

# Study on Oxymatrine-Based Research from 2001 to 2022: A Bibliometric Analysis

Xu Lan, Yao Chen, Jia-jia Duan,\* and Jia Xu\*



Cite This: *ACS Omega* 2024, 9, 9633–9643



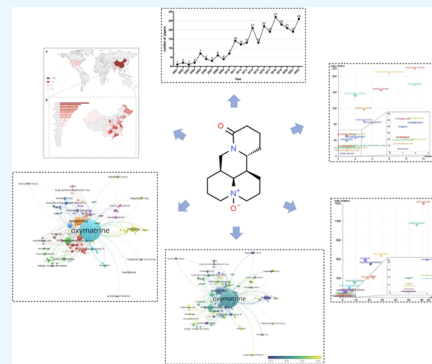
Read Online

ACCESS |

Metrics & More

Article Recommendations

**ABSTRACT:** Oxymatrine is a quinolizidine alkaloid mainly derived from Kushen; it possesses various therapeutic effects, such as organ- and tissue-protective, anticancer, and antiviral effects. The research directions for oxymatrine remain broad. In order to explore the overall status of oxymatrine-based research, we carried out a bibliometric analysis to summarize the oxymatrine-based, English-written studies published in the past 22 years. In total, 267 studies were included, most of which were original. The number of annual studies slowly increased with some fluctuations. Other than China, 11 different countries conducted studies on oxymatrine; the variety in the country of origin of these publications is presented as a recently increasing trend. Many affiliates and researchers have participated in oxymatrine-based research. Various treatment mechanisms involving different oxymatrine pathways have led to research in a wide range of fields, being published in numerous journals. Two particularly popular research fields related to oxymatrine involved anticancer and anti-inflammation. From this research, we concluded that with increasing and continuous in-depth studies, more therapeutic effects and mechanisms will be elucidated, and oxymatrine may present as a viable option for the treatment of additional diseases.



## INTRODUCTION

Oxymatrine is a quinolizidine alkaloid extracted from the roots of *Sophora flavescens* (Kushen), a leguminous plant. Kushen is an important and common traditional Chinese medicine (TCM) herb. According to TCM theory, kushen exhibits dampness drying, heat-clearing, diuretic, and insecticidal effects. Kushen is mainly used to treat damp heat diarrhea, bloody stools, jaundice, eczema, skin itching, and abnormal.<sup>1</sup> At present, more than 200 chemical compounds have been identified in Kushen, with oxymatrine being one of the most important components. The chemical structure of oxymatrine is shown in Figure 1. The molecular structure of oxymatrine is C<sub>15</sub>H<sub>24</sub>N<sub>2</sub>O<sub>2</sub>, and its molecular weight is 264 g/mol. Previous basic and clinical studies have confirmed that oxymatrine displays a variety of effects, such as organ- and tissue-protective, anticancer, and antiviral.<sup>1,2</sup>

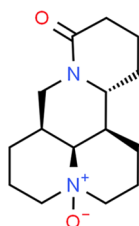


Figure 1. Chemical structure of oxymatrine.

Because of the numerous effects of oxymatrine, the research directions of oxymatrine are extensive. To explore the overall status of oxymatrine-based research, this bibliometric analysis was conducted to summarize oxymatrine-based research written in English over the past 22 years. In this article, annual publications, geographical distributions, publication journals, publication affiliations, citations, keywords, and research hotspots of oxymatrine-based research are summarized and presented. From this study, the overall research status and main effects of oxymatrine can be clearly discerned.

## METHODS

**Retrieval Strategy.** The Web of Science (WoS) database (core collection database) (Thomson Reuters, New York, NY) and PubMed (National Institutes of Health, Bethesda, MD) were searched for studies with the keyword “oxymatrine” in the section of the title and abstract. The retrieval period was set from 2001 to 2022. Only the oxymatrine-based studies written in English were included in this study.

Received: December 2, 2023

Revised: January 20, 2024

Accepted: January 29, 2024

Published: February 13, 2024

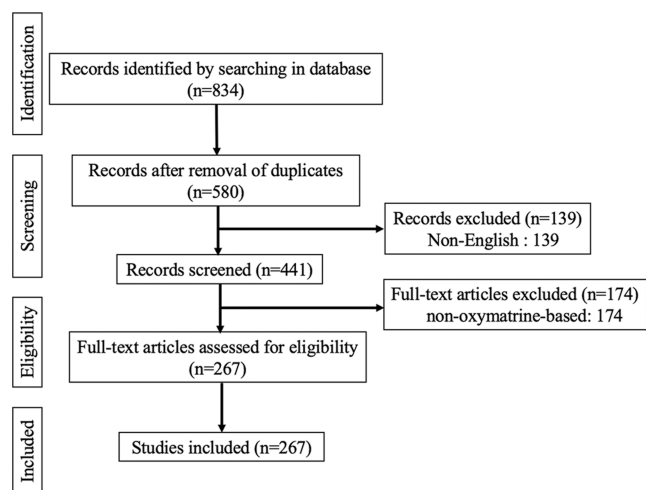


**Data Extraction.** Two researchers extracted the information from the studies separately. A third reviewer would help review the information when different opinions occur. The basic information on the studies was recorded and listed, including the title, research type, publication journal, publication date, institution of the first author and corresponding author, geographic origin, journal impact factor, citation counts, and research theme.

**Statistics.** Endnote X9.3 (Thomson ResearchSoft, Stamford, CT) was used to organize the studies. Excel 2007 (Microsoft, Redmond, WA) was used to classify, descriptively analyze, and report the data extracted from the studies. Edrawsoft 11.5 (Wondershare, Guangdong Province, China) was used to draw figures. The VOSviewer 1.6.15 (Center for Science and Technology Studies, Leiden University, the Netherlands) was used to extract the keywords of the studies and draw a keyword co-occurrence map.

## RESULTS

**General Information on the Included Studies.** A total of 834 studies were searched in the database using the keyword “oxymatrine”. The flowchart of the study extraction process is shown in Figure 2. After removing the duplicates, 580 studies



**Figure 2.** Flowchart of studies extraction process on oxymatrine-based research from 2001 to 2022.

remained; then, 139 non-English studies were additionally excluded. Subsequently, the titles and abstracts of the studies

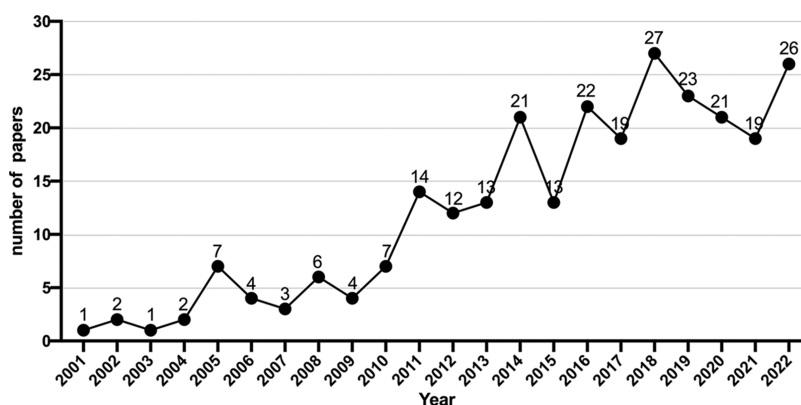
were reviewed, and 174 non-oxymatrine-based studies were further excluded. Finally, 267 oxymatrine-based studies written in English remained and were chosen for the analysis.

Among the 267 studies, 262 (98.1%) were original. Two (0.75%) studies were reviews, one on the anticancer effect of oxymatrine<sup>2</sup> and the other on the organ- and tissue-protective effects of oxymatrine.<sup>1</sup> The remaining three types consisted of one meta-analysis, one systematic review, and one commentary.

