmannia glutinosa*), *Rhizoma dioscoreae* (Shanyao; rhizome of *Dioscorea opposita*), *Fructus corni* (Shanzhuyu; fruit of *Cornus officinalis*), *Cortex*

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moutanradicis (Mudanpi; root bark of *Paeonia suffruticosa*), *Rhizoma Alismatis* (Zexie; rhizome of *Alisma plantago-aquatica*), and *Poria* (Fuling; sclerotia of *Poria cocos*). The use of LW was first recorded in the ancient classical book on TCM titled "*Xiaoer Yaozheng Zhijue*," which was written during the Song Dynasty approximately 900 years ago (1114 A.D.). It has since been used to treat various diseases of kidney yin deficiency, such as dizziness, tinnitus, weakness and soreness of the loins and limbs, and sweating. The long-term therapeutic efficacy of LW has been well established. To date, LW has remained one of the most popular TCM formulae prescribed for primary or adjuvant treatment of many types of diseases (Chen et al., 2012; van Wietmarschen et al., 2013; Yuhong et al., 2013), such as cancer, diabetics, neurosis, neurasthenia, dementia, Parkinson's disease, menopausal syndrome, hypertension, systemic lupus erythematosus, thrombocytopenic purpura, and nephritis (Nie & Zhang, 1998; Zhang, 2000; Feng et al., 2012). Furthermore, the results of our studies have shown that LW exerts a broad spectrum of pharmacological effects, such as ameliorating the decline in learning and memory (Zhou et al., 1999a,b; Zhu & Sun, 2006; Huang et al., 2012a,b; Liu et al., 2013) and the decline in function related to aging processes and geriatric diseases (Sangha et al., 2012; Tseng et al., 2014), as well as enhancing the estrogenic activity during menopause (Limopasmanee et al., 2015; Xie et al., 2015). LW also exerts anti-osteoporotic (Sun et al., 2008; Xia et al., 2014), antihypertensive (Wang et al., 2012), anti-inflammatory (Xie et al., 2009; Liu et al., 2012), antiaging (Zhang & Zhao, 2006; Wang & Shang, 2011), antitumor (Jiang et al., 1989), and antioxidant (Kim et al., 2000; Perry et al., 2014) effects. Although these studies have provided important insights into its pharmacological profile, most of them are focused on the effects of LW in one disease, one symptom, or one mechanism. This can limit our understanding of the integrative effect of LW, especially its pharmacological action in "nourishing the kidney yin" in TCM.

In the TCM theory, the "kidney" is the functional center of the body crucial for modulating and maintaining the body function balance and the homeostasis of the internal environment. Due to the definition of the "kidney" in TCM, it may share functional similarities with the neuroendocrine immunomodulation (NIM) network of modern medicine. The neuroendocrine and immune systems are closely associated both structurally and functionally. Reciprocal modulations and interactions between the neuroendocrine and immune systems are observed, which are mediated by neurotransmitters, neuropeptides, hormones, and cytokines. The balance of NIM network plays a key role in maintaining the physiological function of the body; thus, any imbalance in the NIM network is considered to be closely associated with diseases and the aging process (Besedovsky & Sorkin, 1977; Besedovsky & del Rey, 2002, 2011). Accordingly, a "kidney deficiency" in TCM is similar to the imbalance in the NIM network; in turn, the effect of "kidney"-nourishing herbs or prescriptions correspond to the modulation of the NIM network. Therefore, a kidney yin deficiency may reflect any imbalance in the physiological function of the body, with clinical manifestations indicating various kinds of imbalance in homeostasis, involving malfunctions of the nervous system, endocrine system, and immune system. Thus, it is reasonable to hypothesize that the modern pharmacological effect of LW in terms of "nourishing the kidney yin" is closely associated with maintaining and restoring the balance of the NIM network (Besedovsky & Sorkin, 1977; Besedovsky & del Rey, 2002, 2011; Zhang & Zhao, 2006).

