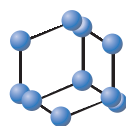


RESEARCH ARTICLE

BENTHAM
SCIENCE

TCM@MPXV: A Resource for Treating Monkeypox Patients in Traditional Chinese Medicine

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Abstract: Introduction: Traditional Chinese Medicine (TCM) has been extensively employed in the treatment of Monkeypox Virus (MPXV) infections, and it has historically played a significant role in combating diseases like contagious pox-like viral diseases in China.

Methods: Various traditional Chinese medicine (TCM) therapies have been recommended for patients with monkeypox virus (MPXV). However, as far as we know, there is no comprehensive database dedicated to preserving and coordinating TCM remedies for combating MPXV. To address this gap, we introduce TCM@MPXV, a carefully curated repository of research materials focusing on formulations with anti-MPXV properties. Importantly, TCM@MPXV extends its scope beyond herbal remedies, encompassing mineral-based medicines as well.

Results: The current iteration of TCM@MPXV boasts an impressive array of features, including (1) Documenting over 42 types of TCM herbs, with more than 27 unique herbs; (2) Recording over 285 bioactivity compounds within these herbs; (3) Launching a user-friendly web server for the docking, analysis, and visualization of 2D or 3D molecular structures; and (4) Providing 3D structures of druggable proteins of MPXV.

Conclusion: To summarize, TCM@MPXV presents a user-friendly and effective platform for recording, querying, and viewing anti-MPXV TCM resources and will contribute to the development and explanation of novel anti-MPXV mechanisms of action to aid in the ongoing battle against monkeypox. TCM@MPXV is accessible for academic use at <http://101.34.238.132:5000/>.

Keywords: Monkeypox, docking simulation, traditional chinese medicine, herbs, molecular structures, therapeutic pathways.

1. INTRODUCTION

On July 23, 2022, the World Health Organization (WHO) officially declared monkeypox, a zoonotic disease, to be an ongoing public health emergency of worldwide concern in various nations and areas [1]. The monkeypox virus (MPXV), which has been identified in West and Central Africa, is a member of the Poxviridae family, along with variola virus (VARV or smallpox), cowpox virus, and camelpox virus (CMPV). MPXV can be recognized by double-stranded DNA (dsDNA) and is usually associated with symptoms, such as fever, headache, muscular pains, back discomfort, fatigue, and enlarged lymph nodes. These are followed by the appearance of a rash that can continue for two to three

weeks [2, 3]. Since the outbreak commenced in early May 2022, there has been a shortage of monkeypox virus (MPXV) vaccinations. Presently, only cidofovir, tecovirimat, and brincidofovir, which are licensed by the US Food and Drug Administration (FDA) for the treatment of smallpox, are available for treating MPXV infection [4].

Throughout the 3500-year history of China, traditional Chinese medicines have been used as the routine treatment regime for acute infectious diseases like malaria and COVID-19 [5-9]. The wide use of artemisinin, which has high potency and low toxicity and is inspired by traditional Chinese medicines (TCM), helps many countries and eventually eradicates malaria [10]. Also, in 2003 and 2020, when severe acute respiratory syndrome (SARS) and COVID-19 were becoming the most serious infectious disease outbreak, traditional Chinese medicine played a significant role in the prevention and treatment of SARS and SARS-CoV-2 [6, 11-16]. In 2022, facing the outbreak of monkeypox around the world, the National Health Commission of China issued a TCM treatment program in the Guidelines for the Diagnosis

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and Treatment of Monkeypox, which included six Chinese formulas [17].

At the time of writing, a series of clinical trial studies from multiple hospitals in East Asia were launched to investigate the efficacy and safety of TCM therapies for MPXV. Here, in this context, we introduce TCM@MPXV, a painstakingly curated repository of scholarly literature encompassing anti-MPXV formulations. Importantly, TCM@MPXV extends its scope beyond herbal remedies, encompassing mineral-based medicines as well. The current iteration of TCM@MPXV boasts an impressive array of features, including (1) Documenting over 42 types of TCM herbs, with more than 27 unique herbs included (2) Recording over 285 compounds with bioactivity within these herbs; (3) Launching a user-friendly web server for the docking, analysis, and visualization of 2D or 3D compound structures; and (4) Providing 4 vital druggable structure target proteins of MPXV.