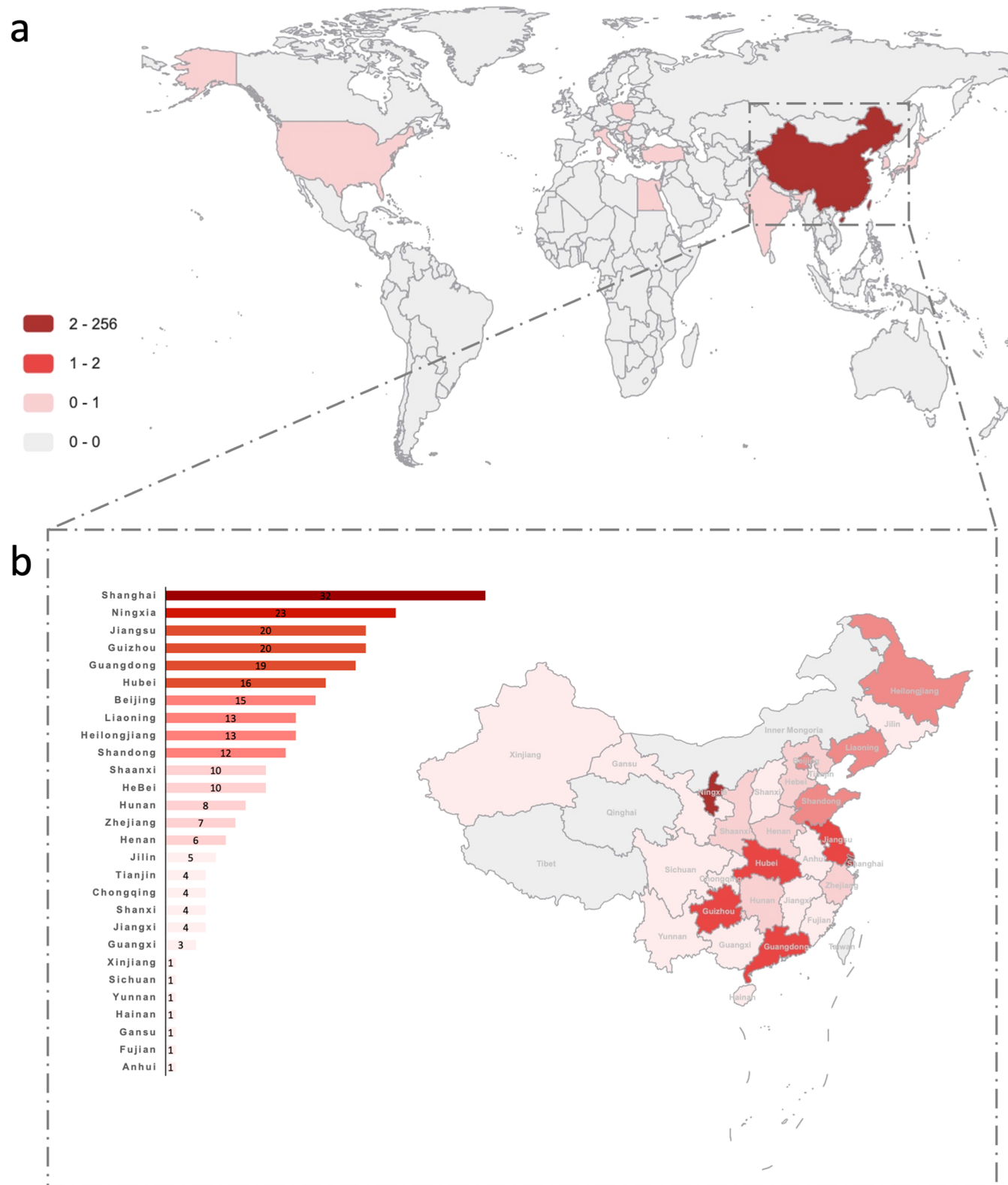
**Annual Publications.** The number of annual studies conducted between 2001 and 2022 is shown in Figure 3. Over the course of 22 years, the number of annual studies increased slowly with fluctuations. The trends in the number of annual studies can be divided into two stages. The first stage is the period of 2001–2010, with 37 studies (13.9%). The second stage is from 2011 to 2022, with an increased number of studies (230 studies, 86.1%) compared to that in the first stage. Among these, the largest number of studies (27 studies, 10.1%) were published during the year 2018. From these results, we found that the research focus on oxymatrine increased in recent years; however, the annual number of oxymatrine-based studies published in English overall remained low.

**Geographical Distribution.** The included studies were conducted primarily in Asia, Europe, and North America. As shown in Figure 4, 255 (95.5%) studies originated from China with the other 12 (4.5%) studies from 11 other different countries, including Singapore (two studies), Egypt, Hungary, India, Italy, Japan, Korea, Poland, Serbia, Turkey, and the United States. Notably, 9 (75.0%) of those 12 studies were published between 2019 and 2022. For the studies originating from China, the majority are from the central and southeastern regions. Among these, 10 separate provinces have published more than 10 studies, the majority of which came from Shanghai, with the publication of 32 studies. These results demonstrate that oxymatrine-based research has mainly been conducted in China; however, research on oxymatrine in countries outside China has gradually increased in recent years.

**Most Active Journals and Affiliations.** A total of 267 studies related to pharmacology, translational medicine, oncology, clinical medicine, and other disciplines were published in 139 journals. Of these journals, only 2 (1.44%) journals published greater than 10 studies; the journal *Molecular Medicine Reports*, published 14 studies (5.24%), and the journal *World Journal of Gastroenterology*, published 12 studies (4.49%). A total of 31 journals (22.3%) published 2



**Figure 3.** Number of annual studies of oxymatrine-based research from 2001 to 2022.



**Figure 4.** Geographical distribution of studies on oxymatrine-based research from 2001 to 2022. (a) Heat map of the global studies on oxymatrine-based research. The number of studies is proportional to the color of the region. (b) Heat map of the studies on oxymatrine-based research from China. The number of studies is proportional to the color of the province. The number of studies published in each province is shown on the left.

studies, and 82 journals (59.0%) published only 1 study. Thus, it can be concluded that different oxymatrine-based studies on various research focus areas have been published in multi-disciplinary journals.

The corresponding authors' affiliations with each study were recorded. A total of 159 institutions published oxymatrine-based research. Among them, 16 (5.99%) corresponding authors came from Ningxia Medical University (between 2010

Table 1. Top 11 Cited Studies on Oxymatrine-Based Research from 2001 to 2022

rank	title	journal	publication year	author	total citations
1	Oxymatrine protects rat brains against permanent focal ischemia and downregulates NF- $\kappa$ B expression	Brain Res.	2009	Liu et al. <sup>3</sup>	89
2	Oxymatrine induces human pancreatic cancer PANC-1 cells apoptosis via regulating expression of Bcl-2 and IAP families, and releasing of cytochrome c	J. Exp. Clin. Cancer Res.	2011	Ling et al. <sup>4</sup>	87
3	Oxymatrine prevents NF- $\kappa$ B nuclear translocation and ameliorates acute intestinal inflammation	Sci. Rep.	2013	Guzman et al. <sup>5</sup>	86
4	Oxymatrine inhibits hepatitis B infection with the advantage of overcoming drug resistance	Antiviral Res.	2011	Wang et al. <sup>6</sup>	85
5	Effects of oxymatrine on proliferation and apoptosis in human hepatoma cells	Colloids Surf. B Biointerfaces	2006	Song et al. <sup>7</sup>	84
6	Design and synthesis of oxymatrine analogues overcoming drug resistance in hepatitis B virus through targeting host heat stress cognate 70	J. Med. Chem.	2011	Gao et al. <sup>8</sup>	81
7	Cardioprotective effects and underlying mechanisms of oxymatrine against Ischemic myocardial injuries of rats	Phytother. Res.	2008	Hong-li et al. <sup>9</sup>	78
8	Oxymatrine liposome attenuates hepatic fibrosis via targeting hepatic stellate cells	World J. Gastroenterol.	2012	Chai et al. <sup>10</sup>	78
9	Oxymatrine Attenuates Tumor Growth and Deactivates STAT5 Signaling in a Lung Cancer Xenograft Model	Cancers (Basel)	2019	Jung et al. <sup>11</sup>	77
10	Anti-inflammatory mechanism of oxymatrine in dextran sulfate sodium-induced colitis of rats	World J. Gastroenterol.	2005	Zheng et al. <sup>12</sup>	76
11	The neuroprotection of oxymatrine in cerebral ischemia/reperfusion is related to nuclear factor erythroid 2-related factor 2 (nrf2)-mediated antioxidant response: role of nrf2 and hemeoxygenase-1 expression	Biol. Pharm. Bull.	2011	Li et al. <sup>13</sup>	76

and 2022). This was followed by Guizhou Medical University, which published 14 (5.24%) studies between 2016 and 2022. Additionally, 116 (73.0%) affiliations publishing only one research study were associated with the corresponding author. These results show that continuous research on oxymatrine has been carried out in only a small number of institutions.

