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KYIV NATIONAL UNIVERSITY OF TECHNOLOGIES AND DESIGN
Faculty of Chemical and Biopharmaceutical Technologies
Department of Biotechnology, Leather and Fur

QUALIFICATION THESIS

on the topic **A biotechnological approach to studying the toxicity of isoniazid and hepatoprotectors**

First (Bachelor's) level of higher education
Specialty 162 "Biotechnology and Bioengineering"
Educational and professional program "Biotechnology"

Completed: student of group BEBT-20
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Faculty: Chemical and Biopharmaceutical Technologies
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Educational and professional program Biotechnology

APPROVE
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ASSIGNMENTS
FOR THE QUALIFICATION THESIS
Wang Zewen

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Scientific supervisor Ihor Hretskyi, Ph.D., As. prof

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SUMMARY

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This article explores the application of artificial intelligence in drug screening and its integration with traditional scientific research, utilizing bibliometrics and network pharmacology methods to analyze and predict the safety evaluation and activity screening of drugs. Through advanced machine learning algorithms and big data analysis techniques, artificial intelligence has significantly enhanced screening efficiency, processing capabilities, and substantially reduced research and development costs. In terms of bibliometric research, the Web of Science database was employed for comprehensive analysis to uncover hotspots and trends in isoniazid toxicity research. Furthermore, an in-depth investigation into the mechanism of isoniazid hepatotoxicity was conducted to provide future research directions. Network pharmacology was utilized to predict for the first time both the hepatoprotective activity as well as its target action of Dracocephalum moldavuca L., thereby offering novel candidate substances for drug discovery and development. In conclusion, this study presents innovative ideas and methodologies for drug research and development while also suggesting further exploration into the application of artificial intelligence within this field. Such investigations will provide a theoretical foundation along with data support for subsequent studies on isoniazid-induced hepatotoxicity mechanisms as well as hepato-protective activities exhibited by natural compounds like vanilla.

Keywords: Artificial intelligence; Bibliometrics; Network pharmacology; Isoniazid; Dracocephalum moldavuca L.

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INTRODUCTION

The relevance of the topic is: The interdisciplinary theories and technical means used in this study and the practical application of artificial intelligence in the field of drug activity screening and safety evaluation will provide a solid technical support for promoting the high-quality development of medical industry.

The purpose of the study is: Drug activity screening and safety evaluation were performed using artificial intelligence technology. Intelligent bibliometrics technology was used to analyze the research status of adverse reactions and toxicity of isoniazid, identify existing problems, and clarify future research direction. Network pharmacology was utilized to predict the hepatoprotective activity and targets of traditional Chinese medicine Dracocephalum moldavuca L., providing a basis for subsequent drug research and development.

The objectives of the study: To analyze the research status of isoniazid toxicity and predict the hepatoprotective activity and action targets of *Dracocephalum moldavuca* L. using artificial intelligence technology.

The object of the study: The development trend of isoniazid-induced hepatotoxicity and the hepatoprotective active components and targets of cyanine green

Research methods: Bibliometrics and network pharmacology.

The scientific novelty: The hepatoprotective activity of Cyan lanceolata and its targets were predicted by network pharmacology method for the first time, which provides a new candidate for drug research and development

The practical significance of the results obtained is: 1. Use intelligent bibliometrics to analyze the research progress of anti-tuberculosis drug isoniazid in the past 10 years, summarize findings, identify problems, predict hotspots, and provide direction for future research. 2.This study used network pharmacology to predict the hepatoprotective activity of Dracocephalum moldavuca L. for the first time, providing a scientific basis for modernizing traditional Chinese medicine and promoting its application in the medical field.

CHAPTER 1
LITERATURE REVIEW

1.1 Background and significance of the study

Artificial intelligence (AI) is a technology that simulates human intelligence and learning ability. Using computer algorithms and large amounts of data, AI systems can perform a variety of commanded tasks, including speech recognition, image recognition, natural language processing, and more. The continuous development of artificial intelligence technology can also bring many benefits to society, such as improving labor productivity, providing medical diagnosis advice, and optimizing the use of resources.

