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Review

Traditional Chinese herbal medicine as a source of molecules with antiviral activity

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ABSTRACT

Traditional Chinese herbal medicine (TCHM) is widely used in the prevention and treatment of viral infectious diseases. However, the operative mechanisms of TCHM remain largely obscure, mainly because of its complicated nature and the fragmented nature of research. In recent years, systematic methodologies have been developed to discover the active compounds in TCHM and to elucidate its underlying mechanisms. In this review, we summarize recent progress in TCHM-based antiviral research in China and other Asian countries. In particular, this review focuses on progress in targeting key steps in the viral replication cycle and key cellular components of the host defense system. Recent developments in centralized and standardized TCHM screening and databases are also summarized.

Contents

1. Introduction

Traditional Chinese herbal medicine (TCHM) is the most important component of the traditional Chinese medicine system, which has long been used for its multiple combinations of compounds in the form of processed natural products. Similar to conventional medicine, TCHMs are prescription or over-the-counter drugs. Today, TCHMs account for 10% of the prescription drugs in China.

Because of the long history of medical usage, from the drug discovery point of view, screening for active lead compounds from TCHMs extracts is considered more efficient compare to random screening from a standard combinatorial chemical library. More functional compounds (“hits”) are likely to be discovered from TCHM extracts in biological screening assays, and the chemical properties of these compounds are often more “drug-like” (e.g. with better pharmacokinetics and bioavailability). TCHM-derived active compounds are thus often better lead compounds for further chemical improvements. These characteristics of TCHMs offer

Abbreviations: TCHM, traditional Chinese herbal medicine; TCM, traditional Chinese medicine; HIV, human immunodeficiency virus; HSV, herpes simplex virus (type 1 and 2); Flu, influenza; HBV, hepatitis B virus; HCV, hepatitis C virus; HCMV, human cytomegalovirus; EVs, enteroviruses; EV71, enterovirus 71; SARS-CoV, SARS coronavirus; NV, norovirus; FMDV, foot-and-mouth disease virus; AdV, adenovirus; PIV, parainfluenza virus.

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major opportunities for finding novel chemical structures active against a variety of therapeutic targets.

However, even with these unique advantages, modernization and globalization of TCHM have been slow. Some of the most difficult issues have been understanding the operative mechanisms of TCHMs and identify their active components. This review summarizes recent progress and advantages of TCHM-based antiviral research in China. In particular, this paper follows the steps of the generalized virus life cycle and reports progress in assay development and in knowledge of the antiviral mechanisms of TCHMs or TCHM-derived compounds.

2. Evidence supporting the efficacy of TCHM

TCHMs are widely used for the prevention and treatment of viral infectious diseases in China and many other Asian countries. However, the international community remains uncertain about the efficacy of TCHMs, because of the lack of supporting clinical evidence collected under international standards (randomized, placebo-controlled, double-blind and multicentered clinical studies). Governments have put forward support aimed at international regulatory approval of TCHMs. Leading the pack is the compound T89 (also known as Dantonic®, a THCM product by Tasly Pharmaceuticals, China), which may become the first traditional Chinese medicine to receive Food and Drug Administration (FDA) approval in the United States. T89 is a TCHM used in China for the management of ischaemic heart disease. It is currently under a global phase III trial (ClinicalTrials.gov identifier: NCT01659580).

A growing number of TCHMs with antiviral activity is also garnering evidence of experimental and/or clinical efficacy. Table 1 shows a partial list of antiviral TCHMs approved by the China Food and Drug Administration (SFDA). TCHMs for respiratory viral infections represent the majority of drugs in the market.

3. Strategies for TCHM-based antiviral screening

The viral replication cycle includes attachment and entry into the host cell (Fig. 1, 1–3), transcription of viral mRNA, viral genome replication (Fig. 1 and 4–6), protein synthesis and the assembly and budding of progeny virus particles (Fig. 1, 7 and 8). These steps provide targets for inhibitors of entry, replication (e.g., protease inhibitors, viral polymerase inhibitors, and integrase inhibitors, among others), assembly and budding. Such inhibitors are classified as direct antiviral agents. Previous studies have provided evidence of the direct antiviral activity of many medicinal herbs used in TCHMs (Sun, 2007; Wang et al., 2007, 2008; Zhao and Han, 2009).