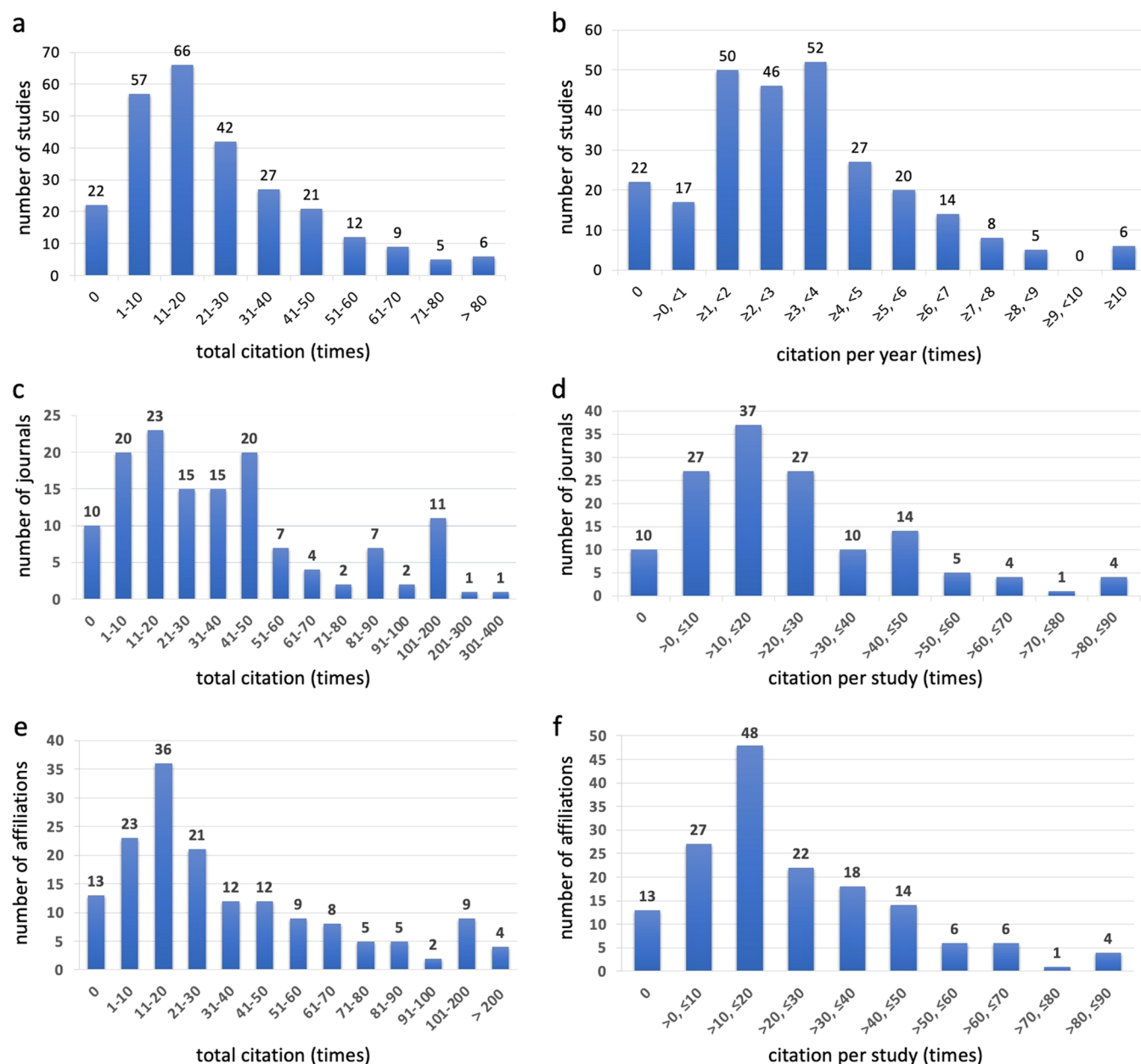
**Studies, Journals, and Affiliations Citations.** The 267 studies were cited 6396 times in total. Among these, “Oxymatrine protects rat brains against permanent focal ischemia and downregulates NF- $\kappa$ B expression” by Liu et al.<sup>3</sup> published in 2009 had the highest with 89 citations. The top 11 cited (greater than 70 citations) studies in oxymatrine-based research are listed in Table 1, and the citation distribution of all studies is shown in Figure 5a. The total number of citations in the majority of the studies (165, 61.8%) ranged from 1 to 30. These results indicate that most were not frequently cited. Studies with large numbers of citations were found to be published earlier; the accumulation of time may have assisted in the increase in total citations of these studies. The journals that published these studies were distributed, with the *World Journal of Gastroenterology* publishing two highly cited studies. The research fields of these 11 studies varied, which included but were not limited to topics such as anti-inflammation, anticancer, and anti-hepatitis B virus.

The study with the highest number of citations per year was “Oxymatrine attenuates tumor growth and deactivates STAT5 signaling in a lung cancer xenograft model” by Jung et al.<sup>11</sup> published in 2019, being cited 19.3 times per year. Six oxymatrine-based studies were cited more than 10 times per year (Table 2). The distribution of citations per year for all studies is shown in Figure 5b. The number of citations per year for most studies (214, 80.1%) ranged from 1 to 5. These data show that the number of citations per year for all oxymatrine-based studies has remained limited. In addition, these six studies were all published in the last 5 years, and the citations per year of the two review studies were 12.3 and 11.3, respectively.

Of the 139 journals, 14 were cited over 100 times. As shown in Table 3, the *World Journal of Gastroenterology* published 12

studies with the greatest number of citations (560 times). The two journals *Molecular Medicine Reports* and *Oncology Reports*, were cited a total of 301 times and 224 times, respectively. The citation distribution for all journals is shown in Figure 5c. The most common number of citations for the journals ranged from 1 to 50, which was applicable for 103 total journals (74.1%). *Brain Research* was associated with the highest number of citations per study. It published only one research article; however, it was cited 89 times. As shown in Table 3, the citations per study for the two journals with the most articles published were 46.7 and 21.5 times, respectively. The distribution of citations per study in all journals is shown in Figure 5d. The citations per study for the majority of the journals (101 studies, 72.7%) ranged from 0 to 30.

Among the 159 affiliations of the corresponding authors shown in Table 4, the total citations for four of these affiliations reached over 200: Second Hospital of Hebei Medical University, Guizhou Medical University, Ningxia Medical University, and China Pharmaceutical University. In addition, there were nine other affiliations with more than 100 total citations. The citation distributions for all affiliations are shown in Figure 5e. The total citations for the majority (117 affiliations, 73.6%) of the institutions ranged from 1 to 50. The affiliation with the highest number of citations per study was the First Affiliated Hospital, Zhejiang University School of Medicine, which published only one research article in 2011 titled “Oxymatrine induces human pancreatic cancer PANC-1 cells apoptosis via regulating the expression of Bcl-2 and IAP families and releasing of cytochrome c”, which was cited 87 times. The distribution of citations per study for all affiliations is shown in Figure 5f. The citations per study for most affiliations (142 affiliations, 89.3%) ranged from 0 to 50. In addition, the citations per study of the four affiliations with the highest total citations were 51.6 times, 17.6 times, 15.4 times, and 41 times, respectively. These results show that no affiliations were associated with high numbers of citations regarding their publications in the field of oxymatrine-based research.



**Figure 5.** Histogram of the citations of studies, journals, and affiliations on oxymatrine-based research from 2001 to 2022. (a) Citation distribution of all of the studies. (b) Distribution of citations per year of all of the studies. (c) Citation distribution of all of the journals. (d) Distribution of citations per research of all of the journals. (e) Citation distribution of all of the affiliations. (f) Distribution of citations per research of all of the affiliations.

**Table 2. Studies of Citations Per Year More Than 10 Times on Oxymatrine-Based Research from 2001 to 2022**

rank	title	journal	publication year	author	citations per year
1	Oxymatrine Attenuates Tumor Growth and Deactivates STAT5 Signaling in a Lung Cancer Xenograft Model	Cancers	2019	Jung et al. <sup>11</sup>	19.3
2	Oxymatrine exerts organ- and tissue-protective effects by regulating inflammation, oxidative stress, apoptosis, and fibrosis: From bench to bedside	Pharmacol. Res.	2020	Lan et al. <sup>1</sup>	12.3
3	Oxymatrine protects against DSS-induced colitis via inhibiting the PI3K/AKT signaling pathway	Int. Immunopharmacol.	2017	Chen et al. <sup>14</sup>	11.3
4	Anticancer effects of oxymatrine are mediated through multiple molecular mechanism(s) in tumor models	Pharmacol. Res.	2019	Halim et al. <sup>2</sup>	11.3
5	Oxymatrine Ameliorates Doxorubicin-Induced Cardiotoxicity in Rats	Cell Physiol. Biochem.	2017	Zhang et al. <sup>15</sup>	10.2
6	Oxymatrine Inhibits Influenza A Virus Replication and Inflammation via TLR4, p38 MAPK and NF- $\kappa$ B Pathways	Int. J. Mol. Sci.	2018	Dai et al. <sup>16</sup>	10.0

**Table 3. Total Citations More Than 100 Times of Journals on Oxymatrine-Based Research from 2001 to 2022**

rank	journal	no. of studies	total citations	citations per study
1	World J. Gastroenterol.	12	560	46.7
2	Mol. Med. Rep.	14	301	21.5
3	Oncol. Rep.	7	224	32
4	Phytother. Res.	3	181	60.3
5	Int. Immunopharmacol.	7	160	22.9
6	Phytomedicine	6	155	25.8
7	J. Ethnopharmacol.	4	138	34.5
8	Tumour Biol.	3	122	40.7
9	Eur. J. Pharmacol.	6	115	19.7
10	Inflammation	4	110	27.5
11	Chin. Med. J. (Engl.)	3	108	36
12	Antiviral Res.	2	107	53.5
13	Biol. Pharm. Bull.	2	106	53
14	PLoS One	3	101	33.7

