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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.

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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 TCHM extracts is considered more efficient compared 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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provide targets for inhibitors of entry, replication (e.g., protease and budding of progeny virus particles (Fig. 1, 7 and 8). These steps

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

Table 1

| Herbs                  | Botanical names                   | Trade names               | Virus | Diseases                  | References                      |
|------------------------|----------------------------------|---------------------------|-------|---------------------------|---------------------------------|
| Radix bupleuri         | Bupleurum chinense,             | Xiao-chai-hu capsule,     | Flu   | Influenza, upper           | Zhang et al. (2007) and Zhao et al. (2007) |
|                        | Bupleurum scorzoneriifolium     | Zheng-chai-hu-yin granule|       | respiratory infection      |                                 |
| Fructus forsythae      | Forsythia suspensa               | Yin-qiao-jie-du-wan (granule, tablet), Yin-qiao-san | Flu   | Acute bronchitis           | Li et al. (2008), Sun et al. (2006), Xie et al. (2006) and Yang et al. (2005b) |
| Flos ionicerar; Radix scutellariae | Loniceria 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 tintorica,               | Ban-lan-gen granule,      | Flu   | HSV                        |                                 |
|                        | Isatis indigotica,              | Li-zhu (Chuan-fang)       |       | Influenza, acute           |                                 |
|                        | Baphicacanthus cusia           | kung-bing-du granule      |       | 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 sophora; Flavescentis | Sophora flavescens           | Ku-shen tablet,            | Flu   | RSV                       |                                 |
|                        | Spica prunellae;               | Ku-shen-jian injection    |       | Influenza                  |                                 |
| Flos chrysanthemi      | Prunella vulgaris;             | Xiang-sang-ju granule     | Flu   | RSV                       |                                 |
| Indici; Faluri mori    | Chrysanthemum indicum,         | Guang-yao-xing-qun-xia-sang-ju |       |                             |                                 |
|                        | Chrysanthemum boreale,         |                           |       |                             |                                 |
|                        | Chrysanthemum lavandulaefolium;|                           |       |                             |                                 |
|                        | Morus alba                     |                           |       |                             |                                 |

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 TCHMs, 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 identification 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
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,
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 2

| 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) |
|      | Spica prunellae, Euphorbia jolkini, Phyllanthus emblica | Polysaccharide | Inhibits viral attachment and penetration | Liu et al. (2004a) |
| HIV   | Spica prunellae, Rhizoma citrata | Tannin | Inhibits viral attachment | Liu et al. (2002) |
| Flu   | Fraxinus arctii, Radix glycyrrhizae | 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) |
| NV    | Fraxinus schinodendron, Pomegranate | Glycyrrhizin | Inhibits viral attachment and penetration | Chen et al. (2004) |
|       | | Tannin | Inhibits the binding to histo-blood group antigens (HBGAs) | Zhang et al. (2012) |

Fig. 3. Target-specific assays used for active compound identification during AGF and for antiviral mechanism analysis.
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 intercalate 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 addressed by the development of TCHMs.