2. MATERIALS AND METHODS

2.1. Data Collection and Processing

The basic data collection and processing stages of TCM are illustrated in Fig. (1). The information on Herbs, formulas, and ingredients was searched in PubMed using the keyword “TCM or MXPV or Monkeypox”. The lists of formulas were recorded in the Guidelines for the Diagnosis and Treatment of Monkeypox (2022 Version) by the National Health Commission of China. The herbs and ingredients were obtained by HERB (<http://herb.ac.cn/>) and TCMsp(<https://old.tcmsp-e.com/tcmsp.php>). All the data were stored in PostgreSQL (an object-relational database

(<https://www.postgresql.org/>). All the structural files of the molecules can be downloaded by pressing Mol2 files.

2.2. Modeling of Targets of MPXV

Four druggable sites in the process of replication of the monkeypox virus within the host cell cytoplasm have been identified in the previous study. Therefore, we used I-TASSER (<https://zhanggroup.org/I-TASSER/>), AlphaFold 2.3.2 (<https://colab.research.google.com/github/deepmind/alphafold/blob/main/notebooks/AlphaFold.ipynb?pli=1>), and Swiss-Model (<https://swissmodel.expasy.org/>) to model the 3D structure of the target proteins by the sequences. Given that the structure could be predicted by different models in PDB bank, we selected the best one of five models in I-TASSER, AlphaFold 2.3.2 and Swiss-Model by the given regular parameter.

3. RESULTS

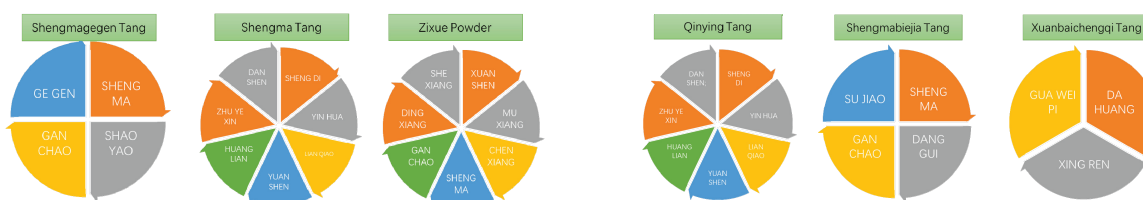
3.1. Web Interface

TCM@MPXV provides a user-friendly online interface for retrieving data on anti-MPXV traditional Chinese medicine (TCM) therapies. For formula similarity analysis, a special web server has been established (Fig. 1). The navigation bar allows you to quickly access the Home, Search, Download, Target, and Contact pages. Users can search for TCM formulations, herbs, and ingredients using keywords (Chinese/Mandarin, Pinyin, English, or Latin names) on the Search page. The Home page also contains connections to other key websites for the user's convenience. The data can be downloaded from the Download page. TCM@MPXV

TCM@MPXV

Home Search Download Target Contact Us

TCM@MPXV: A Free Anti-Monkeypox Drug Resource



Six Traditional Chinese Medicine Formulas for MPXV

TCM@MPXV is a free anti-monkeypox drug resource in Traditional Chinese Medicine. TCM@MPXV is freely for education, academic, and other non-profit purposes. If you want to use TCM@MPXV for any commercial purpose or medical purpose, you should contact Ph. D Xin Zhang or MD Pinglu Zhang.

Fig. (1). The home page of website. (A higher resolution / colour version of this figure is available in the electronic copy of the article).

also gives thorough instructions and an example on the help page.

3.2. Search Page

TCM@MPXV offers three distinct search methods on the Search page to enhance user convenience in exploring data. These methods include "Formula" (enabling users to search for a formula by entering its Chinese name or Pinyin name), "Herb" (allowing users to search for an herb using its Chinese name, Pinyin name, or Latin name), and "Ingredients" (facilitating the search for an ingredient by entering its Compound ID or PubChem CID name) (Fig. 2).

