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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)

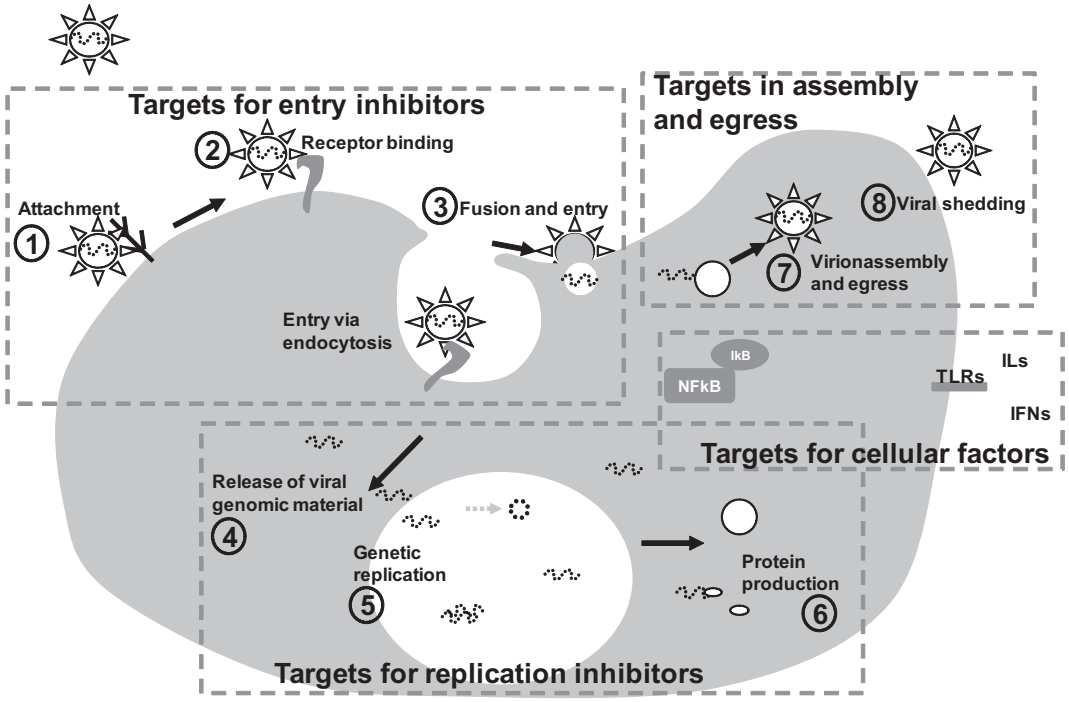

Fig. 1. Major steps in the generalized viral life cycle. Potential targets for inhibitors of entry, replication, assembly and egress and cellular factors are indicated.

high-throughput capabilities have been developed (Fig. 3). These assays enhance the chances of success of AGF and provide data for understanding the mechanisms of action of the identified compounds.

In addition to classical bioscreening, computer-aided molecular design and docking-based virtual screening technologies are also being applied to the antiviral screening of TCHM. Progress in this area depends heavily on the availability of structural databases and bioinformatics. In the past, databases were scattered among individual laboratories, and included an insufficient number of compounds and limited associated information. However, several larger databases have recently been constructed. The TCM Database@Taiwan (http://tcm.cmu.edu.tw), built by a team led by Prof. Calvin Yu-Chian Chen from China Medical University in Taiwan contains the chemical structures of over 20,000 compounds (Chen, 2011). Using this database, the team has identified quinic acid,