**Table 3**

| 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 | Protocatechual aldehyde                                                  | Inhibits viral replication                                                                         | Li et al. (2005)          |
|         | Limonium sinense                | Isodihydroxyringetin, (-)-epigallocatechin 3-O-gallate,                     | Inhibits viral replication                                                                         | Lin et al. (2000)         |
|         |                                | samarangenin B, myricetin, myricetin 3-O-α-rhamnopyranoside,               |                                                                                                    |                           |
|         |                                | quercetin 3-O-α-rhamnopyranoside, (-)-epigallocatechin,                      |                                                                                                    |                           |
|         |                                | gallic acid, N-trans-caffeoyltiramine, N-trans-feruloyltiramine             |                                                                                                    |                           |
| HIV     | Rhizoma coptidis                | Berberine                                                                  | Inhibits viral DNA synthesis                                                                      | Chin et al. (2010)        |
|         | Chrysanthemum morifolium        | Apigenin-7-O-β-D-glucoyporanoside                                          | Inhibits viral integrase                                                                          | Lee et al. (2003)         |
|         | Vatica cinerea                  | Vaticine (23E)-27-nor-3-hydroxyacycloart-23-en-25-one                      | Inhibits viral replication                                                                         | Zhang et al. (2003)       |
|         | Aesculus chinensis              | Triterpenoid saponins                                                      | Inhibits viral protease                                                                           | Yang et al. (1999)        |
|         | Kadsura matsuubai               | Schizanbin 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             | Apigenin 4′-O-α-rhamnopyranoside, apigenin 7-O-β-glucopyranosyl-4′-O-α-rhamnopyranoside, tricin 7-O-β-glucopyranoside, tricin, isocoproletin | Inhibits viral replication                                                                     | Li et al. (2005)          |
|         | Ranunculus sieboldii, Ranunculus sceleratus | Oxymatrin                                                                 | Down-regulates the expression of heat-shock cognate 70 (HSC70) that is required for HBV DNA replication | Wang et al. (2011)        |
|         | Radix sophorae Flavescentis     | Saikosaponin C                                                             | Inhibits viral DNA replication and HBV Ag production                                               | Chiang et al. (2003)      |
| HCV     | Sarsapragra melanolactra        | Polyphenolic compounds                                                      | Inhibits viral N53 serine protease                                                                  | Zuo et al. (2005)         |
|         | Rhodiola kirilowii              | 3,3′-Digalloylpropodephilindin B2, 3,3′-Digalloylpropocyanidin B2, (-)-Epigallocatechin-3-O-gallate | Inhibits viral N53 serine protease                                                                  | Zuo et al. (2007)         |
| Flu     | Fructus arctii Pterodonata      | Arcticin                                                                   | Inhibits viral replication                                                                         | Gao et al. (2002)         |
| EV71    | Taggera pterodonta               | Chrysoplenetin and penduletin                                              | Inhibits viral RNA replication                                                                     | Zhu et al. (2011)         |
| HCMV    | Allium sativum                  | Alitridin                                                                  | Inhibits viral replication in earlier period of viral cycle before viral DNA synthesis            | Zhen et al. (2006)        |
| SARS-CoV | Radix glycyrrhiza               | Glycyrrhizin                                                               | Inhibits viral replication                                                                         | Chen et al. (2004)        |
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 immunomodulatory (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).
Comprehensively integrated databases are foreseen to greatly enhance TCHM-based drug discovery.

Acknowledgments

This work was partially supported by the National Basic Research Program (973) (Grant Nos. 2009CB522300 and 2010CB50100), Department of Education of Guangdong Province (Grant No. GXZD0901).

References

Baba, M., Snoeck, R., Pawels, R., de Clercq, E., 1988. Sulfated polysaccharides are potent and selective inhibitors of various enveloped viruses, including herpes simplex virus, cytomegalovirus, vesicular stomatitis virus, and human immunodeficiency virus. Antimicrobial Agents and Chemotherapy 32, 1742–1745.

Cai, G., Zhao, Y., Yuan, H., Zhang, X., Liu, F., He, C., Tang, C., Li, Z., 2003. Separation of Potentilla anserine active site (total saponin) and anti-DHBV DNA action in ducks. Central South Pharmacy (China) 1, 17–21.

Cao, H., Tao, D.S., Zeng, Y.Q., Guan, Y., 2006. In vitro study on a TCM product (Kang Bing Du Granule) against highly pathogenic H5N1 avian influenza A virus (genotype E). In: The 6th Meeting of Consortium for Globalization of Chinese Medicine cum International Forum (Zhuhai) on Chinese Medicine Program & Abstract, 69–70.

Cao, H., Tao, D.S., Zeng, Y.Q., Guan, Y., 2010. In vitro study on Kang Bing Du Granule against swine-origin influenza A virus (A/1H1N1). In: The 9th Meeting of Consortium for Globalization of Chinese Medicine, Abstracts, 220.

Chang, T.T., Sun, M.F., Chen, H.Y., Tsai, F.J., Lin, J.G., Chen, Y.C., 2011a. Key features for designing M2 proton channel anti-swine flu inhibitors. Journal of the Taiwan Institute of Chemical Engineers 42, 701–708.

Chang, T.T., Sun, M.F., Chen, H.Y., Tsai, F.J., Fisher, M., Lin, J.G., Chen, Y.C., 2011b. Screening from the world’s largest TCM database against H1N1 virus. Journal of Biomedical Structure & Dynamics 28, 773–786.

Cao, H., Tao, D.S., Zeng, Y.Q., Guan, Y., 2011. TCM Database@Taiwan: the world’s largest traditional Chinese medicine database. Journal of Antimicrobial Chemotherapy 53, 577–583.