By definition, a virus depends on the cellular machinery to complete its replication cycle (e.g., cellular peptidase, transcription factors, and elongation factors). Following co-evolution with the host, many viruses have established sophisticated mechanisms to interact with the host immune system for immune evasion. These mechanisms provide cellular targets for antiviral drug intervention. Among the classes of antiviral agents, immunomodulators are the most abundant in TCHM.

Based on TCM theory, a remedy contains multiple active components (mainly herbs) with multiple targets. Some of these components work directly on the therapeutic targets, whereas others counteract drug toxicity or enhance the bioavailability of the medicine. Thus, a TCHM remedy is often composed of a hierarchy of different components, the so-called "monarch," "minister," "assistant," and "guide components" (Yu et al., 2006). Considering the complicated nature of TCHM, experiments in laboratory animals have been considered the "gold standard" for pharmacological screening. The process is very important for medical evaluation, because it reflects the efficacy, side effects, and toxicity of medicines as a whole. In general, TCHM whole extracts are often tested first for their ability to protect animals against viral challenges (Fig. 2). However, such *in vivo* methods are costly and have low throughput. For TCHM testing, optimized cell-based assays are often carried out directly for the initial evaluation of whole extracts that show clinical evidence of antiviral activity. This practice is based on the assumption that compounds with direct antiviral activity are present in whole TCHM extracts. These compounds are measured by their ability to protect cells against virus-induced cytotoxicity (Fig. 2).

Activity-guided fractionation (AGF) is often performed for subsequent identificaton of active fractions and further isolation of pure compounds (Koehn and Carter, 2005) (Fig. 2). The basic principle of AGF is that a TCHM fraction is further separated only when its antiviral activity is confirmed. In recent years, with improved understanding of viral replication mechanisms at the cellular and molecular level, highly specific assays with

Table 1
Partial list of TCHM approved by the SFDA for the treatment of viral diseases.

Herbs	Botanical names	Trade names	Virus	Diseases	References
Radix bupleuri	*Bupleurum chinense*, *Bupleurum scorzonerifolium*	Xiao-chai-hu capsule, Zheng-chai-hu-yin granule	Flu	Influenza, upper respiratory infection	Zhang et al. (2007) and Zhao et al. (2007)
Fructus forsythiae	*Forsythia suspensa*	Yin-qiao-jie-du-wan (granule, tablet), Yin-qiao-san	Flu	Acute bronchitis, pneumonia, influenza	Li et al. (2008), Sun et al. (2006), Xie et al. (2006) and Yang et al. (2005b)
Flos lonicerae; *Radix scutellariae*	*Lonicera japonica*; *Scutellaria baicalensis*	Shuang-huang-lian-he-ji (granule, capsule, tablet), Yin-huang granule (tablet)	Flu, EVs, HSV, AdV, RSV, PIV	Influenza, tonsillitis, pharyngitis, upper respiratory infection, mumps, pneumonia	Chen et al. (2001, 2007), Shen et al. (2008), Sun et al. (2009), Wang et al. (2005) and Wu et al. (2004, 2005)
Radix isatidis	*Isatis tinctoria*, *Isatis indigotica*, *Baphicacanthus cusia*	Ban-lan-gen granule, Li-zhu (Chuan-fang) kang-bing-du granule	Flu, HSV	Influenza, acute tonsillitis, mumps	Cao et al. (2006, 2007, 2010), Chen and Li (2006), Fang et al. (2005), Hu and Zheng (2003) and Sun et al. (2010)
Panax ginseng; *Radix ophiopogonis*	*Panax ginseng*; *Ophiopogon japonicus*	Sheng-mai-yin (granule, capsule, injection)	EVs	Viral myocarditis	Zhang et al. (2005) and Zhang and Zeng (2009)
Radix sophorae Flavescentis	*Sophora flavescens*	Ku-shen tablet, Ku-shen-jian injection	HBV	Chronic hepatitis	Hou et al. (2005) and Shi and Wang (2012)
Spica prunellae; *Flos chrysanthemi Indici*; *Folium mori*	*Prunella vulgaris*; *Chrysanthemum indicum*, *Chrysanthemum boreale*, *Chrysanthemum lavandulaefolium*; *Morus alba*	Xia-sang-ju granule, Guang-yao-xing-qun-xia-sang-ju	Flu, RSV	Influenza	Huang et al. (2007) and Zhan and Dong (2006)