**Table 4. Total Citations More Than 100 Times Affiliations on Oxymatrine-Based Research from 2001 to 2022**

rank	affiliation	no. of studies	total citations	citations per research
1	Second Hospital of Hebei Medical University	5	258	51.6
2	Guizhou Medical University	14	246	17.6
3	Ningxia Medical University	16	246	15.4
4	China Pharmaceutical University	5	205	41
5	Renji Hospital, Shanghai Second Medical University	5	189	37.8
6	Union Hospital, Tongji Medical College of Huazhong University of Science and Technology	7	185	26.4
7	Chinese Academy of Medical Science & Peking Union Medical College	2	166	83
8	Changzheng Hospital, Second Military Medical University	3	131	43.7
9	Yong Loo Lin School of Medicine, National University of Singapore	2	122	61
10	Harbin Medical University	3	122	40.7
11	Yantai University	8	121	15.1
12	Wujiang No.1 People's Hospital	3	103	34.3
13	Tangdu Hospital of the Fourth Military Medical University	3	102	34

**Keywords and Research Hotspots.** A total of 693 keywords were extracted from 267 studies. Among these, the keyword “oxymatrine” appeared most frequently (217 times). Additionally, 5 other keywords appeared over 10 times. “Apoptosis” appeared 36 times, “inflammation” appeared 21 times, “nuclear factor  $\kappa$ -b” appeared 17 times, “matrine” appeared 14 times, and “oxidative stress” appeared 12 times. A total of 583 keywords appeared only once. The number of keyword occurrences that appeared 2 times or more (110 total keywords) was analyzed using VOSviewer. Network visualization of the keywords is shown in Figure 6a. The size of the label is proportional to the occurrence of each keyword; different colors are present in different clusters, and a thickening of the line between the two labels indicates a closer relationship between them. These keywords were classified into 20 clusters and marked using different colors. The overlay visualization of the keywords is shown in Figure

6b, where a lightening of the color represents its closeness to the actual date of the publication.

A detailed list of the research fields for the 267 studies is shown in Figure 7a. Here, the abscissa value represents the number of studies published in each field, the ordinate value represents the total number of citations of the publications, and the size of the point is proportional to the number of citations per study. From these data, it was found that “anticancer” and “anti-inflammation” were the two most popular research fields of oxymatrine, followed by “antifibrosis,” “antiviral,” and “antihypoxic/ischemic”. We further analyzed the anticancer studies involving oxymatrine, as shown in Figure 7b. The two most popular research fields included “ant colorectal cancer” and “ant lung cancer”, with 9 studies each. Research on colorectal cancer had the highest total number of citations (219 times) for the nine studies. Research on pancreatic cancer received the highest number of citations per study (with 76.5 citations per study). A total of 56 (21.0%) studies discussed the anti-inflammatory effects of oxymatrine with 1254 citations. Of these, 32 (57.1%) studies were published in the last five years. A total of 17 studies (6.37%) were focused on the antiviral effect of oxymatrine. Among these, 14 studies focused on the anti-hepatitis B virus effects of oxymatrine, with 562 citations.

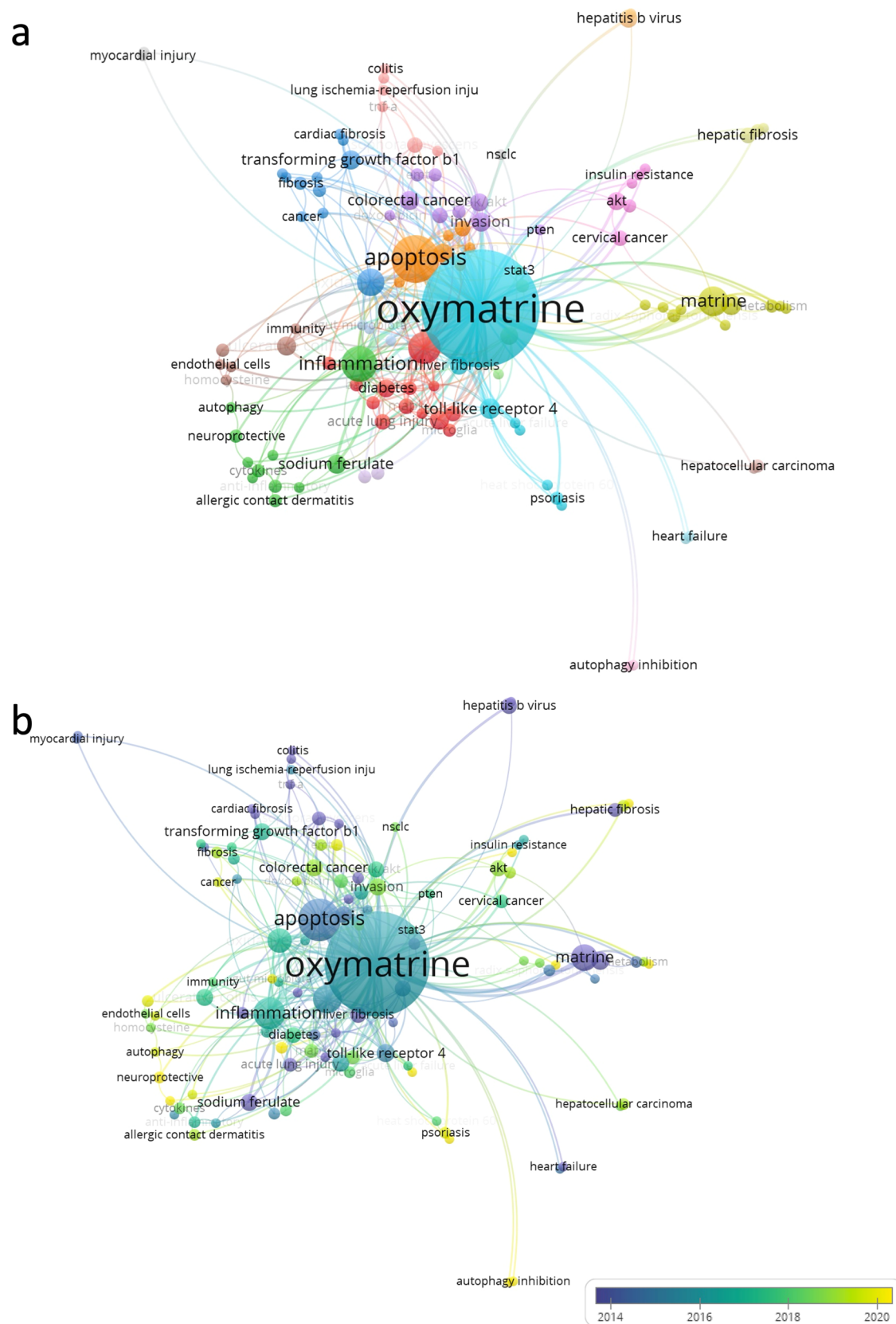
## DISCUSSION

In this bibliometric analysis of oxymatrine-based studies published between 2001 and 2022, 267 studies were included and analyzed. Oxymatrine, an extract of TCM herb, has been investigated with increasing attention and frequency, particularly over the past decade. Most of these were original studies. In addition, most studies were conducted in Southeast China. Various other countries have also paid increasing attention to oxymatrine in recent years. A considerable number of associations and researchers have participated in oxymatrine-based research; however, only a few have conducted continuous studies on oxymatrine.

In the analysis of keywords, we found shifting research of oxymatrine. In the early studies, there were many studies on the treatment of hepatitis B of oxymatrine. With the transformation of disease types and the increase in research methods, studies on inflammation, cancer, metabolism, ischemia-reperfusion, and apoptosis have gradually become a research focus in recent years. Moreover, the study of inflammatory bowel disease has become a new topic of inflammation research. The research on fibrosis continues to be hot, with a continuously increasing trend in recent years, indicating that oxymatrine has a clear role in the process of anti-tissue fibrosis.

Regarding the research content, oxymatrine-based research covered pharmacology, disease treatment, the mechanism of action, and clinical transformation, which led to these studies being published in a wide variety of journals. Oxymatrine plays a therapeutic role in many disease models through anti-inflammation, anticancer, antifibrosis, antiapoptosis, and antihypoxic/ischemic mechanisms.

