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Application Of Traditional Chinese Medicine In The Field Of Prevention And Treatment Of Influenza A

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Abstract. Traditional Chinese Medicine (TCM) has demonstrated multifaceted therapeutic potential in the prevention and treatment of H1N1 influenza (swine flu), leveraging its antiviral, immunomodulatory, and anti-inflammatory properties. Studies highlight the efficacy of classic formulations such as Yinqiao San (Honeysuckle and Forsythia Powder) and Yupingfeng San (Jade Screen Powder) in alleviating symptoms (e.g., fever, cough), shortening disease duration, and reducing complications. Active compounds like chlorogenic acid (from honeysuckle) and epigoitrin (from Isatis root) inhibit viral replication by targeting neuraminidase and PB2 proteins, while enhancing host immunity through interferon induction. Clinical trials suggest that integrating TCM with conventional antivirals (e.g., oseltamivir) improves recovery rates and mitigates post-infection fatigue. However, challenges persist, including insufficient high-quality randomized controlled trials (RCTs), variability in herbal quality control, and undefined mechanisms of multi-component synergism. Future directions emphasize large-scale RCTs, AI-driven component screening, and global guideline development to standardize TCM applications. This integrative approach may redefine pandemic preparedness by harmonizing TCM's holistic principles with evidence-based medicine.

Keywords: Traditional Chinese Medicine (TCM); H1N1 influenza; antiviral activity; clinical efficacy; integrated medicine.

1. Introduction

Influenza A (H1N1 influenza) is an acute respiratory infectious disease caused by influenza A virus, characterized by rapid transmission, high pathogenicity, genetic mutability, and cross-species transmission capability. The virus spreads through airborne droplets, mucosal contact, contaminated fomites, and aerosols, causing cyclical global pandemics. According to World Health Organization (WHO) statistics, approximately 1 billion seasonal influenza cases occur annually, including 3-5 million severe cases. Current clinical management primarily relies on neuraminidase inhibitors (e.g., oseltamivir) and vaccination. However, the development of viral resistance and the lag in vaccine strain matching have become increasingly prominent issues, driving global research efforts to explore novel antiviral agents.

Traditional Chinese Medicine (TCM), as a holistic medical system characterized by multi-component formulations and multi-target synergistic interventions, demonstrates unique potential in combating viral infectious diseases. Official guidelines such as the COVID-19 Diagnosis and Treatment Protocol have repeatedly included Lianhua Qingwen Capsule in recommended regimens, underscoring TCM's growing significance in modern infectious disease control. Recent advances in pharmacological and molecular biological technologies have partially elucidated the mechanisms underlying TCM's anti-influenza effects, though comprehensive systematic research remains lacking.

Contemporary studies confirm that TCM intervenes in influenza progression through dual pathways: direct antiviral action and immunomodulation. In vitro, studies demonstrate that epigoitrin from Isatidis Radix (Banlangen) exhibits significant anti-influenza activity, while its nucleotide components improve microcirculation to inhibit viral DNA/RNA replication and suppress viral proliferation [1]. Chlorogenic acid from Lonicerae Japonicae Flos (Jinyinhua) effectively inhibits neuraminidase activity, thereby blocking progeny virion release [2]. Randomized controlled trials

(RCTs) reveal comparable clinical efficacy between Lianhua Qingwen Capsule and oseltamivir phosphate in terms of overall effectiveness rate, viral nucleic acid clearance time, and fever resolution duration, with superior symptom relief in cough amelioration and cephalgia reduction [3]. Besides, experiment also elucidates that active compound in Maxing Shigan Decoction modulate TLR4/NF-κB signaling through multiple mechanisms, attenuating inflammatory responses and synergistically inhibiting cytokine storms.

Despite these advancements, challenges persist in standardizing quality control protocols for compound TCM preparations and insufficient multinational multicenter clinical trial data, which currently hinder the global integration of TCM therapeutics. Therefore, by studying the epidemiology of influenza A and the mechanism, obstacles and countermeasures of Chinese medicine against influenza A, this paper scientifically verified the potential of Chinese medicine against influenza A and proved the complementary advantages of Chinese and western medicine treatment strategies, so as to promote the internationalization and modernization of Chinese medicine.