In this review, we provide an overview of the pharmacological effects of LW on the NIM network, including the effects of LW on the central nervous system (CNS), endocrine system, and immune system. In particular, we focus on the effects of LW on learning and memory, and its potential contributions to the immune and neuroendocrine systems. We also describe the recent advances in chemical studies on LW, including the bioactive components found in LW and their unique combinational effects on the immune system.

2. Pharmacological effects of LW on the neuroendocrine–immune system

TCM is a holistic medicinal practice that places importance on the integrity of the body (Tang et al., 2008). TCM originated from ancient Chinese philosophy, with the focus on maintaining and restoring balance in the body. Therefore, the treatment of kidney yin deficiency syndrome in TCM is based on the concept that common pathophysiological responses arise from disorders of the NIM network (Besedovsky & Sorkin, 1977; Zhang & Zhao, 2006; Tang et al., 2008; Besedovsky & del Rey, 2011). The effects of LW on the balance of nervous, endocrine, and immune system disturbances in several pathological conditions were investigated in our laboratory.

2.1. Effects of LW on the CNS

2.1.1. Effects of LW on learning and memory

Many studies have shown that LW exerts beneficial effects on normal learning and memory and cognitive impairment. For instance, LW was found to significantly enhance passive avoidance (Rho et al., 2005) and spatial learning and memory abilities (Lee et al., 2005) in normal male Sprague–Dawley rats. Some studies have also described the longstanding use of LW in improving or restoring functions that decline due to the aging process and geriatric diseases in China (Zhang & Zhao, 2006; Wang & Shang, 2011). Several studies have demonstrated that LW ameliorates cognitive deterioration is associated with aging. The senescence-accelerated mouse/prone 8 (SAMP8) strain is one of the most widely accepted murine models for studying the etiopathogenesis of Alzheimer's disease, particularly for investigating aging-related learning and memory deficits, and developing effective therapies (Takeda et al., 1994, 1997; X.R. Cheng et al., 2014). In a previous study, we investigated the effects of LW on learning and memory behavior in SAMP8 by assessing passive avoidance performance in step-through and step-down tests, the shuttle-box test, and water-maze behavioral tests (Zhou et al., 1999a,b; Wei, 2000). A significant decline was noted in memory registration and retention abilities, spatial memories, as well as conditioned avoidance responses in SAMP8 administered a vehicle control. However, in SAMP8 mice, the administration of LW for 5 months was found to significantly enhance memory registration and retention in passive avoidance performance tests, to promote the spatial memory ability in the water-maze tests, and to partially improve learning behaviors in conditioned avoidance performance tests. These results suggested that chronic administration of LW significantly ameliorated age-related decline in learning and memory performance in SAMP8 mice (Zhou et al., 1999a,b). In another study on hydrocortisone-treated mice in our laboratory, we found that LW significantly decreased the degree of active avoidance in the shuttle-box tests and reduced the latency in the Morris water-maze test. These results indicated that LW can also enhance learning and prevent memory deterioration induced by an overload of glucocorticoids (Wei, 2000).

Other studies further showed that LW has beneficial effects on deficits of learning and memory induced by other harmful agents, such as scopolamine, *p*-chloroamphetamine (Hsieh et al., 2003), cycloheximide (Wu et al., 2007), ibotenic acid (Kang et al., 2006), *D*-galactose (Zhu & Sun, 2006; Zhang et al., 2011), and streptozotocin (Liu et al., 2013).

2.1.2. Effects of LW on long-term potentiation

Long-term potentiation (LTP) has been found to be a putative neural mechanism underlying the formation or storage of associative memory in the mammalian brain. In a previous study, we showed that LW enhanced synaptic plasticity. We also found that LW significantly increased the spike amplitudes induced by subthreshold stimulation (60 Hz, 20 pulses), although it did not affect LTP formation induced by suprathreshold tetanic stimulation (60 Hz, 30 pulses) in anesthetized rats (Zhou et al., 1999a,b). In BALB/c mice, LW showed a protective