Artificial intelligence is an emerging technology that focuses on the study of how to make computer systems have human-like intelligence capabilities, such as learning, reasoning, perception, understanding language, recognizing images and processing sounds. Artificial intelligence technology not only covers multiple disciplines such as computer science, mathematics, statistics, but also involves many fields such as psychology, behavior, philosophy, etc., showing the characteristics of strong interdisciplinary [1]. The core goal of AI technology is to build computer systems that can imitate human intelligence, and promote innovation and progress in various industries through intelligent data analysis, decision making and action.

With the rapid development of science and technology, artificial intelligence (AI) has become one of the most revolutionary technologies in contemporary society [2], and its application in the field of biomedicine has gradually shown its great potential and far-reaching influence. From new drug research and development to drug safety evaluation, from drug target analysis to drug active ingredient screening, and then to drug research and development status summary and development direction prediction, artificial intelligence is promoting medicine related research into a new historical stage.

The application of artificial intelligence can not only improve productivity and work efficiency, but also bring more welfare and convenience to human beings [3]. This paper will focus on the research scope and application of artificial intelligence technology, and analyze its future development prospects.

Although AI technology has made remarkable progress, it still faces many challenges, such as data security and privacy protection, algorithm bias and ethical issues, and the interpretability of AI technology [4]. In the future, with the continuous progress of technology and the deep understanding of AI in society, it is reasonable to believe that AI technology will play an important role in more fields and make important contributions to the development and progress of human society [5].

1.2 Application of artificial intelligence in drug screening

Artificial intelligence is a technology in which computers imitate the unique intellectual abilities of humans. In the medical field, the application of artificial intelligence technology in drug therapy includes matching the best drug to patients, predicting drug targets and interactions, optimizing treatment regimens, and assisting clinical decision-making [6]. These technologies are prominent in drug management and treatment plan optimization. Artificial intelligence can provide more accurate personalized treatment plan by analyzing a large number of medical record data [7] help doctors reduce the repeated use of drugs, predict drug concentration and dosage, improve patient compliance, and reduce unnecessary risks [8].

In recent years, with the progress of deep learning and machine learning algorithms, the improvement of hardware level and the expansion of databases, artificial intelligence technology has ushered in the third climax of development, which provides strong assistance for drug research and development. For example, intelligent bibliometrics can be used to efficiently and comprehensively summarize and analyze adverse drug reactions, analyze existing problems in drug research and development, and clarify the direction of drug research and development, and network pharmacology

can be used to predict the activity, active ingredients and action targets of traditional Chinese medicine [9].

Artificial intelligence is playing an increasingly important role in the development of new drugs. Using intelligent data processing technology, adverse drug reactions can be quickly and comprehensively studied, and difficulties in the development of new drugs can be explored, which can point out the direction for future research. It can also help doctors make the correct diagnosis and diagnose the patient's condition, thereby reducing the patient's mortality [10].

AI techniques also have significant advantages in predicting drug targets or drug interactions. Drug target refers to the site of action of a drug in the human body, which has a decisive impact on the efficacy of a drug. AI technology can find new drug targets and provide new ideas for drug research and development by simulating and predicting the interaction between drug molecules and biological macromolecules (such as proteins, DNA, etc.) [11]. In addition, AI can also predict the interaction between different drugs, avoid the negative effects of drugs, and improve the safety of drug therapy.

On this basis, the use of artificial intelligence, machine learning and other methods is of great significance for pharmacodynamics, quantitative systems pharmacology, monitoring and early warning of drug interactions and drug side effects, and formulation of combined drug administration strategies [9]. For example, simulation and analysis of its metabolism in the human body can predict its efficacy and possible adverse reactions. By studying the interaction of various drugs, it can provide a basis for clinical application. In general, artificial intelligence has had a significant impact on the pharmaceutical industry, promoting the improvement of new drug development and efficacy evaluation. With the development of medical technology, future drug use will be more accurate, efficient and safe, benefiting more patient [12]. At present, with the rapid development of artificial intelligence, its application in medicine will be more extensive, and it will play a greater role in drug

management and treatment optimization, bringing more possibilities and innovations to the medical industry.