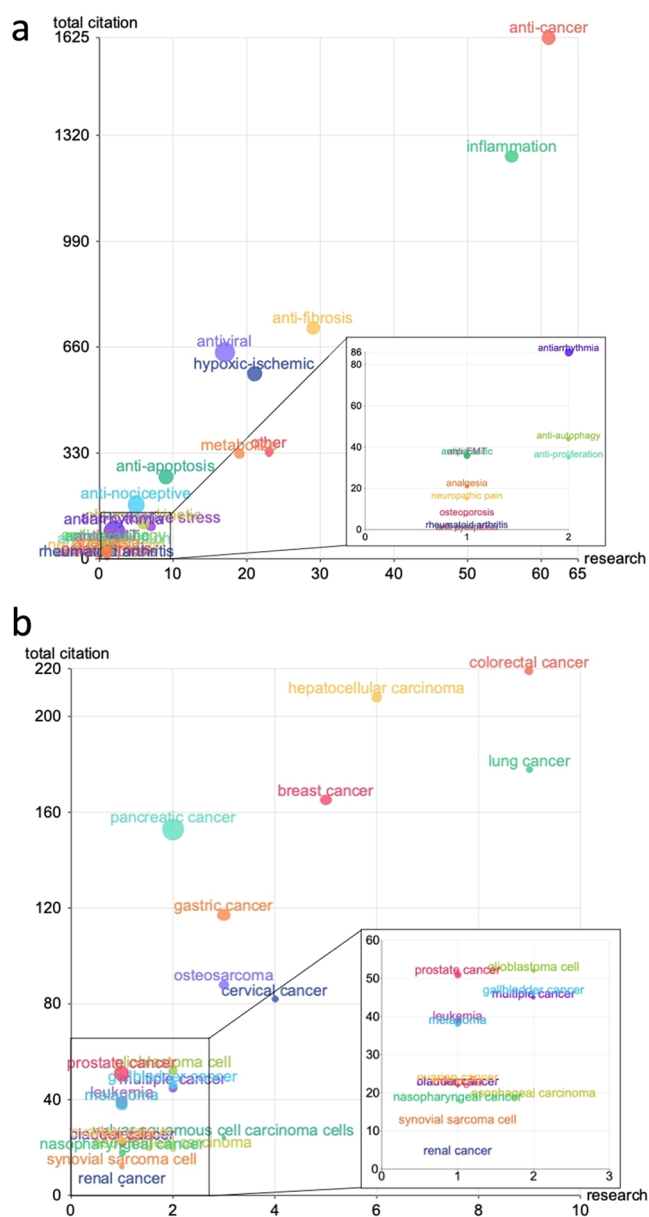
In brain-related diseases, such as amyotrophic lateral sclerosis, cerebral ischemia/reperfusion injury, and Alzheimer's disease, oxymatrine induces neuroprotective and memory impairment effects by influencing the PI3K/Akt/mTOR, PI3K/Akt/GSK3 $\beta$ , TLR4/NF- $\kappa$ B, and HMGB1/TLR4/NF- $\kappa$ B pathways.<sup>17–23</sup> In cardiopulmonary-related diseases, oxymatrine could ameliorate myocardial ischemia/reperfusion



**Figure 6.** Analysis of the keywords on oxymatrine-based research from 2001 to 2022 by VOSviewer. (a) Network visualization of the keywords. The size of the point is proportional to the appearance times of each keyword, and different colors present in different clusters. (b) Overlay visualization of the keywords. The lighter the color presents, the closer the time of the study.

induced acute lung injury in diabetic rats by inhibiting autophagy and endoplasmic reticulum stress and alleviating

myocardial fibrosis induced by acute myocardial infarction via the TGF- $\beta$ 1-Smads pathway.<sup>24–26</sup> In a model of septic-shock-



**Figure 7.** Hotspot research fields of oxymatrine-based research from 2001 to 2022. (a) Bubble chart of the studies' fields on oxymatrine-based research. (b) Bubble chart of the anticancer studies' fields on oxymatrine-based research. The abscissa value presents the number of studies published in each field, the ordinate value presents the total citations of the studies, and the size of the point is proportional to the citations per study.

induced myocardial injury, oxymatrine reduced the severity of the infection and protected cardiomyocytes by inhibiting the TNF- $\alpha$ /p38 MAPK/caspase-3 and JAK2/STAT3 signaling pathways.<sup>27,28</sup> In an isoproterenol-induced heart failure rat model, oxymatrine attenuated the severity of heart failure by regulating the COX-2/PGE<sup>2</sup> and DDAH/ADMA metabolism pathways.<sup>29,30</sup> Additionally, in a rat model of myocardial injury caused by chemotherapeutic drugs, such as doxorubicin, oxymatrine induced protective effects by partially inhibiting cardiac apoptosis and oxidative stress.<sup>15</sup> In lung diseases, oxymatrine could attenuate hypoxia- and monocrotaline-induced pulmonary hypertension, bleomycin-induced pulmonary fibrosis, and acute lung injury by regulating the N(G),

N(G)-dimethyl-L-arginine metabolism pathway, JNK, TGF- $\beta$ /Smad signaling pathway.<sup>31–34</sup>

The liver is an important metabolic organ that plays an indispensable role in the body. Several studies have explored the effects of oxymatrine on liver-related diseases. In metabolic-related research, oxymatrine was shown to alleviate hepatic lipid metabolism and ameliorate nonalcoholic fatty liver disease by either regulating miR-182 or activating the Sirt1/AMPK and PPAR $\alpha$  signaling pathway.<sup>35–37</sup> Liver gluconeogenesis was also shown to be regulated by oxymatrine through PEPCK and G6Pase expression, and AKT phosphorylation.<sup>38</sup> The therapeutic effect of oxymatrine on hepatic fibrosis, a common liver disease, has been demonstrated both in vivo and in vitro. In these studies, most hepatic fibrosis models were created using CCL4, and oxymatrine could alleviate the severity and delay the development of hepatic fibrosis through different mechanisms, such as suppressing endoplasmic reticulum stress, regulating TLR4-dependent inflammatory and TGF- $\beta$ 1 signaling pathways, and through the p38 MAPK signaling pathway.<sup>10,39–47</sup> Oxymatrine has additionally been found to be capable of regulating stellate cells through different mechanisms to achieve certain effects. It could attenuate arsenic-induced hepatic stellate cell endoplasmic reticulum stress and calcium dyshomeostasis,<sup>48</sup> inhibit the expression of pro-collagen I, and further alleviate hepatic fibrosis induced by hepatic stellate cells.<sup>49</sup> Oxymatrine showed a definite antiviral effect, particularly against the hepatitis B virus.<sup>16,50–52</sup> Both clinical and basic studies have demonstrated that oxymatrine not only inhibits replication but also overcomes drug resistance.<sup>6,8,53</sup>

The anticancer effects of oxymatrine have been extensively investigated.<sup>2</sup> Oxymatrine can achieve anticancer effects by reducing cancer cell viability, inducing cancer cell cycle arrest, promoting cancer cell apoptosis, and inhibiting epithelial-mesenchymal transition of lung cancer cells, breast cancer cells, hepatocellular carcinoma cells, gallbladder cancer cells, and cervical cancer cells.<sup>54–61</sup> It can also enhance the anticancer effects of both chemotherapeutics and immune cells, such as doxorubicin, oxaliplatin, 5-fluorouracil, and CD8<sup>+</sup> T cells.<sup>62–65</sup> Moreover, multiple signaling pathways were involved in the oxymatrine antitumor effects, such as Wnt/ $\beta$ -Catenin, TGF- $\beta$ 1/Smad, PI3K/AKT/mTOR, and other signaling pathways.<sup>63,66–68</sup>

However, this study has some limitations. First, in order to ensure the quality of the research, only oxymatrine-based studies written in English were included, which resulted in a relative decrease in the number of included studies. Second, the collaborative relationship between researchers in each study was not able to be analyzed. This is because there were fewer studies published by each single center, and there were fewer connections between centers. Third, the self-citation of studies may have some impact on the citation data of studies and journals, which is also worth noting. In addition, different journals expressed the author names in different ways, and when the Chinese names translated into English names, there may be a problem in which the English name is the same but the Chinese name is different. Due to these reasons, it led to difficulties and decreased accuracy in analyzing researcher collaboration relationships.

In conclusion, this study analyzed the overall status of oxymatrine-based research written in English. Oxymatrine-based studies have been conducted in many research areas, and oxymatrine has been shown to have therapeutic effects on



various diseases through different mechanisms and pathways. However, oxymatrine-based research appears relatively scattered; and continuous, focused, and in-depth studies to provide direction for future research are lacking. In addition, as anti-inflammation and anticancer are two main therapeutic effects of oxymatrine, it is necessary to further explore the mechanism of these effects. In addition, antifibrosis is an advantage of various traditional Chinese medicines, including oxymatrine. Although there have been many studies combined with new research methods and ideas, new discoveries may be achieved. And these provide directions for future studies. We believe that the therapeutic effects and mechanisms of oxymatrine can be elucidated through continuous and in-depth research and that oxymatrine may become an option for the treatment of more diseases.