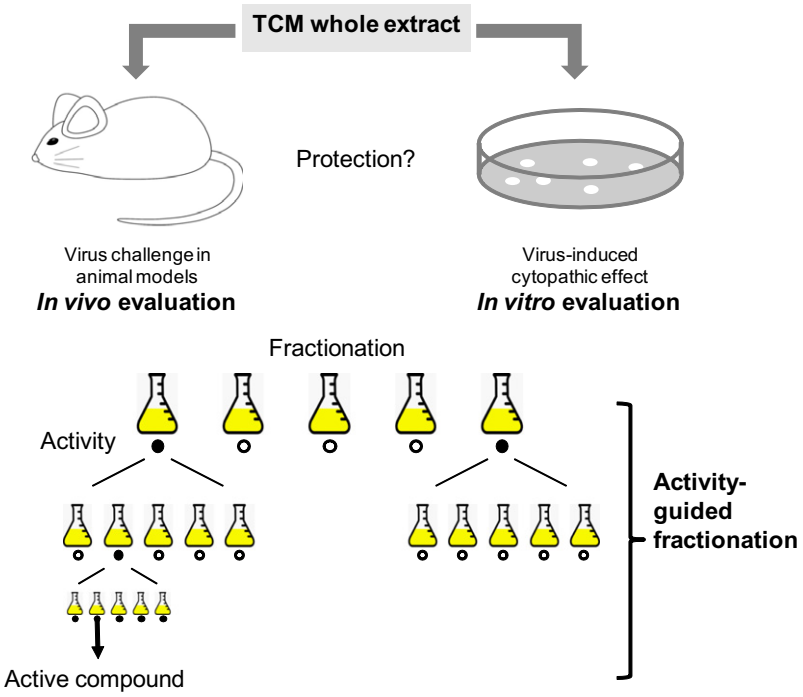

Fig. 2. Schematic diagram of activity-guided fractionation. A TCHM whole extract is evaluated for its antiviral activity in laboratory animals and/or cell-based assays. To identify the active component, AGF is performed, and the fraction with antiviral activity is further fractionated until the active compound is identified.

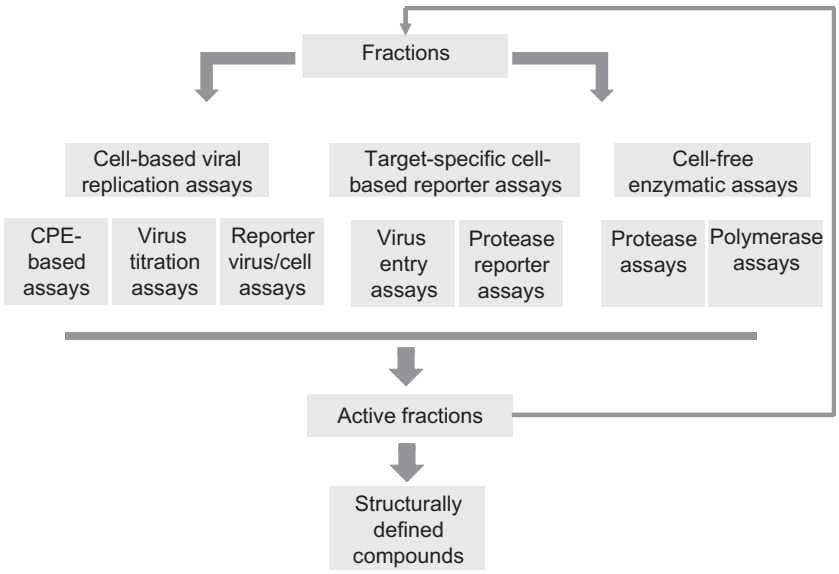

Fig. 3. Target-specific assays used for active compound identification during AGF and for antiviral mechanism analysis.

Table 2
TCHM-derived ompounds inhibiting viral entry.

Virus	Herbs	Compounds	Mechanism	References
HSV	*Radix achyranthis bidentatae*	Polysaccharide sulfuric ester derivatives	Binds to viral glycoproteins and interferes with viral attachment	Liu et al. (2004b)
	Ganoderma lucidum, *Spica prunellae*	Polysaccharide	Inhibits viral attachment and penetration	Liu et al. (2004a)
	Euphorbia jolkini	Putranjivain A	Inhibits viral attachment and penetration	Cheng et al. (2004)
	Phyllanthus emblica	Pentagalloylglucose	Down-regulates cofilin1 to inhibit viral-induced rearrangements of actin cytoskeleton	Pei et al. (2011)
	Pericarpium granati	Tannin	Inhibits viral attachment	Zhang et al. (1995)
HIV	*Spica prunellae*, *Rhizoma cibotte*	Tannin	Inhibits the gp41 six-helix bundle formation	Liu et al. (2002)
Flu	*Fructus arctii*	Arctigenin	Exhibits hemagglutination inhibition	Yang et al. (2005a,b)
EVs	*Radix glycyrrhizae*	Polysaccharide	Attaches to the cell surface and inhibits viral attachment and entry	Wang et al. (2001)
SARS-CoV	*Radix et Rhizoma Rhei*, *Radix Polygoni Multiflori*	Emodin	Blocks the S protein and ACE2 interaction	Ho et al. (2007)
	Radix glycyrrhizae	Glycyrrhizin	Inhibits viral attachment and penetration	Chen et al. (2004)
NV	*Fructus schisandrae*, *Pomegranate*	Tannin	Inhibits the binding to histo-blood group antigens (HBGAs)	Zhang et al. (2012)