1.3 The new combination of artificial intelligence technology and traditional scientific research

AI provides new tools and methods for scientific research, and is becoming a new scientific research model after experiment, theory and calculation, promoting the revolution in the field of science. At the same time, with the help of AI data processing ability and automation technology, the efficiency and accuracy of scientific research work have been significantly improved [13]. The permeability and diffusion of AI technology have promoted the cross integration between different disciplines and spawned more innovative research results.

The data mining technology of artificial intelligence plays a pivotal role in the process of drug research and development. Through in-depth mining of massive biomedical literature and experimental data, researchers can rapidly locate new drug targets, promote drug screening and design, and thus greatly reduce the cycle of drug development [14]. In addition, data mining technology can also play a huge role in drug research and development, helping researchers accurately predict and evaluate the effect and safety of drugs, and providing strong support for drug research and development [14].

Various artificial intelligence and machine learning have been used to reduce the reuse of drugs, drug concentration or exposure prediction, dose optimization, pharmacodynamics, quantitative systems pharmacology, drug interaction and adverse drug reaction monitoring and prediction, and drug combination regimen formulation [14]. Bibliometrics can help researchers systematically sort out and analyze the achievements and progress in related research fields. The use of bibliometrics can not only improve the breadth and depth of research in the research field, but also provide more possibilities and opportunities for academic exchange and cooperation.

At the same time, artificial intelligence has been widely used in the field of traditional Chinese medicine research and development. A comprehensive and complex data foundation has been constructed in network pharmacology research, which provides convenience for the application of artificial intelligence technology in this field. Network pharmacology relies on rich database platforms in biology, pharmacology and other fields to reveal the interaction mechanism between drugs and organisms through the study of molecular interaction networks in human biological systems. Based on the database platforms of many biological and pharmacological directions, network pharmacology can systematically collect the multiple components of traditional Chinese medicine and their corresponding targets, and then construct the network connection between components and targets [15], so as to understand the pharmacological effects of traditional Chinese medicine more comprehensively.

In addition, network pharmacology can also be combined with other research methods, such as genomics and proteomics, to further explore the mechanism of action of traditional Chinese medicine. As a new research method of traditional Chinese medicine, network pharmacology is gradually showing its strong potential and value. It not only provides a new perspective for researchers to deeply explore the complex mechanism of traditional Chinese medicine, but also helps to provide research directions for new drug development, drug action mechanism exploration, disease mechanism analysis and biomarker exploration [16].

Network pharmacology and artificial intelligence can help accelerate the process of drug discovery, development and application, and improve the efficiency and accuracy of drug research and development, especially in the field of traditional Chinese medicine research and development. Wu Zhihong et al. [17] used molecular docking and computer network pharmacology methods to rapidly screen the active components of heat-clearing traditional Chinese medicine in the treatment of coronary atherosclerotic heart disease (CHD), and constructed the drug-target-disease network of heat-clearing traditional Chinese medicine in the treatment of CHD, so as to reveal the molecular mechanism of the interaction between the active components of heat-

clearing traditional Chinese medicine in the treatment of CHD and the related target [18]. Li Xiang and Wu Leihong et al. [19] took compound Salvia Decoction as the carrier and used the network pharmacology method to explore the network association between nine active ingredients of compound Salvia decoction and cardiovascular diseases and related genes through the multi-component, gene-cardiovascular disease network of compound Salvia decoction, and studied the complex network relationship between multi-components, multi-targets and various diseases of compound Salvia decoction. It opens up a new way for the research of traditional Chinese medicine and provides new ideas and strategies.