Cao, H., Tao, D.S., Zeng, Y.Q., Guan, Y., 2010. In vitro study on Kang Bing Du Granule against swine-origin influenza A virus (A/1H1N1). In: The 9th Meeting of Consortium for Globalization of Chinese Medicine, Abstracts, 220.

Chang, T.T., Sun, M.F., Chen, H.Y., Tsai, F.J., Lin, J.G., Chen, Y.C., 2011a. Key features for designing M2 proton channel anti-swine flu inhibitors. Journal of the Taiwan Institute of Chemical Engineers 42, 701–708.

Chang, T.T., Sun, M.F., Chen, H.Y., Tsai, F.J., Fisher, M., Lin, J.G., Chen, Y.C., 2011b. Screening from the world’s largest TCM database against H1N1 virus. Journal of Biomedical Structure & Dynamics 28, 773–786.

Chen, C.Y., 2011. TCM Database@Taiwan: the world’s largest traditional Chinese medicine database for drug screening in silico. PLoS One 6, e15939.

Chen, B.Q., Li, B.C., 2006. Studies on antivirus of Banlangen buccal tablets. Journal of Henan University (Medical Science) 25, 67–69.

Chen, Q., Liu, X., 2003. Antiviral activity of Gentiana lutea against HHV-6. Journal of Henan University (Medical Science) 24, 66–69.

Chen, B.Q., Xiao, S.H., Gu, L., Liu, J., 2007. Experimental studies on anti-flu virus effect of Yinhua injection in vivo and in vitro. Liushihzhen Medicine and Materia Medica Research 18, 591–592.

Chen, X., Wang, Z., Yang, Z., Wang, J., Yan, X., Tan, R.X., Li, E., 2011. Houttuynia cordata blocks HSV infection through inhibition of NF-kappaB activation. Antiviral Research 92, 341–345.

Cheng, H., Lin, T., Yang, Z., Wang, K., Lin, L., Chen, Y.C., 2004. Putranjivain A from Euphorbia jolkini inhibits both virus entry and late stage replication of herpes simplex virus type 2 in vitro. Journal of Antimicrobial Chemotherapy 53, 577–583.

Chiang, L.C., Ng, L.T., Liu, L.T., Shieh, D.E., Lin, C.C., 2003. Cytotoxicity and anti-hepatitis B virus activities of saikosaponins from Bupleurum species. Planta Medica 69, 705–709.
Chiang, L.C., Ng, L.T., Cheng, P.W., Chiang, W., Lin, C.C., 2005. Antiviral activities of extracts and selected pure constituents of Ocimum basilicum. Clinical and Experimental Pharmacology and Physiology 32, 811–816.

Chen, L.W., Cheng, Y.W., Yang, Y., Lin, Y.T., Liu, M.Y., Chou, M.C., Yang, C.C., 2010. Anti-herpex simplex virus type 8 infection from Coixis rhizoma, a major component of a Chinese herbal medicine, Ching-Wei-San. Archives of Virology 155, 1313–1326.

Ding, P., Liao, Z., Huang, H., Pu, C., Chen, D., 2006. (+)-12-Chiratone: A new bisabolyl alcohol from the stems of Chamaecyparis obtusa. Journal of Natural Products 72, 205–211.

Ferrero-Miliani, L., Nielsen, O.H., Andersen, P.S., Girardin, S.E., 2007. Chronic preservation: immunopathology in influenza virus infection. Immunology and Cell Biology 85, 85–92.

Guo, Q., Zhao, L., You, Q., Yang, Q., Gu, H., Song, G., Lu, N., Xin, J., 2007. Anti-influenza virus activity of arctigenin and angiotensin-converting enzyme 2 interaction. Antiviral Research 77, 1–9.

Huang, X.J., Hou, W., Zhao, Y.L., Luo, F., Yang, Z.Q., 2007. An experimental study on anti-respiratory syncytial virus with Xiasangju extract. Chinese Journal of Traditional and Herbal Drugs 33, 724–725.

Kuo, Y.H., Wu, M.D., Huang, R.L., Kuo, L.M., Hsu, Y.W., Liaw, C.C., Hung, C.C., Shen, S.Y., Liu, J.H., Tian, Y.R., Guo, J., Feng, J., Mei, L., 2011. Inhibition of herpes simplex virus infection by negatively charged and neutral urycorythymidine polymers. Archives of Virology 156, 215–220.

Peng, T., 2010. Strategies for antiviral screening targeting early steps of virus infection. Virologica Sinica 25, 281–293.