genipin, syringic acid, cucurbitine, fagarine, methyl isoferulate and their derivatives as potent anti-influenza compounds, through blocking of the viral M2 ion channel (Lin et al., 2011). Using the same approach, they also identified xynopine-2, rosmaricine-14 and rosmaricine-15 as strong antagonists of the binding of hemagglutinin subtype H1 to sialic acid (Chang et al., 2011b).

4. Viral entry inhibitors

Entry into host cells is the first step of the viral life cycle, and its machinery has been proven an excellent target for antiviral therapeutics. Advanced assays have been developed to identify compounds that inhibit this critical step of the viral life cycle (Peng, 2010). For many viruses, cell-surface attachment is accomplished through interaction with cell surface glycans. Polysaccharides have been observed to saturate the cell surface of viral attachment proteins and inhibit viral entry, as confirmed by antiviral TCM studies (Table 2).

Polysaccharides and their derivatives are the most frequently found viral entry inhibitors. Mechanism studies show that these sugars target the viral attachment and/or internalization steps mediated by specific interactions with viral particles or cell-surface molecules, resulting in viral serotype- or host cell type-dependent activity (Baba et al., 1988; Marchetti et al., 1995). The composition of the sugar units and the diversity of the linkage chemistry are also factors that determine the functional properties and the target specificity of these compounds. Thus, while polysaccharides are considered to be broad-spectrum virus entry inhibitors, their derivatives display significant levels of virus-specific activity (Zhou and Meng, 1997). Because polysaccharides are also ligands for immunoregulatory cell-surface receptors such as the toll-like receptors, they might also function as immunomodulators (Takeda et al., 2003).

After attachment, viral surface proteins interact with cell-surface receptors, triggering conformational changes which initiated the entry process. Inhibition of formation of the entry machinery

Table 3
TCHM-derived compounds inhibiting viral replication.