2. Application status of Chinese medicine in the treatment of influenza A

2.1. Application of single Chinese medicine

Isatis root (Isatidis Radix) is the dried root of the cruciferous plant Isatis tinctoria (Isatis indigotica). In TCM, it is associated with the lung and stomach meridians and has the effects of clearing heat, detoxifying, cooling blood, and benefiting the throat. It is commonly used to treat febrile diseases caused by warm pathogens and sore throats. Its antiviral properties have been documented in medical texts throughout history, covering both direct antiviral action and suppression of host inflammatory responses. Studies show that the polysaccharides, lignans, indole alkaloids, and sterols in Isatis root are the core substances responsible for its anti-H1N1 influenza effect.

The polysaccharides in Isatis root can specifically bind to the hemagglutinin (HA) protein on the surface of influenza viruses, interfering with the virus's binding to host cell receptors and thus inhibiting the viral invasion process. Experiments have shown that Isatis root polysaccharides significantly inhibit subtypes such as H1N1 and H3N2, and long-term passage does not induce drug resistance. Additionally, this component can also inhibit the TLR3 signaling pathway, reducing the excessive release of pro-inflammatory factors like IL-6 and TNF-α, thereby alleviating immune overactivation induced by the virus. Therefore, Isatis root can exert its anti-H1N1 effect through both blocking viral replication and immune regulation.

The lignans in Isatis root can inhibit the replication of influenza A virus and block inflammatory storms in a dual manner. Lignan components, represented by Cepharanthine B and larch glycosides, have shown direct inhibitory effects on the PR8 strain of influenza A virus in vitro experiments. Mechanism studies have found that these compounds can downregulate the phosphorylation levels of key proteins in the NF-κB signaling pathway (such as P-P65), blocking the expression of virus-mediated inflammatory factors (such as IL-8, MCP-1), thereby reducing lung tissue damage. Animal models further confirmed that lignans can significantly reduce viral loads in lung tissues of infected mice and improve pathological symptoms [4,5].

Indole alkaloids in Isatis root (such as Cappariloside A) exhibit broad-spectrum inhibitory effects against influenza A virus and other respiratory pathogens. The mechanism of action involves regulating the host interferon pathway, suppressing the activation of STAT1 protein, thereby disrupting the host environment required for viral replication. In vivo experiments have shown that this component can effectively reduce mortality in influenza model animals and alleviate complications such as pulmonary edema.

At the same time, although β -stigmasterol in isatis root did not show direct antiviral activity, it could reduce the abnormal secretion of interferon by inhibiting RIG-I pathway, and regulate the infiltration of CD8+ T cells in the lungs, so as to balance the immune response and reduce tissue damage, providing auxiliary support for the overall efficacy of isatis root.

2.2. Therapeutic effect of honeysuckle on influenza A

Honeysuckle (Lonicera japonica), as a TCM, has demonstrated unique molecular mechanisms in the prevention and treatment of influenza A. Its core active component is atypical microRNA——MIR2911. Studies have shown that MIR2911 directly targets the influenza virus genome to inhibit viral replication and modulate host immune responses, thereby exerting multi-dimensional anti-influenza effects [6].

The decoction of honeysuckle contains most miRNAs degraded during high-temperature boiling, but MIR2911 exhibits significant stability due to its high GC content and unique sequence structure. Experiments show that after decoction, MIR2911 accounts for over 70% of the total miRNA in the honeysuckle decoction (concentration about 0.06 pmol/ml). Animal experiments further confirm that oral administration of honeysuckle decoction or synthetic MIR2911 allows the molecule to be absorbed through the gastrointestinal tract and accumulate in lung tissue, reaching a functional threshold (about 300-400 copies per cell) in infected mice, comparable to endogenous miRNA levels.

MIR2911 exerts antiviral effects by directly targeting viral genes. MIR2911 binds to the conserved regions of key genes such as the influenza virus polymerase basic protein 2 (PB2) and non-structural protein 1NS1 in H1N1, H5N1, and H7N9 influenza viruses through base pairing. In vitro experiments show that synthetic MIR2911 or total RNA from honeysuckle decoction can significantly inhibit viral replication, reducing the TCID50 of H1N1 from 5.43 to 3.80 within 24 hours (a decrease>30%). This suggests that certain RNAs in MIR2911 and honeysuckle may contain antiviral active components, potentially making them as potential antiviral drugs. By mutating the binding sites of viral genes, the inhibitory effect is completely eliminated, confirming the targeting specificity. Additionally, MIR2911 downregulates the expression of viral PB2 and NS1 proteins, interfering with the function of the viral RNA polymerase and the immune escape mechanism.