Although traditional Chinese medicine has complex characteristics such as multi-component, multi-target, multi-pathway and synergistic effects, these characteristics also lead to the ambiguity of the mechanism of traditional Chinese medicine treatment, increase the difficulty of research, and make the research process subject to many restriction [15]. In addition, the interaction between multiple components and multiple targets is not clear, which has also become a difficulty restricting the modernization of traditional Chinese medicine. These factors undoubtedly hinder the development of Chinese Materia Medica [20].

In general, the combination of artificial intelligence and traditional scientific research not only greatly promotes the innovation and development of science and technology, but also provides researchers with powerful tools and means to help them explore unknown areas with unprecedented speed and precision and achieve scientific breakthroughs. Therefore, this paper uses the research methods of bibliometrics and network pharmacology to deeply explore the mechanism of isoniazid-induced liver injury, and aims to screen out components with liver protective activity, in order to provide useful reference for clinical research and the treatment of related symptoms, and provide reference and enlightenment for future researchers [21].

Conclusions to chapter 1

1. Artificial intelligence (AI) is a technology that mimics human intelligence and learning capabilities and can be applied to command tasks such as speech recognition and image recognition, bringing benefits in society such as increased productivity and medical diagnosis.

2. Artificial intelligence technology focuses on making computer systems have human intelligence capabilities, involving multi-disciplinary fields, aiming to promote innovation and progress in various industries, especially in the field of biomedicine with great potential.

3. Although AI technology has made significant progress, it still faces challenges, such as data security, algorithmic bias, and other issues. However, with the development of technology and the deepening of social cognition, artificial intelligence is expected to play an important role in more fields and make contributions to social development.

4. Data mining technology and artificial intelligence are crucial in drug research and development, which can accelerate drug discovery and design, improve research efficiency and accuracy, and provide strong support for drug research and development.

5. Network pharmacology and bibliometrics combined with artificial intelligence are widely used in the research and development of traditional Chinese medicine, which is helpful to explore the mechanism of action of traditional Chinese medicine, accelerate the process of drug discovery and application, and provide new ideas and strategies for the research of traditional Chinese medicine.

CHAPTER 2
OBJECT, PURPOSE, AND METHODS OF THE STUDY

2.1 Introduction

As an interdisciplinary discipline, bibliometrics uses mathematics, statistics, philology and other methods to quantitatively describe academic information, and then combines statistical analysis to reveal the quantitative characteristics and potential rules of literature[1]. To date, bibliometric analysis has been used as an effective tool to map data on published articles and has been significant in assessing and predicting trends in the development of research on specific topics [22].

This study focuses on Isoniazid (INH), the main drug used to treat tuberculosis, which has saved countless patients' lives worldwide since its introduction in the 1950s. However, with the wide application of isoniazid, the study of its toxicity and side effects has gradually attracted wide attention. The main side effect of isoniazid is liver injury, and the incidence of this adverse reaction in drug-induced liver injury is as high as 2.51% [23]. This side effect seriously harms human health and poses challenges to the medical community. Therefore, the in-depth understanding and research of drug-induced liver injury caused by INH is very important to ensure the safety of patients and improve the therapeutic effect. At present, understanding the pathogenesis of liver injury caused by INH and how to prevent and manage this adverse effect is critical, which will help standardize clinical medication guidance, minimize drug risk for patients, and ensure the safety and effectiveness of treatment. However, the mechanism of isoniazid induced liver injury is not clear, and there is no specific drug for isoniazid induced liver injury in the medical field. Therefore, this paper will use the Web of Science database to discuss the research status and trend of isoniazid toxicity through the method of econometric analysis, and systematically analyze the literature related to isoniazid toxicity. A comprehensive understanding of current research hotspots, main research topics and future research directions.

In this paper, the intelligent bibliometrics method is used to analyze the latest progress and research hotspots in isoniazid related research fields through the number of literatures, citation frequency, author, institution, country/region distribution and other indicators. Through in-depth study of the toxicity characteristics, mechanism of action and toxicity evaluation methods of isoniazid, it can better guide clinical practice, reduce the adverse effects brought by isoniazid, and improve the treatment effect and quality of life of tuberculosis patients.