Virus	Herbs	Compounds	Mechanism	References
HSV	*Chamaecyparis obtuse*	Yatein	Inhibits HSV-1 ICP0 and ICP4 expression as well as viral DNA synthesis	Kuo et al. (2006)
	Euphorbia jolkini	Putranjivain A	Affects the late stage of HSV-2 replication	Cheng et al. (2004)
	Limonium sinense	Samarangenin B	Inhibits viral replication	Kuo et al. (2002)
	Ranunculus sieboldii, Ranunculus sceleratus	Protocatechuyl aldehyde	Inhibits viral replication	Li et al. (2005)
	Limonium sinense	Isodihydrosyringetin, (−)-epigallocatechin 3-O-gallate, samarangenin B, myricetin, myricetin 3-O-α-rhamnopyranoside, quercetin 3-O-α-rhamnopyranoside, (−)-epigallocatechin, gallic acid, N-trans-caffeoyltyramine, N-trans-feruloyltyramine	Inhibits viral replication	Lin et al. (2000)
	Rhizoma coptidis	Berberine	Inhibits viral DNA synthesis	Chin et al. (2010)
HIV	*Chrysanthemum morifolium*	Apigenin-7-O-β-D-g-lucopyranoside	Inhibits viral integrase	Lee et al. (2003)
	Vatica cinerea	Vaticinone (23E)-27-nor-3-hydroxycycloart-23-en-25-one	Inhibits viral replication	Zhang et al. (2003)
	Aesculus chinensis	Triterpenoid saponins	Inhibits viral protease	Yang et al. (1999)
	Kadsura matsudai	Schizanrin B, C, D, and E	Inhibits viral replication	Kuo et al. (2001)
	Trichosanthes kirilowii	Trichosanthin	Inhibits viral replication	Wang et al. (2002)
HBV	*Radix scutellariae*	Wogonin	Inhibits viral DNA polymerase	Guo et al. (2007)
	Salvia miltiorrhiza	Protocatechuic aldehyde	Inhibits viral replication	Zhou et al. (2007)
	Ranunculus sieboldii, Ranunculus sceleratus	Apigenin 4′-O-α-rhamnopyranoside, apigenin 7-O-β-glucopyranosyl-4′-O-α-rhamnopyranoside, tricin 7-O-β-glucopyranoside, tricin, isoscopoletin	Inhibits viral replication	Li et al. (2005)
	Radix sophorae Flavescentis	Oxymatrine	Down-regulates the expression of heat-stress cognate 70 (HSC70) that is required for HBV DNA replication	Wang et al. (2011)
	Radix bupleuri	Saikosaponin C	Inhibits viral DNA replication and HBeAg production	Chiang et al. (2003)
HCV	*Saxifraga melanocentra*	Polyphenolic compounds	Inhibits viral NS3 serine protease	Zuo et al. (2005)
	Rhodiola kirilowii	3,3′-Digalloylproprodelphinidin B2, 3,3′-Digalloylprocyanidin B2, (−)-Epigallocatechin-3-O-gallate, (−)-Epicatechin-3-O-gallate	Inhibits viral NS3 serine protease	Zuo et al. (2007)
Flu	*Fructus arctii*	Arctigenin	Inhibits viral replication	Gao et al. (2002)
EV71	*Laggera pterodonta*	Chrysosplenetin and penduletin	Inhibits viral RNA replication	Zhu et al. (2011)
HCMV	*Allium sativum*	Allitridin	Inhibits viral replication in earlier period of viral cycle before viral DNA synthesis	Zhen et al. (2006)
SARS-CoV	*Radix glycyrrhizae*	Glycyrrhizin	Inhibits viral replication	Chen et al. (2004)

or of required conformational changes can prevent viral entry. As indicated in Table 2, aside from polysaccharides, tannins are the most identified entry inhibitors. Multiple mechanisms have been proposed for this activity, including the ability of tannins to interact with and precipitate proteins. Tannins have been shown to inhibit fusion completion in HIV infection (Liu et al., 2002). Although polysaccharides and tannins are not typical drug-like molecules, they display broad antiviral activity. Their development as topically applied medicines such as microbicides is actively pursued.

5. Replication inhibitors

Replication represents the core of the viral life cycle, and involves most viral protein functions. Inhibitors of viral proteases, polymerases, integrases (helicases), and reverse transcriptases of HIV, HCV, and herpesviruses have been clinically successful, and most current antiviral agents target this stage. Considering these unique scenarios, development of TCHMs with antiviral activity is focused principally on this stage of infection (Table 3). Compared with anti-entry TCHMs, compounds targeting replication are more chemically diverse and more virus-specific. Furthermore, considering that cellular machinery is required for viral replication, the mechanisms of many antiviral TCHMs involve cellular factors.

6. Inhibitors of packaging and assembly

The assembly and release of infectious virions is the final step in the viral life cycle. In this stage, vial structural proteins (often as pre-structural proteins such as P1 of enterovirus 71) mature until they are assembled into viral capsids. During this step, viral genomes are packaged into capsids for intracellular transport, enveloped (for enveloped viruses), then released. Despite the absolute requirement for sustained viral infection, no antiviral agents that target this stage have been developed. This limitation is partially

Table 4
TCHM-derived compounds inhbiting viral packaging and assembly.