In addition, MIR2911 has antiviral mechanisms and immune regulatory effects in the body. In H1N1-infected mouse models, daily gavage with 0.1 nmol synthetic MIR2911 or drinking honeysuckle decoction can significantly reduce viral load in lung tissue (viral titer decreased by 1.5 log units after 3 days of infection) and alleviate weight loss (20% weight reduction in the control group, <10% in the treatment group). For highly pathogenic H5N1 virus, MIR2911 treatment increased survival rates from 25% to 62.5%. Mechanistic studies show that MIR2911 alleviates virus-induced excessive inflammatory responses by inhibiting NF-κB pathway activation and reducing the release of inflammatory factors such as IL-6 and TNF-α.

Not only that, MIR2911 has shown inhibitory effects on multiple influenza A subtypes (H1N1, H3N2, H5N1, H7N9). For instance, in the H7N9 infection model, MIR2911 treatment reduced the viral TCID50 from 6.24 to 5.49 within 24 hours and partially alleviated weight loss in mice (from 30% to 20%). This broad-spectrum activity stems from MIR2911 targeting conserved regions of viral genes, potentially offering new strategies for combating viral mutations.

2.3. Clinical effects of compound preparations

Lianhua Qingwen (Lianhua Qingwen, LHQW) is a TCM compound preparation based on Mahuang Xingren Shigao Decoction and Yinqiao Powder. It consists of 13 herbs including honeysuckle, isatis root, and ephedra. Its active components include quercetin, luteolin, β-sitosterol, and others, which exert antiviral and immune regulatory effects through multi-target synergy [7]. Studies have shown that LHQW's therapeutic effects on influenza A (IA) cover multiple aspects, including direct inhibition of viral replication, regulation of host inflammatory responses, and improvement of clinical symptoms.

The various components in Lianhua Qingwen Capsules work together to exert antiviral effects. In LHQW, quercetin and luteolin competitively bind to the HA of influenza viruses, preventing viral fusion with host cell membranes. In vitro experiments show that the half-inhibitory concentration (IC50) for subtypes such as H1N1 and H3N2 is 50 $\mu g \cdot mL^{-1}$ (SI> 4). Additionally, indole alkaloids

from Isatis root can interfere with viral RNA polymerase activity, inhibiting the expression of PB2 and NS1 proteins, thereby blocking the viral replication cycle. Animal models have confirmed that treatment with LHQW reduces the viral load in lung tissue of H1N1-infected mice by 1.5 log units ($P<0.01$) and significantly extends survival time.

Influenza A virus infection can excessively activate the NF-κB pathway, leading to a cytokine storm of pro-inflammatory factors such as IL-6 and TNF-α. LHQW reduces the release of inflammatory factors by downregulating the phosphorylation level of p65 protein (Western blot verified, inhibition rate>60%). A clinical Meta-analysis (including 32 RCTs, n=3592) showed that combination therapy with oseltamivir can lower CRP (SMD=1.08, $P<0.001$), IL-6 (SMD=0.69, $P=0.002$), and TNF-α (SMD=0.49, $P=0.003$), while also increasing the CD4+/CD8+ ratio (SMD=1.61, $P<0.001$), indicating its regulatory function in immune homeostasis.

At the same time, clinical data show that combination therapy can significantly shorten the symptom relief time for influenza A patients: fever subsides 1.8 days earlier (SMD= -2.36, $P <0.001$), cough alleviates 1.5 days faster (SMD= -2.06, $P <0.001$), and the improvement efficiency of respiratory symptoms such as nasal congestion and sore throat increases by 40% ($P <0.01$). Additionally, the time to viral negativity is shortened by 1.2 days compared to monotherapy (SMD= -0.64, $P = 0.004$), and hospital stay is reduced by 2.3 days (SMD= -1.59, $P <0.001$). In terms of safety, the incidence of adverse reactions in the LHQW group is reduced by 30% (RR = 0.70, $P = 0.04$), primarily mild gastrointestinal reactions, with no reports of serious adverse events. This study demonstrates that combination therapy shows significant advantages in treating influenza A. Combination therapy can comprehensively and rapidly alleviate clinical symptoms in patients. At the same time, it can more effectively inhibit viral replication, demonstrating good tolerability and safety, making it suitable for clinical application. However, this study may have some limitations. For example, the sample size and follow-up duration could affect the generalizability of the results. Future research should consider conducting larger, multicenter clinical trials to further validate these findings.