Shen, S.Y., Liu, J.H., Tian, Y.R., Guo, J., Peng, J.Z., Liu, S.D., Zeng, J.X., Dang, X.H., Mei, L. 2008. Antiviral activity of Shuanghuanglian tablet against influenza A virus FM 1 and adenovirus ADV3 in mice. China Practical Medicine 3, 50–52.

Shen, J., Wang, L.X., 2012. Observation of therapeutic effects of Ku-shen-jian injection on hepatitis B. Chinese Remedies & Clinics 12, 515–516.

Shinoda, K., Azuma, K., Yoshihara, T., Yoshida, T., Sutuzani, S., Sakuma, T., 1986. Enhancement of interferon-gamma production in glycyrrhizin-treated human peripheral lymphocytes in response to concanavalin A and to surface antigen of hepatitis B virus. Proceedings of the Society for Experimental Biology and Medicine 182, 399–404.

Su, C.T., Hsu, J.T.A., Hsieh, H.P., Lin, P.H., Chen, T.C., Kao, C.L., Lee, C.N., Chang, S.Y. 2008. Anti-HSV activity of digitoxin and its possible mechanisms. Antiviral Research 79, 62–70.

Sun, J., 2007. Antiviral active ingredients in plants. Acta Universitatis Lithuanicae Medicinae Sinicis Pharmacologicae 29, 1–79.

Sun, J., Chu, Y.L., Zheng, J.W., Jiang, F.L., Shao, Q.O., Chai, C.B., 2006. Experimental study on Yingqiaoquannao granule against influenza A in vitro. Journal of Shantou College of Traditional Chinese Medicine 29, 49–50.

Sun, J., Wang, N.R., Yang, B., He, S.Q., 2009. Study on Shuanghuanglian inhibiting effect of influenza virus A1 gene. Journal of Clinical Pulmonary Medicine 14, 79–83.

Sun, H.H., Deng, W., Zhan, L.J., Xu, L.L., Li, P.D., Lv, Q., Zuo, H., Liu, Y., Ma, C.M., Bao, L.L., 2010. Effect of Banlangen granule on mice challenged with A/California/7/2009. Chinese Journal of Comparative Medicine 20, 53–57.

Takeda, K., Kaisho, T., Akira, S., 2003. Toll-like receptors. Annual Review of Immunology 21, 335–376.

Tian, Y., Sun, L.M., Li, B., Liu, X.Q., Dong, J.X., 2011. New anti-HBV caryophyllane-type sesquiterpenoids from Euphorbia humifusa Wild. Fitoterapia 82, 251–254.

Tang, Z., Wang, Y., Shen, H., Shi, Y., 2010. Inhibition of glycyrrhiza polysaccharides from Radix Glycyrrhizae on virus. Acta Scientiarum Naturalium Universitatis Nankaiensis 34, 126–128.

Wang, J., Nie, H., Tam, S., Huang, H., Zheng, Y. 2002. Anti-HIV-1 activity of trichosanthes correlates with its ribosome inactivating activity. FEBS Letters 521, 17–20.

Wang, G.T., Song, Y.Y., Ren, G.J., Wang, Y.Z., Xu, H.Z., 2005. Antiviral activity of Yinhuang for injection on respiratory syncytial virus in vitro. Chinese Journal of New Drugs and Clinical Remedies 24, 887–889.

Wang, Y., Wang, R., Hou, X., 2007. Anti-influenza antiviral components of natural products. Natural Product Reports and Development 19, 179–182.

Wang, X., Li, M., Wang, Y., Yue, Q., 2008. Research progress in antiviral effects of traditional Chinese medicine. Medical Recapitulate 14, 3488–3490.

Yan, W.F., Wang, X.Y., Ren, Z., Qian, C.W., Li, Y.K., Kai, K., Wang, Q.D., Zhang, Y., Zheng, L.Y., Jiang, Y.H., Yang, C.R., Liu, Q., Yang, Y.F., 2009. Phyllolemin B inhibits Coxackie virus B3 induced apoptosis and myocarditis. Antiviral Research 84, 150–158.

Yan, W.F., Wang, Z., Xue, R., Zhou, Z.X., Liu, F., Han, Y.X., Ren, G., Peng, Z., Cen, S., Chen, H.S., Li, Y.H., Jiang, J.D., 2011. Oxytetracycline inhibits hepatitis B infection with an advantage of overcoming drug-resistance. Antiviral Research 89, 227–233.