Virus	Herbs	Compounds	Antiviral effect	References
HSV	*Digitalis purpurea*	Digitoxin	Inhibits viral release	Su et al. (2008)
Flu	Identified from TCM database@Taiwan (http://tcm.cmu.edu.tw)	Canavanine, α-(methylenecyclopropyl)glycine, quinic acid, 2-hydroxy-3-(3,4-dihydroxyphenyl)propanoic acid, β-D-fructofuranose	Binds to the M2 ion channel during simulation	Chang et al. (2011a)
	Identified from TCM database@Taiwan (http://tcm.cmu.edu.tw)	Quinic acid, genipin, syringic acid, cucurbitine, fagarine, methyl isoferulate	Blocks the M2 channel activity	Lin et al. (2011)
EVs	*Phyllanthus emblica*	Phyllaemblicin B	Inhibits viral infection both in *in vitro* and *in vivo* assays	Wang et al. (2009)

due to limited knowledge of the packaging and assembly mechanisms of most viruses, resulting in a limited number of specific assays available. Studies of some TCHMs have revealed that their mechanisms of action involve viral packaging and assembly (summarized in Table 4), but the number remains limited, and the level of understanding is still preliminary.

7. Immunomodulators

As host cell invaders, viruses must escape the immune response to survive. Host innate and adaptive responses against viral infection and replication oppose viral strategies (escaping and blocking) against the host immune response. An excessive reaction of the host immune response may also lead to tissue damage and multi-organ injury (Ferrero-Miliani et al., 2007; La Gruta et al., 2007), which in turn may cause related diseases. TCHMs that enhance host antiviral immune responses or block viral immune escape mechanisms therefore display antiviral activity through immunoregulatory mechanisms.

Considering that many TCHMs have immunoregulatory activities (Table 5), many such remedies also display antiviral activities. This class of TCHMs includes multi-target compounds. For example, polysaccharides are potent interferon inducers and good viral entry inhibitors. Another example is glycyrrhizin, which has activity against entry, replication (Chen et al., 2004), and immunomodulation (Shinada et al., 1986).

8. Future directions

The major goal of current research is to meet international standards for the modernization of TCHMs. To achieve this goal, a TCHM must satisfy all requirements set by international standards, including evidence-supported efficacy (particularly through randomized, double-blind, placebo-controlled, multicenter clinical trials), safety assessment, and quality control. A centralized and standardized research system, aimed at achieving a better understanding of medicinal chemistry and the mechanism of action of TCHMs, is fundamental to achieving this goal.

8.1. Government support

Realizing these needs, the Twelfth Five-Year (2011–2016) Plan for the National Economic and Social Development of the People's Republic of China laid out a national strategy for TCM development. Compared with former Plans, it reflects the equal importance of TCM and Western medicine at the national level. The project for "Supporting the Development of TCM" stipulates that "the protection, research, and rational utilization of Chinese *materia medica* resources, and establishment of quality evaluation and standardization system" has the highest priority in terms of government support (http://www.news.cn, 2011). This initiative shows a determination to solve the bottleneck of underdeveloped Chinese *materia medica*. Thus, based on the Plan, it is expected that TCM-based medical systems will be greatly enhanced through increased funding for basic research and improved education. This government support will undoubtedly result in advanced phytochemistry, assay development, and bioinformatics, which will in turn provide platform technologies and tools for the modernization and commercialization of TCM.

8.2. Centralized screening facilities

Supported by central and local governments, drug screening centers have been established in China in recent years (Table 6). These centers are operated by scientists with extensive experience in global pharmaceutical industries, and are equipped with state-of-the-art equipment, including robots capable of high-throughput screening. Large pharmaceutical companies such as Novartis have also set up research centers in China. Compounds originating from TCHMs are among their foci for drug discovery.

8.3. Centralized databases

Information fragmentation poses a significant challenge to TCM research. Benefiting from strong financial support, large TCM-focused databases are now becoming available (Table 7).

Table 5
TCHM-derived compounds with immunomodulatory activity.