3. Integrated Chinese and Western medicine treatment mode

China, as a country that combines traditional and modern medical systems, clearly states in the "Chinese Influenza Diagnosis and Treatment Guidelines" that, based on following the diagnostic and treatment standards of the World Health Organization (WHO), combined interventions with TCM can be used to optimize therapeutic effects. This model not only reflects the integration of medical cultures but also validates its clinical value through empirical research.

3.1. Complementary advantages of Chinese and Western medicine

TCM emphasizes holistic diagnosis and symptom relief. Representative formulas such as Mahuang Xingshi Gan Tang-Yinqiao San (Maxing Shigan-Yinqiaosan) have shown significant efficacy in mild cases of influenza A. A randomized controlled trial demonstrated that using this formula alone or in combination with Oseltamivir (Oseltamivir) for treating mild H1N1 influenza patients resulted in fever reduction rates comparable to those of the placebo group, and both were better than the untreated group. This finding suggests that TCM may exert its effects through antiviral or antipyretic mechanisms, but its specific active ingredients still require further analysis. In contrast, Western medicine focuses on targeted therapy against pathogens, especially in severe cases, where systematic interventions can be achieved through antiviral drugs and respiratory support, thereby reducing the risk of complications.

3.2. Application scenarios and evidence of combination therapy

The current guidelines recommend that patients with mild symptoms prioritize TCM to alleviate fever and cough, while severe or high-risk patients should combine Western medicine for comprehensive treatment. This stratified strategy not only aligns with the natural course of the disease but also takes into account patient preferences and safety. For example, personalized TCM diagnosis and treatment

can improve subjective discomfort, whereas laboratory monitoring and precise medication use in Western medicine provide a safeguard against worsening conditions. Moreover, the combined use of TCM and Western medicine may produce synergistic effects, such as reducing the dosage of Western drugs and shortening the course of illness, although the mechanisms need further validation through multicenter clinical trials.

4. Application of TCM in the prevention and rehabilitation stage of influenza A

According to TCM, it is advisable to consume warming foods in winter to nourish yang energy. However, one should avoid overly dry and greasy foods to prevent the production of phlegm-dampness, which can affect spleen and stomach functions. Foods that strengthen the spleen and benefit qi, as well as moisten the lungs and generate body fluids, such as yam, lily, silver ear fungus, red dates, and barbary wolfberry, can be consumed more frequently. Additionally, some foods that have both medicinal and culinary value, like astragalus, codonopsis, chrysanthemum, and honeysuckle, can also be appropriately consumed.

In addition, TCM sachets are also one of the preventive methods in TCM. They use herbs with aromatic and dampness-resolving properties, such as agastache, ephedra, mugwort leaves, borneol, atractylodes, and mint, which are ground into powder according to specific proportions and placed in sachets for personal wear. The medicinal scent emitted by the sachets can stimulate the respiratory mucosa, activate the body's immune function, and enhance resistance to influenza viruses. Studies have shown that after taking Yin-Nourishing Lung-Clearing Decoction (prepared with rehmannia, ophiopogon, and scrophularia) for two weeks, the improvement rate in fatigue scores was 40% higher than in the control group, and the absorption time for lung inflammation was shortened by 3-5 days.

At the same time, moxibustion has the effects of warming and unblocking meridians, dispelling cold and removing dampness, harmonizing qi and blood, and supporting the body's defenses while expelling pathogens. Traditional exercises such as Tai Chi and Baduanjin can regulate the flow of qi and blood in the body, enhance cardiorespiratory function, and promote metabolism, thereby boosting the body's resistance and immunity. During the peak flu season, choosing some acupoints with health-preserving functions for moxibustion and complementing them with appropriate exercise can stimulate yang energy in the body, strengthen immunity, and prevent the occurrence of influenza.

During the recovery process, in addition to taking TCM orally, external treatments such as cupping and gua sha can also be used as auxiliary therapies for influenza. Cupping can target acupoints like Dazhui, Fengmen, and Feishu, while gua sha can be applied to areas like the bladder meridian on the back and the lung meridian on the arms. By stimulating these meridians and acupoints, they help expel pathogenic factors from the body and alleviate symptoms.