3.3. Target Page

The 3D structural druggable targets are very important for drug development, design, and discovery. Four druggable sites in the process of replication of the monkeypox virus within the host cell cytoplasm have been identified [18, 19]. *In vitro* studies have demonstrated that tecovirimat (ST-246) inhibits the function of the orthopoxvirus's VP37 protein. This inhibition inhibits the virus from maturing and releasing from the infected cell, preventing the virus from spreading throughout the host [20]. The E9L DNA polymerase has emerged as an attractive target for the development of antiviral medicines due to its critical involvement in viral DNA replication and sensitivity to nucleoside and nucleotide analogs [21]. Two nucleoside kinase homologs encoded by the vaccinia virus are thought to operate as viral DNA precursors. Meanwhile, prior studies have indicated that the thymidylate kinase A48R has the capability to bind with thymidine diphosphate [22]. As for A50R, it serves as a DNA ligase and plays a crucial role in sealing nicks in double-stranded DNA during various processes, including replication, recombination, and repair [18].

The Protein Data Bank (PDB) currently lacks most protein structures of the monkeypox virus. Due to the time and funding requirements associated with wet experiments, we utilized ColabFold (<https://github.com/sokrypton/ColabFold>) [23], the Swiss-Model servers (<https://swissmodel.expasy.org/>) [24], and I-TASSER (<https://seq2fun.dcmf.med.umich.edu/I-TASSER/>) [25] to predict protein structures from their respective sequences. Halign [26-28] was employed for multiple sequence alignment. Our aim is to provide users with immediate access to these protein structures for efficient virtual screening. Users can identify the targets by name and the MPXV sequence and download the corresponding protein structure files (Fig. 3).

3.4. Webserver for Other Linkers

To enhance the understanding of the users on drug discovery, there are docking simulation software and ADMET study web services. Hence, we added some links to TCM@MPXV for virtual screening and the ADMET study. On the homepage, a dedicated module allows users to access four tools for related studies with compounds in TCM *via*

docking simulation (Fig. 4). GHECOM [29] enables users to identify the docking pocket or docking site by uploading the protein files. ADMETlab2.0 [30] helps users discover the ADMET characteristics of compounds of TCM. HERB [31] and TCMsp [32] provide users with the ability to investigate the ingredients of TCM immediately.

4. DISCUSSION

Traditional Chinese medicine (TCM) is extremely important in China, Korea, and some East Asian countries. Ongoing research is actively investigating TCM's integrative processes *via* a thorough examination of anti-MPXV TCM recipes [33]. TCM@MPXV, which serves as a comprehensive database, diligently records extensive information about anti-MPXV therapies in response to these requests. It is certainly a great toolset that contributes considerably to the resolution of continuing controversies about the effects and processes of TCM therapy. The current version of TCM@MPXV systematically consolidates information on Traditional Chinese Medicine (TCM) formulations and ingredients from books and public sources, serving two main purposes. Firstly, it elucidates the potential therapeutic mechanisms of the recorded TCM therapies within TCM@MPXV, offering valuable guidance for pharmacological studies and the functional characterization of innovative anti-MPXV TCM treatments. Secondly, the ongoing collection of clinical trial data and treatment outcomes related to anti-MPXV therapies establishes the groundwork for comprehensive clinical research and disease-specific therapy methods. TCM@MPXV incorporates a web server for docking simulation pages to enhance user convenience. Thirdly, this platform facilitates the smooth searching, analysis, and display of documented formulas, including those provided by users. Consequently, it is undeniably a valuable tool for both basic and clinical research into innovative anti-MPXV Traditional Chinese Medicine remedies.

TCM@MPXV does have certain limitations. Firstly, the database lacks information about the proportions and significance of herbs within the documented formulas, such as adherence to the "monarch, ministerial, assistant, and guide" principle. This information is missing because the majority of the original sources did not provide it. Secondly, we have identified a gap in the reporting of side effects and adverse reactions in the clinical utilization of traditional Chinese medicine prescriptions. This absence of data also impacts the clinical application of traditional Chinese medicine.

Given that monkeypox cannot be eradicated overnight, we will continue to gather and compile data to fill these gaps. As a result, we intend to constantly upgrade TCM@MPXV in the future.