Virus	Herbs	Compounds	References
HSV	*Rhizoma polygonati*	Polysaccharide	Gu et al. (2003)
	Herba houttuyniae	Quercetin, quercitrin or isoquercitrin	Chen et al. (2011)
HBV	*Radix sophorae Flavescentis*	(+)-12a-Hydroxysophocarpine	Ding et al. (2006) and Liu et al. (2003)
	Potentilla anserina	Total saponin	Cai et al. (2003)
	Flos caryophylli	Total saponin	(Gao et al., 2003)
	Kadsura japonica	C19 homolignans: taiwanschirins A, B, C; heteroclitin F; kadsurindutins A, kadsulignan L, and neokadsuranin	Kuo et al. (2005) and Ma et al. (2007)
	Ocimum basilicum	Pigenin	Chiang et al. (2005)
	Kadsura matsudai	Schizarin B, D, and E,	Kuo et al. (2001)
	Phyllanthus	Niranthin, hinokinin	Huang et al. (2003)
	Euphorbia humifusa	Humifusane A and humifusane B	Tian et al. (2011)
FMDV	*Raidx astragali*	Polysaccharide	Li et al. (2011)

Table 6
Drug screening and research centers focusing on TCHM and supported by central and local governments in China.

Center Name		Affiliated Organization	Website
The National Center for Drug Screening		Shanghai Institute of Materia Medica, Chinese Academy of Sciences	http://www.screen.org.cn
National Engineering Research Center	National Engineering Research Center for TCM Pharmaceutical Technology	Yangtze River Pharmaceutical Group Nanjing Hailing Pharmaceutical Co., Ltd.	http://www.hailingyy.com/Center.asp
	National Pharmaceutical Engineering Center for Solid Preparation in Chinese Herbal Medicine	Jiangxi Herbfine Hi-tech Co., Ltd.	http://www.herbfine.com
	National Engineering Research Center for Modernization of Extraction and Separation Process of TCM	Guangzhou Hanfang Pharmaceutical Co., Ltd.	http://www.hovfo.com
	National Engineering Research Center for TCM New Medicine (Compound) Development	Beijing Zhongyan TRT Medicine R&D Co., Ltd.	http://www.tongrentang.com/en/fellowsub/randd.php
Chinese National Engineering Research Center	Chinese National Engineering Research Center for Modernization of TCM	Livzon Pharmaceutical Group, Inc.	http://www.livzon.com.cn/fzjg/zyyjzxView_214.Html
	Chinese National Engineering Research Center for Gelatin	Shangdong Donggeejiao, Inc.	http://www.dongeejiao.com
	Chinese National Engineering Research Center for TCM, SHZJ	Shanghai Pharmaceutical Technology for TCM Co., Ltd.	http://www.nercmtcm.com
National Center for Pharmaceutical Screening		Institute of Materia Medica, Chinese Academy of Medical Sciences	http://ncps.imm.ac.cn
New Drug Screening Center, China Pharmaceutical University		China Pharmaceutical University	http://screen.cpu.edu.cn
National Innovation Center of TCM Modernization in Shanghai		Shanghai Innovation Research Center of Traditional Chinese Medicine	http://www.sirc-tcm.sh.cn

Table 7
TCHM-focused databases in China.

Names of databases	Data volume	Affiliated organization	Website
China traditional Chinese medicines database	14,032	Institute of Information on Traditional Chinese Medicine, China Academy of Chinese Medical Sciences	http://cowork.cintcm.com/engine/wdbintro.jsp
database of effective components in traditional Chinese medicines	600	Scientific Database of Chinese Academy of Sciences	http://www.medicine.csdb.cn/viewTable.jsp?ds=dataset@@medicine&tab=CMP
Traditional Chinese medicines database	23,033	NeoTrident Technology Co.,Ltd	http://www.neotrident.com/newweb/Product_View.asp?ProID=63
Database of compounds from traditional Chinese medicine	30,000	Shanghai TCM Data Center	http://www.tcm120.com/1w2k/tcm_compound.asp
Database of compounds from traditional Chinese medicines metabolism	1,741	Shanghai TCM Data Center	http://temdb.sgst.cn/tcm_metabolize.asp
Database of compounds and components of traditional Chinese medicine	3,500	Shanghai TCM Data Center	http://temdb.sgst.cn/tcm_compcontent.asp
Traditional Chinese medicine and chemical components database	19,700	Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences	http://www.organchem.csdb.cn/scdb/main/tcm_introduce.asp

Comprehensively integrated databases are foreseen to greatly enhance TCHM-based drug discovery.

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