## AUTHOR INFORMATION

### Corresponding Authors

**Jia-jia Duan** – Beijing University of Chinese Medicine Third Affiliated Hospital, Beijing 100029, China; Phone: 0086-010-52075386; Email: [dj\\_1142@163.com](mailto:dj_1142@163.com)

**Jia Xu** – Beijing University of Chinese Medicine Third Affiliated Hospital, Beijing 100029, China; Phone: 0086-010-52075386; Email: [wryd1976@sina.com](mailto:wryd1976@sina.com)

### Authors

**Xu Lan** – Beijing University of Chinese Medicine Third Affiliated Hospital, Beijing 100029, China; [orcid.org/0000-0003-0838-6473](https://orcid.org/0000-0003-0838-6473)

**Yao Chen** – Xiyuan Hospital, China Academy of Chinese Medical Sciences, Beijing 100091, China

Complete contact information is available at:

<https://pubs.acs.org/10.1021/acsomega.3c07880>

### Author Contributions

X.L.: Conception and design, data analysis and interpretation, manuscript writing, financial support. Y.C.: Data analysis and interpretation, manuscript writing. J.X. and J.-j.D.: Conception and design, administrative support, final approval of the manuscript.

### Funding

This work was supported by the National Natural Science Foundation of China (no. 82004190) and 2023 New Teacher Launch Fund Project of Beijing University of Chinese Medicine (no. 303-02-01-05-245).

### Notes

The authors declare no competing financial interest.

## ACKNOWLEDGMENTS

The authors thank Editage ([www.editage.cn](http://www.editage.cn)) for English language editing.

## REFERENCES

- (1) Lan, X.; Zhao, J.-N.; Zhang, Y.; Chen, Y.; Liu, Y.; Xu, F.-Q. Oxymatrine exerts organ- and tissue-protective effects by regulating inflammation, oxidative stress, apoptosis, and fibrosis: From bench to bedside. *Pharmacol. Res.* **2020**, *151*, No. 104541.
- (2) Halim, C.-E.; Xinjing, S.-L.; Fan, L.; Vitarbo, J.-B.; Arfuso, F.; Tan, C.-H.; Narula, A.-S.; Kumar, A.-P.; Sethi, G.; Ahn, K.-S. Anti-cancer effects of oxymatrine are mediated through multiple molecular mechanism(s) in tumor models. *Pharmacol. Res.* **2019**, *147*, No. 104327.
- (3) Liu, Y.; Zhang, X.-J.; Yang, C.-H.; Fan, H.-G. Oxymatrine protects rat brains against permanent focal ischemia and down-regulates NF- $\kappa$ B expression. *Brain Res.* **2009**, *1268*, 174–180.
- (4) Ling, Q.; Xu, X.; Wei, X.; Wang, W.; Zhou, B.; Wang, B.; Zheng, S. Oxymatrine induces human pancreatic cancer PANC-1 cells apoptosis via regulating expression of Bcl-2 and IAP families, and releasing of cytochrome c. *J. Exp. Clin. Cancer Res.* **2011**, *30*, No. 66, DOI: [10.1186/1756-9966-30-66](https://doi.org/10.1186/1756-9966-30-66).
- (5) Guzman, J.-R.; Koo, J.-S.; Goldsmith, J.-R.; Mühlbauer, M.; Narula, A.; Jobin, C. Oxymatrine prevents NF- $\kappa$ B nuclear translocation and ameliorates acute intestinal inflammation. *Sci. Rep.* **2013**, *3*, No. 1629.
- (6) Wang, Y.-P.; Zhao, W.; Xue, R.; Zhou, Z.-X.; Liu, F.; Han, Y.-X.; Ren, G.; Peng, Z.-G.; Cen, S.; Chen, H.-S.; Li, Y.-H.; Jiang, J.-D. Oxymatrine inhibits hepatitis B infection with an advantage of overcoming drug-resistance. *Antiviral Res.* **2011**, *89*, 227–231.
- (7) Song, G.; Luo, Q.; Qin, J.; Wang, L.; Shi, Y.; Sun, C. Effects of oxymatrine on proliferation and apoptosis in human hepatoma cells. *Colloids Surf., B* **2006**, *48*, 1–5.
- (8) Gao, L.-M.; Han, Y.-X.; Wang, Y.-P.; Li, Y.-H.; Shan, Y.-Q.; Li, X.; Peng, Z.-G.; Bi, C.-W.; Zhang, T.; Du, N.-N.; Jiang, J.-D.; Song, D.-Q. Design and synthesis of oxymatrine analogues overcoming drug resistance in hepatitis B virus through targeting host heat stress cognate 70. *J. Med. Chem.* **2011**, *54*, 869–876.
- (9) Hong-li, S.; Li, L.; Shang, L.; Zhao, D.; Dong, D.; Qiao, G.; Liu, Y.; Chu, W.; Yang, B. Cardioprotective effects and underlying mechanisms of oxymatrine against Ischemic myocardial injuries of rats. *Phytother. Res.* **2008**, *22*, 985–989.
- (10) Chai, N.-L.; Fu, Q.; Shi, H.; Cai, C.-H.; Wan, J.; Xu, S.-P.; Wu, B.-Y. Oxymatrine liposome attenuates hepatic fibrosis via targeting hepatic stellate cells. *World J. Gastroenterol.* **2012**, *18*, 4199–4206.
- (11) Jung, Y.-Y.; Shanmugam, M.-K.; Narula, A.-S.; Kim, C.; Lee, J.-H.; Namjoshi, O.-A.; Blough, B.-E.; Sethi, G.; Ahn, K.-S. Oxymatrine Attenuates Tumor Growth and Deactivates STAT5 Signaling in a Lung Cancer Xenograft Model. *Cancers* **2019**, *11* (1), 49 DOI: [10.3390/cancers11010049](https://doi.org/10.3390/cancers11010049).
- (12) Zheng, P.; Niu, F.-L.; Liu, W.-Z.; Shi, Y.; Lu, L.-G. Anti-inflammatory mechanism of oxymatrine in dextran sulfate sodium-induced colitis of rats. *World J. Gastroenterol.* **2005**, *11*, 4912–4915, DOI: [10.3748/wjg.v11.i31.4912](https://doi.org/10.3748/wjg.v11.i31.4912).
- (13) Li, M.; Zhang, X.; Cui, L.; Yang, R.; Wang, L.; Liu, L.; Du, W. The neuroprotection of oxymatrine in cerebral ischemia/reperfusion is related to nuclear factor erythroid 2-related factor 2 (nrf2)-mediated antioxidant response: role of nrf2 and hemeoxygenase-1 expression. *Biol. Pharm. Bull.* **2011**, *34*, 595–601.
- (14) Chen, Q.; Duan, X.; Fan, H.; Xu, M.; Tang, Q.; Zhang, L.; Shou, Z.; Liu, X.; Zuo, D.; Yang, J.; Deng, S.; Dong, Y.; Wu, H.; Liu, Y.; Nan, Z. Oxymatrine protects against DSS-induced colitis via inhibiting the PI3K/AKT signaling pathway. *Int. Immunopharmacol.* **2017**, *53*, 149–157.
- (15) Zhang, Y.-Y.; Yi, M.; Huang, Y.-P. Oxymatrine Ameliorates Doxorubicin-Induced Cardiotoxicity in Rats. *Cell. Physiol. Biochem.* **2017**, *43*, 626–635.
- (16) Dai, J.-P.; Wang, Q.-W.; Su, Y.; Gu, L.-M.; Deng, H.-X.; Chen, X.-X.; Li, W.-Z.; Li, K.-S. Oxymatrine Inhibits Influenza A Virus Replication and Inflammation via TLR4, p38 MAPK and NF- $\kappa$ B Pathways. *Int. J. Mol. Sci.* **2018**, *19* (4), 965 DOI: [10.3390/ijms19040965](https://doi.org/10.3390/ijms19040965).
- (17) Zhang, J.; Li, D.; Yang, G.; Zhang, X.; Chen, L.; Zhang, Y.; Qi, X.; Li, Y.; Guo, Y. Oxymatrine Extends Survival by Attenuating Neuroinflammation in a Mouse Model of Amyotrophic Lateral Sclerosis. *Neuroscience* **2021**, *465*, 11–22.
- (18) Yu, J.-Y.; Liu, Q.-Q.; Li, X.; Zhao, M.; Sun, T.; Hu, N.; Jiang, W.; Zhang, R.-T.; Yang, P.; Yang, Q. Oxymatrine improves blood-brain barrier integrity after cerebral ischemia-reperfusion injury by downregulating CAV1 and MMP9 expression. *Phytomedicine* **2021**, *84*, No. 153505, DOI: [10.1016/j.phymed.2021.153505](https://doi.org/10.1016/j.phymed.2021.153505).
- (19) Dong, P.-L.; Li, Z.; Teng, C.-L.; Yin, X.; Cao, X.-K.; Han, H. Synthesis and evolution of neuroprotective effects of oxymatrine

derivatives as anti-Alzheimer's disease agents. *Chem. Biol. Drug Des.* **2021**, *98*, 175–181.