5. Challenges and future outlook

Currently, the quality of clinical studies on TCM for treating influenza A is uneven, with most studies having design flaws and methodological issues. For example, many studies have small sample sizes [8,9], lack strict randomization and double-blind control, which affects the reliability and persuasiveness of the results. Additionally, some studies do not evaluate outcome indicators objectively or standardly enough, making it difficult to compare and synthesize findings across different studies. To overcome these limitations, more high-quality, large-sample, multicenter RCTs are needed, using internationally recognized research methods and standards, to provide stronger scientific evidence.

Although TCM has achieved certain clinical effects in treating influenza A, its specific mechanisms of action remain unclear [10]. Traditional Chinese medical theory emphasizes treating diseases by adjusting the body's yin-yang balance and the circulation of qi and blood, but this theory struggles to directly explain how TCM affects viruses. Modern research attempts to explain the effects of TCM

from aspects such as antiviral activity, anti-inflammatory properties, and immune regulation, yet it has not fully elucidated its complex mechanisms of action.

Most clinical trials of TCM for treating influenza A do not report adverse reactions in detail [11-13], and the safety of these drugs remains uncertain. Moreover, due to the wide range of sources and varying quality of traditional Chinese herbs, it is difficult to ensure consistency and stability of the medication. For example, the content of active ingredients in herbs from different origins and harvest times can vary significantly, affecting their efficacy. Strengthening quality control of traditional Chinese herbs, standardizing planting, harvesting, processing, and storage procedures, and establishing a comprehensive quality testing system to ensure the safety and effectiveness of the drugs are significant challenges faced by TCM in treating influenza A.

At the same time, TCM emphasizes personalized treatment tailored to individual differences and local conditions, which is difficult to achieve on a large scale and standardize in practice. During the H1N1 pandemic, with a large number of patients, it was challenging to provide one-on-one personalized diagnosis and treatment. Moreover, the varying levels of expertise and experience among TCM practitioners also affect the effectiveness of personalized treatment. Therefore, utilizing modern information technology to develop intelligent TCM diagnostic and therapeutic systems can improve the accuracy and efficiency of diagnosis and treatment. Additionally, strengthening standardized training for TCM practitioners is a possible solution to this issue.

In addition, the international recognition of TCM is relatively low, partly due to the lack of internationally recognized diagnostic and therapeutic standards. Compared with modern medicine, the terminology and concepts of TCM are difficult for the international medical community to understand and accept, which limits its promotion and application internationally. Establishing and promoting internationally recognized TCM standards, including diagnostic criteria, treatment guidelines, and drug quality standards, is an important task for enhancing the international status of TCM. Through international exchanges and cooperation, drawing on the methods used in modern medicine to set standards, it will make the theories and practices of TCM more readily accepted globally.

6. Conclusion

TCM has demonstrated multi-target and multi-level effects in the prevention and treatment of influenza A, with its core value lying in the holistic medical philosophy of "preventing disease before it occurs, preventing changes after onset, and preventing recurrence after recovery." By synergizing antiviral, immune regulation, and anti-inflammatory actions, TCM shows clear potential in alleviating clinical symptoms (such as fever and cough), shortening the course of illness, and promoting recovery. Classic formulas like Yin Qiao San and Yu Ping Feng San, along with single herbs such as Isatis root and honeysuckle, inhibit viral adsorption, block key enzymes for replication, and modulate host immune responses, embodying the principle of "strengthening the body to expel pathogens." Clinical studies have shown that integrated TCM-Western medicine treatment can significantly improve fever reduction efficiency, reduce the risk of severe complications, and enhance the quality of life for patients during the recovery phase.

However, the modernization and globalization of TCM still face challenges such as insufficient evidence-based support, lack of standardized quality control, and unclear mechanisms of action. In the future, it is necessary to validate therapeutic effects through RCTs, use artificial intelligence to analyze the active ingredient network of compound formulas, and promote the development of international diagnostic and treatment guidelines. On this basis, building an "integrated disease and syndrome" precision intervention system, incorporating TCM into comprehensive influenza prevention and control strategies, can not only enrich treatment options but also provide a model for collaborative innovation between traditional Chinese and Western medicine in responding to emerging and sudden infectious diseases.

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