Therefore, the significance of this study is not only to provide scientific basis and data support for researchers and policymakers to help them make more informed research and development decisions, but also to improve the efficiency and success rate of new drug research and development.

2.2 Literature and Methods

2.2.1 Data sources

The Web of Science published by the Institute for Scientific Information of the United States was used as the statistical source [24]. Web of Science is a large comprehensive, multi-disciplinary and core journal citation index data platform [25].

In addition, this study used VOS viewer 1.6.10 software to conduct a cluster analysis of authors and keywords. VOS viewer is a software developed by Waitman and Van of Leiden University Science and Technology Research Center in the Netherlands in 2009 to visualize and construct bibliometric networks. VOS viewer has shown good functions in the co-occurrence of subject terms [26]. In the network diagram, the size of nodes is directly proportional to the frequency of the occurrence of the theme, the connecting line between nodes represents the co-occurrence frequency, and the thickness of the connecting line reflects the closeness between node [27]. Keyword co-occurrence measures the keywords with the highest frequency in the same literature, and the analysis of co-cited literature and co-occurrence keywords can reveal the research hotspots related to isoniazid and toxicity.

2.2.2 Screening OF DATA

In the context of the widespread use of standardized and comprehensive data in academia, the Web of Science Core Collection (WoSCC) was used to pool the publication dataset in this study. The time span was set from 2014 to 2023 to explore global trends in isoniazid research over the long term. The search opened on 18 January 2024. At the beginning of bibliometrics analysis, using "isoniazid AND toxicity" as the search strategy, 755 relevant English literatures were found in the WoSCC database, covering various types of literatures (such as articles, proceedings, reviews and book chapters) from 2014 to 2023. Among the various types of literature, only original articles and reviews were selected for research. Finally, 448 publications (391 articles and 51 reviews) were included in this study. The detailed screening procedure is shown in Figure 2-1.

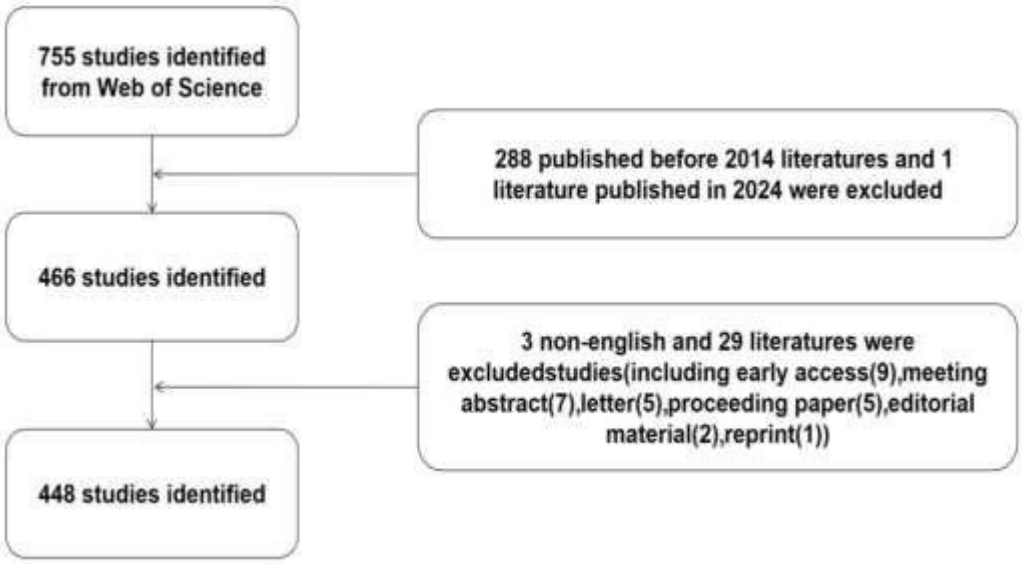


Figure 2.1 – Literature search flow chart

2.2.3 Key Measures

The key indicators in bibliometrics include those that measure the number of papers and citations. Publication number (Np) is often used to evaluate productivity, while non-self-citation number (Nc) is used to represent impact, both of which are important indicators to evaluate research level. In recent years, H index has attracted