(20) Wei, W.; Lu, M.; Lan, X.-B.; Liu, N.; Su, W.-K.; Dushkin, A.-V.; Yu, J.-Q. Neuroprotective Effects of Oxymatrine on PI3K/Akt/mTOR Pathway After Hypoxic-Ischemic Brain Damage in Neonatal Rats. *Front. Pharmacol.* **2021**, *12*, No. 642415.

(21) Wang, X.-L.; Chen, F.; Shi, H.; Zhang, M.; Yan, L.; Pei, X.-Y.; Peng, X.-D. Oxymatrine inhibits neuroinflammation by Regulating M1/M2 polarization in N9 microglia through the TLR4/NF- $\kappa$ B pathway. *Int. Immunopharmacol.* **2021**, *100*, No. 108139.

(22) Liu, Y.; Wang, H.; Liu, N.; Du, J.; Lan, X.; Qi, X.; Zhuang, C.; Sun, T.; Li, Y.; Yu, J. Oxymatrine protects neonatal rat against hypoxic-ischemic brain damage via PI3K/Akt/GSK3 $\beta$  pathway. *Life Sci.* **2020**, *254*, No. 116444.

(23) Dong, P.; Ji, X.; Han, W.; Han, H. Oxymatrine attenuates amyloid beta 42 (A $\beta$ (1–42))-induced neurotoxicity in primary neuronal cells and memory impairment in rats. *Can. J. Physiol. Pharmacol.* **2019**, *97*, 99–106.

(24) Xiong, Z.; Xu, J.; Liu, X. Oxymatrine exerts a protective effect in myocardial ischemia/reperfusion-induced acute lung injury by inhibiting autophagy in diabetic rats. *Mol. Med. Rep.* **2021**, *23* (3), No. 183, DOI: 10.3892/mmr.2021.11822.

(25) Huang, Y.; Long, X.; Li, X.; Li, S.; He, J. The Role of Oxymatrine in Amelioration of Acute Lung Injury Subjected to Myocardial I/R by Inhibiting Endoplasmic Reticulum Stress in Diabetic Rats. *Evidence-Based Complementary Altern. Med.* **2020**, *2020*, No. 8836904, DOI: 10.1155/2020/8836904.

(26) Shen, X.-C.; Yang, Y.-P.; Xiao, T.-T.; Peng, J.; Liu, X.-D. Protective effect of oxymatrine on myocardial fibrosis induced by acute myocardial infarction in rats involved in TGF- $\beta$ 1-Smads signal pathway. *J. Asian Nat. Prod. Res.* **2011**, *13*, 215–224.

(27) Zhang, M.; Wang, X.; Bai, B.; Zhang, R.; Li, Y.; Wang, Y. Oxymatrine protects against sepsis-induced myocardial injury via inhibition of the TNF- $\alpha$ /p38-MAPK/caspase-3 signaling pathway. *Mol. Med. Rep.* **2016**, *14*, S51–S59.

(28) Zhang, M.; Wang, X.; Wang, X.; Hou, X.; Teng, P.; Jiang, Y.; Zhang, L.; Yang, X.; Tian, J.; Li, G.; Cao, J.; Xu, H.; Li, Y.; Wang, Y. Oxymatrine protects against myocardial injury via inhibition of JAK2/STAT3 signaling in rat septic shock. *Mol. Med. Rep.* **2013**, *7*, 1293–1299.

(29) Zhou, R.; Xu, Q.; Xu, Y.; Xiong, A.; Wang, Y.; Ma, P. Oxymatrine attenuated isoproterenol-induced heart failure in rats via regulation of COX-2/PGI(2) pathway. *Biomed. Pharmacother.* **2016**, *84*, 1359–1366.

(30) Zhang, W.; Zhang, J.; Liu, Y. K.; Liu, J.; Wang, X.; Xu, Q.; Wang, Y.; Xu, X.; Dai, G. Cardioprotective effects of oxymatrine on isoproterenol-induced heart failure via regulation of DDAH/ADMA metabolism pathway in rats. *Eur. J. Pharmacol.* **2014**, *745*, 29–35.

(31) Dai, G.; Li, B.; Xu, Y.; Zeng, Z.; Yang, H. Oxymatrine prevents the development of monocrotaline-induced pulmonary hypertension via regulation of the N(G), N(G)-dimethyl-L-arginine metabolism pathways in rats. *Eur. J. Pharmacol.* **2019**, *842*, 338–344.

(32) Jin, B.; Jin, H. Oxymatrine attenuates lipopolysaccharide-induced acute lung injury by activating the epithelial sodium channel and suppressing the JNK signaling pathway. *Exp. Anim.* **2018**, *67*, 337–347.

(33) Zhang, B.; Niu, W.; Xu, D.; Li, Y.; Liu, M.; Wang, Y.; Luo, Y.; Zhao, P.; Liu, Y.; Dong, M.; Sun, R.; Dong, H.; Li, Z. Oxymatrine prevents hypoxia- and monocrotaline-induced pulmonary hypertension in rats. *Free Radical Biol. Med.* **2014**, *69*, 198–207.

(34) Li, Z.; Lu, W.; Ma, Z.; Li, Z. Oxymatrine attenuates bleomycin-induced pulmonary fibrosis in mice via the inhibition of inducible nitric oxide synthase expression and the TGF- $\beta$ /Smad signaling pathway. *Int. J. Mol. Med.* **2012**, *29*, 815–822, DOI: 10.3892/ijmm.2012.923.

(35) Shi, L.; Shi, L.; Zhang, H.; Hu, Z.; Wang, C.; Zhang, D.; Song, G. Oxymatrine ameliorates non-alcoholic fatty liver disease in rats through peroxisome proliferator-activated receptor- $\alpha$  activation. *Mol. Med. Rep.* **2013**, *8*, 439–445.

(36) Xu, H.; Chen, G.-F.; Ma, Y.-S.; Zhang, H.-W.; Zhou, Y.; Liu, G.-H.; Chen, D.-Y.; Ping, J.; Liu, Y.-H.; Mou, X.; Fu, D. Hepatic Proteomic Changes and Sirt1/AMPK Signaling Activation by Oxymatrine Treatment in Rats With Non-alcoholic Steatosis. *Front. Pharmacol.* **2020**, *11*, No. 216, DOI: 10.3389/fphar.2020.00216.

(37) Zhang, H.; Yang, L.; Wang, Y.; Huang, W.; Li, Y.; Chen, S.; Song, G.; Ren, L. Oxymatrine alleviated hepatic lipid metabolism via regulating miR-182 in non-alcoholic fatty liver disease. *Life Sci.* **2020**, *257*, No. 118090.

(38) Zhu, Y.-X.; Hu, H.-Q.; Zuo, M.-L.; Mao, L.; Song, G.-L.; Li, T. M.; Dong, L.-C.; Yang, Z.-B.; Ali Sheikh, M.-S. Effect of oxymatrine on liver gluconeogenesis is associated with the regulation of PEPCK and G6Pase expression and AKT phosphorylation. *Biomed. Rep.* **2021**, *15*, 56.

(39) Wu, J.; Pan, L.; Jin, X.; Li, W.; Li, H.; Chen, J.; Yang, W. The role of oxymatrine in regulating TGF- $\beta$ 1 in rats with hepatic fibrosis. *Acta Cir. Bras.* **2018**, *33*, 207–215.

(40) Zhao, H.-W.; Zhang, Z.-F.; Chai, X.; Li, G.-Q.; Cui, H.-R.; Wang, H.-B.; Meng, Y.-K.; Liu, H.-M.; Wang, J.-B.; Li, R.-S.; Bai, Z.-F.; Xiao, X.-H. Oxymatrine attenuates CCl4-induced hepatic fibrosis via modulation of TLR4-dependent inflammatory and TGF- $\beta$ 1 signaling pathways. *Int. Immunopharmacol.* **2016**, *36*, 249–255.

(41) Zhang, S.; Wu, J.; Wang, H.; Wang, T.; Jin, L.; Shu, D.; Shan, W.; Xiong, S. Liposomal oxymatrine in hepatic fibrosis treatment: formulation, in vitro and in vivo assessment. *AAPS PharmSciTech* **2014**, *15*, 620–629.

(42) Jian, Y.-C.; Li, W.; He, Y.; Jiang, M.; Liu, Y.-B.; Xiong, W.-J. Effect of oxymatrine on hepatic gene expression profile in experimental liver fibrosis of rats. *Chin. J. Integr. Med.* **2012**, *18*, 445–450.