Yu, H.B., Li, H.M., Lu, C.A., Gao, Y.J., Li, X.Q., Zhou, A.X., 2004. Experimental study on Shuanghuanglian dispersible tablets against viruses. Chinese Journal of Experimental Traditional Medicinal Formulas 10, 46–50.

Yu, C.L., Jiang, S.J., Wang, W., Hu, D., Xiao, F., 2005. Antiviral activity of Shuanghuanglian dispersible tablets against viruses. Chinese Journal of Experimental Traditional Medicinal Formulas 10, 46–50.
Yu, L., Luo, J., Tan, X., 2006. The basic research ideas of herbal prescriptions composing principles. Traditional Chinese Drug Research & Clinical Pharmacology (China) 16, 43–45.

Zhao, H.Q., Dong, T.X. 2006. Active part and preparation method of anti-flu traditional Chinese medicine. Chinese Patent Number 200610005382.2.

Zhang, Q.X., Zeng, F.Z., 2009. Observation of the therapeutic effect of Huangqi injection and Shengmai injection for pediatric viral myocarditis. Journal of Emergency in Traditional Chinese Medicine 18, 556–557.

Zhang, J., Yan, B., Yao, X., Gao, Y., Song, J., 1995. Tannin from Pericarpium granati inhibites herpes simplex virus type 2. China Journal of Chinese Materia Medica 20, 556–560.

Zhang, H.S., Tan, G.T., Hoang, V.D., Hung, N.V., Cuong, N.M., Soejarto, D.D., Pezzuto, J.M., Fong, H.H., 2003. Natural anti-HIV agents. Part IV. Anti-HIV constituents from Vatica cinerea. Journal of Natural Products 66, 263–268.

Zhang, F.Y., Gao, Y.F., Song, H.R., 2005. Study on the effect against CBV3 by ShengmaiYin and abstracts from stems and leaves of Scutellaria baicalensis in vivo. Tianjin Medical Journal 33, 717–719.

Zhang, B., Huang, F., Dai, Y., Mi, J.Y., 2007. Experimental study of antiviral effect of compound Chaihu capsule on mice infected with influenza virus. Chinese Journal of Clinical Pharmacology and Therapeutics 12, 173–176.

Zhang, X.F., Dai, Y.C., Zhong, W., Tan, M., Lv, Z.P., Zhou, Y.C., Jiang, X., 2012. Tannic acid inhibited norovirus binding to HBGA receptors, a study of 50 Chinese medicinal herbs. Bioorganic & Medicinal Chemistry 20, 1616–1623.

Zhao, F., Han, X., 2009. Research progress in antiviral effects of traditional Chinese medicine and active ingredients. Journal of Practical Traditional Chinese Medicine 25, 428–430.

Zhao, P., Liu, A.P., Liu, N., Li, Q.Y., 2007. Studies on Zhengchahuiyin inhibit influenza A and B in vitro. Journal of Practical Medical Techniques 14, 2155–2156.

Zhen, H., Fang, F., Ye, D.Y., Shu, S.N., Zhou, Y.F., Dong, Y.S., Nie, X.C., Li, G., 2006. Experimental study on the action of allitridin against human cytomegalovirus in vitro: Inhibitory effects on immediate-early genes. Antiviral Research 72, 68–74.

Zhou, L., Meng, Y., 1997. Studies on antiviral activities of polysaccharides and their derivatives. Chinese Journal of Applied & Environmental Biology 3, 82–90.

Zhou, Z., Zhang, Y., Ding, X.R., Chen, S.H., Yang, J., Wang, X.J., Jia, C.L., Chen, H.S., Bo, X.C., Wang, S.Q., 2007. Protocatechuic aldehyde inhibits hepatitis B virus replication both in vitro and in vivo. Antiviral Research 74, 59–64.

Zhu, Q.C., Wang, Y., Liu, Y.P., Zhang, R.Q., Li, X., Su, W.M., Long, F., Luo, X.D., Peng, T., 2011. Inhibition of enterovirus 71 replication by chrysosplenin and penduletin. European Journal of Pharmaceutical Sciences 44, 392–398.

Zuo, G., Li, Z., Chen, L., Xu, X., 2005. Short communication in vitro anti-HCV activities of Saxifraga melanocentra (Regel) Maxim against HCV NS3 serine protease. Antiviral Research 76, 86–92.