CONCLUSION

In summary, TCM@MPXV comprehensively documents more than 6 TCM formulas, encompassing over 27 unique herbs and records over 288 ingredients. This website

Formula
Herb
Ingredients

Search page

Please input keyword

Search

Results page

药方中文名(Chinese name)	药方拼音名(Pinyin name)	药材组成(Herbs)
宣白承气汤	Xuanbaichengqi Tang	<ul style="list-style-type: none"> ● Shengshigao ● Dahuang ● Xingrenfen ● Gualoupi

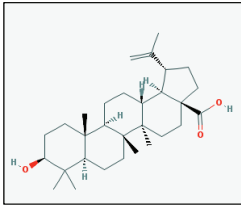
中文名(Chinese name)	中文拼音名(Pinyin name)	拉丁名(Latin name)	组分(Ingredients)
沉香	Chenxiang	Linderae Radix	<ul style="list-style-type: none"> ● MOL000098 ● MOL000358 ● MOL000359

Detail page

Compound Information

Compound ID:	MOL000211
Compound Name:	Mairin
PubChem CID:	64971

2D Image



3D Structure

Download Mol2

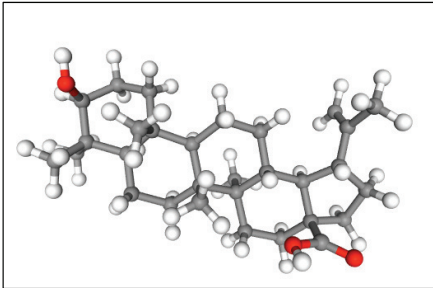


Fig. (2). The search page, result page and detail page (Using Xuanbaichengqi Tang, 沉香/Chenxiang, and MOL000211 as example). (A higher resolution / colour version of this figure is available in the electronic copy of the article).

Target ID	Protein Name	Sequence	AF2 Results	Swiss-Model	I-TASSER
TARGET1	Palmitoylated EEV membrane glycoprotein, VP37 protein	ProteinVP37.fasta	VP37-AF2.pdb	VP37-Swissmodel.pdb	VP37-I-TASSER.pdb
TARGET2	A48R	ProteinA48R.fasta	A48R-AF2.pdb	A48R-Swissmodel.pdb	A48R-I-TASSER.pdb
TARGET3	A48R	ProteinA50R.fasta	A50R-AF2.pdb	A50R-Swissmodel.pdb	A50R-I-TASSER.pdb
TARGET4	E9L DNA-Polymerase	ProteinE9L.fasta	E9L-AF2.pdb	E9L-Swissmodel.pdb	E9L-I-TASSER.pdb

Fig. (3). The target page of TCM@MPXV website. (A higher resolution / colour version of this figure is available in the electronic copy of the article).

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Other Linkers

- GHECOM: Grid-based HECOMi(Pocket) Finder (pd bj.org)
- ADMETlab2.0
- HERB
- TCMsp

Fig. (4). Project leader and developers and other linkers. (A higher resolution / colour version of this figure is available in the electronic copy of the article).

provides an easy-to-use platform for recording, searching, and exploring anti-MPXV therapies from Traditional Chinese Medicine (TCM). It will contribute to the creation and understanding of new anti-MPXV therapeutic pathways, eventually aiding continuing efforts to battle MPXV disorders.

HIGHLIGHTS

1. TCM@MPXV documents over 6 TCM formulas (including over 27 herbs) with detailed clinical evidence and therapeutic mechanism information.

2. TCM@MPXV records over 285 ingredients with detailed potential therapeutic mechanisms.
3. TCM@MPXV launches a useful web server for docking, analyzing, and visualizing four protein targets of MPXV generated by AlphaFold2, Swiss-model, and I-TASSER.

AUTHORS' CONTRIBUTIONS

Conceptualization X.Z. and Q.Z.; Methodology X.Z. and P.Z. ; Investigation, X.Z. and F.Z. ; Analysis, X.Z. and P.Z. ; Writing original draft, X.Z. and Y.Z.; Writing - Review and

Editing, X.Z., P.Z., Q.Z., and Y.Z. ; Project administration, X.Z. and Y.Z.; Project administration, X.Z. and Q.Z.; Funding Acquisition, X.Z., Q.Z., and Y.Z. X.Z. and F.Z. contributed equally to this work.

LIST OF ABBREVIATIONS

FDA	=	Food and Drug Administration
MPXV	=	Monkeypox Virus
SARS	=	Severe Acute Respiratory Syndrome
TCM	=	Traditional Chinese Medicine
WHO	=	World Health Organization

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

Not applicable.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

The data and supportive information are available within the article.

FUNDING

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CONFLICT OF INTEREST

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