(43) Deng, Z.-Y.; Li, J.; Jin, Y.; Chen, X.-L.; Lü, X.-W. Effect of oxymatrine on the p38 mitogen-activated protein kinases signalling pathway in rats with CCl4 induced hepatic fibrosis. *Chin. Med. J.* **2009**, *122*, 1449–1454.

(44) Wu, X.-L.; Zeng, W.-Z.; Jiang, M.-D.; Qin, J.-P.; Xu, H. Effect of Oxymatrine on the TGF $\beta$ 1-Smad signaling pathway in rats with CCl4-induced hepatic fibrosis. *World J. Gastroenterol.* **2008**, *14*, 2100–2105.

(45) Wu, C.-S.; Piao, X.-X.; Piao, D.-M.; Jin, Y.-R.; Li, C.-H. Treatment of pig serum-induced rat liver fibrosis with *Boschniackia rossica*, oxymatrine and interferon-alpha. *World J. Gastroenterol.* **2005**, *11*, 122–126.

(46) Shi, G.-F.; Li, Q. Effects of oxymatrine on experimental hepatic fibrosis and its mechanism in vivo. *World J. Gastroenterol.* **2005**, *11*, 268–271.

(47) Liu, X.; Wang, D.; Yang, W.; Wu, X. Oxymatrine exerts anti-fibrotic effects in a rat model of hepatic fibrosis by suppressing endoplasmic reticulum stress. *J. Int. Med. Res.* **2020**, *48*, No. 300060520961681.

(48) Wang, H.; Han, B.; Wang, N.; Lu, Y.; Gao, T.; Qu, Z.; Yang, H.; Yang, Q. Oxymatrine attenuates arsenic-induced endoplasmic reticulum stress and calcium dyshomeostasis in hepatic stellate cells. *Ann. Transl. Med.* **2020**, *8*, 1171.

(49) Du, M.; Zhang, J.; Xu, D.; Li, W.; Liu, J.; Liu, F. Inhibition of pro-collagen I expression by oxymatrine in hepatic stellate cells is mediated via nuclear translocation of Y-box binding protein 1. *Mol. Med. Rep.* **2015**, *12*, 8101–8106.

(50) Ding, Y.; Li, N.; Sun, J.; Zhang, L.; Guo, J.; Hao, X.; Sun, Y. Oxymatrine Inhibits Bocavirus MVC Replication, Reduces Viral Gene Expression and Decreases Apoptosis Induced by Viral Infection. *Viral Sin.* **2019**, *34*, 78–87.

(51) Jiang, Y.; Zhu, Y.; Mu, Q.; Luo, H.; Zhi, Y.; Shen, X. Oxymatrine provides protection against Cocksackievirus B3-induced myocarditis in BALB/c mice. *Antiviral Res.* **2017**, *141*, 133–139.

(52) He, M.; Wu, Y.; Wang, M.; Chen, W.; Jiang, J. Meta-analysis of the clinical value of oxymatrine on sustained virological response in chronic hepatitis B. *Ann. Hepatol.* **2016**, *15*, 482–491.

(53) Xu, W.-S.; Zhao, K.-K.; Miao, X.-H.; Ni, W.; Cai, X.; Zhang, R.-Q.; Wang, J.-X. Effect of oxymatrine on the replication cycle of hepatitis B virus in vitro. *World J. Gastroenterol* **2010**, *16*, 2028–2037.

(54) Guo, L.; Yang, T. Oxymatrine Inhibits the Proliferation and Invasion of Breast Cancer Cells via the PI3K Pathway. *Cancer Manage. Res.* **2019**, *11*, 10499–10508.

(55) Wu, J.; Cai, Y.; Li, M.; Zhang, Y.; Li, H.; Tan, Z. Oxymatrine Promotes S-Phase Arrest and Inhibits Cell Proliferation of Human Breast Cancer Cells in Vitro through Mitochondria-Mediated Apoptosis. *Biol. Pharm. Bull.* **2017**, *40*, 1232–1239.

(56) Pei, Z.; Zeng, J.; Gao, Y.; Li, F.; Li, W.; Zhou, H.; Yang, Y.; Wu, R.; Chen, Y.; Liu, J. Oxymatrine inhibits the proliferation of CaSki cells via downregulating HPV16E7 expression. *Oncol. Rep.* **2016**, *36*, 291–298.

(57) Li, M.; Su, B.-S.; Chang, L.-H.; Gao, Q.; Chen, K.-L.; An, P.; Huang, C.; Yang, J.; Li, Z.-F. Oxymatrine induces apoptosis in human cervical cancer cells through guanine nucleotide depletion. *Anti-Cancer Drugs* **2014**, *25*, 161–173.

(58) Wu, X.-S.; Yang, T.; Gu, J.; Li, M.-L.; Wu, W.-G.; Weng, H.; Ding, Q.; Mu, J.-S.; Bao, R.-F.; Shu, Y.-J.; Cao, Y.; Wang, X.-A.; Ding, Q.-C.; Dong, P.; Xie, S.-F.; Liu, Y.-B. Effects of oxymatrine on the apoptosis and proliferation of gallbladder cancer cells. *Anti-Cancer Drugs* **2014**, *25*, 1007–1015.

(59) Chen, K.; Zhu, P.; Ye, J.; Liao, Y.; Du, Z.; Chen, F.; Juanjuan, H.; Zhang, S.; Zhai, W. Oxymatrine inhibits the migration and invasion of hepatocellular carcinoma cells by reducing the activity of MMP-2/-9 via regulating p38 signaling pathway. *J. Cancer* **2019**, *10*, 5397–5403.

(60) Wang, B.; Han, Q.; Zhu, Y. Oxymatrine inhibited cell proliferation by inducing apoptosis in human lung cancer A549 cells. *Bio-Med. Mater. Eng.* **2015**, *26* (Suppl.1), S165–172.

(61) Liang, L.; Huang, J. Oxymatrine inhibits epithelial-mesenchymal transition through regulation of NF- $\kappa$ B signaling in colorectal cancer cells. *Oncol. Rep.* **2016**, *36*, 1333–1338.

(62) Pan, D.; Zhang, W.; Zhang, N.; Xu, Y.; Chen, Y.; Peng, J.; Chen, Y.; Zhang, Y.; Shen, X. Oxymatrine Synergistically Enhances Doxorubicin Anticancer Effects in Colorectal Cancer. *Front. Pharmacol.* **2021**, *12*, No. 673432.

(63) Liu, Y.; Bi, T.; Wang, Z.; Wu, G.; Qian, L.; Gao, Q.; Shen, G. Oxymatrine synergistically enhances antitumor activity of oxaliplatin in colon carcinoma through PI3K/AKT/mTOR pathway. *Apoptosis* **2016**, *21*, 1398–1407.

(64) Liu, Y.; Bi, T.; Dai, W.; Wang, G.; Qian, L.; Gao, Q.; Shen, G. Oxymatrine synergistically enhances the inhibitory effect of 5-fluorouracil on hepatocellular carcinoma in vitro and in vivo. *Tumour Biol.* **2016**, *37*, 7589–7597.

(65) Ye, J.; Zou, M.-M.; Li, P.; Lin, X.-J.; Jiang, Q.-W.; Yang, Y.; Huang, J.-R.; Yuan, M.-L.; Xing, Z.-H.; Wei, M.-N.; Li, Y.; Shi, Z.; Liu, H. Oxymatrine and Cisplatin Synergistically Enhance Anti-tumor Immunity of CD8(+) T Cells in Non-small Cell Lung Cancer. *Front. Oncol.* **2018**, *8*, No. 631, DOI: 10.3389/fonc.2018.00631.

(66) Xie, W.; Zhang, Y.; Zhang, S.; Wang, F.; Zhang, K.; Huang, Y.; Zhou, Z.; Huang, G.; Wang, J. Oxymatrine enhanced anti-tumor effects of Bevacizumab against triple-negative breast cancer via abating Wnt/ $\beta$ -Catenin signaling pathway. *Am. J. Cancer Res.* **2019**, *9*, 1796–1814.

(67) Wang, X.; Liu, C.; Wang, J.; Fan, Y.; Wang, Z.; Wang, Y. Oxymatrine inhibits the migration of human colorectal carcinoma RKO cells via inhibition of PAI-1 and the TGF- $\beta$ 1/Smad signaling pathway. *Oncol. Rep.* **2017**, *37*, 747–753.

(68) Huang, Y.; Zhang, J.; Wang, G.; Chen, X.; Zhang, R.; Liu, H.; Zhu, J. Oxymatrine exhibits anti-tumor activity in gastric cancer through inhibition of IL-21R-mediated JAK2/STAT3 pathway. *Int. J. Immunopathol. Pharmacol.* **2018**, *32*, No. 2058738418781634.