more and more attention in evaluating the academic contributions of researchers and predicting future scientific achievements. This index achieves the unification of productivity and influence by finding a threshold that connects Np to Nc. That is, if a researcher publishes H papers and each paper is cited at least H times, the researcher has an H-index [28]. Although the H-index was originally developed to assess individual academic achievement, it can also be extended to describe countries, regions, institutions, or journal publishers.

In addition, impact factor (IF) has been widely recognized as one of the main indicators to measure the quality and influence of medical journals. The Global Citation Score (GCS) represents all citations worldwide, regardless of whether the citation comes from the same research field [28]. GCS is a key indicator of academic influence and visibility, and to a certain extent, it can reflect the degree of innovation of the article in the knowledge field.

2.3 Results AND ANALYSIS

2.3.1 Number of publications and citations

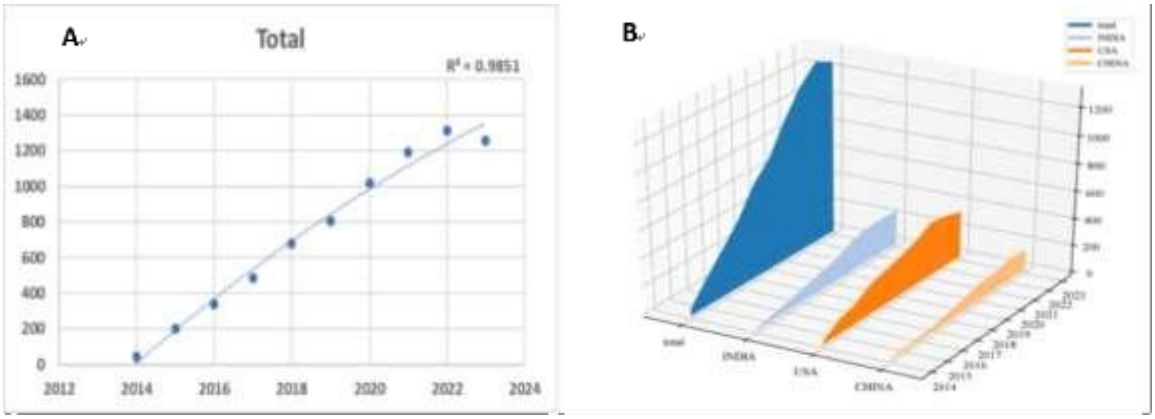


Figure 2.2 – (A) The annual growth trend and polynomial fitting curve of the total number of related publications in WosCC database from 2013 to 2023 (R^2 = 0.9851);(B) Annual output trends of the top three publishing countries and total publications

The trend of publication can reflect the overall development process of each research field. Figure 2.2 reveals the results of the bibliometric analysis based on the

search strategy, showing the publications of articles and reviews in the field of isoniazid toxicity research in the top three countries with the highest volume of publications in the last decade.

Figure 2.2A shows the polynomial fitting curve of the annual trend of the number of papers published. There is a significant correlation between the annual number of papers published and the publication year, and the correlation coefficient R^2 is as high as 0.9851, which shows that they are closely related. Figure 2-2B compares the total number of publications from 2014 to 2023 and the changes in the annual number of publications in the top three countries. In general, although the number of papers published in 2023 decreased slightly compared with 2022, the number of papers published increased from 44 in 2014 to 1256 in 2023, and the number of papers published peaked in 2022. Since 2014, the annual number of publications in India and China has maintained a steady increase, while the annual number of publications in the United States has shown a rapid growth in this field.

In summary, isoniazid toxicity research is gradually becoming the focus of attention and entering a stage of rapid development.

2.3.2 Visual analysis of highly cited literature and co-cited literature

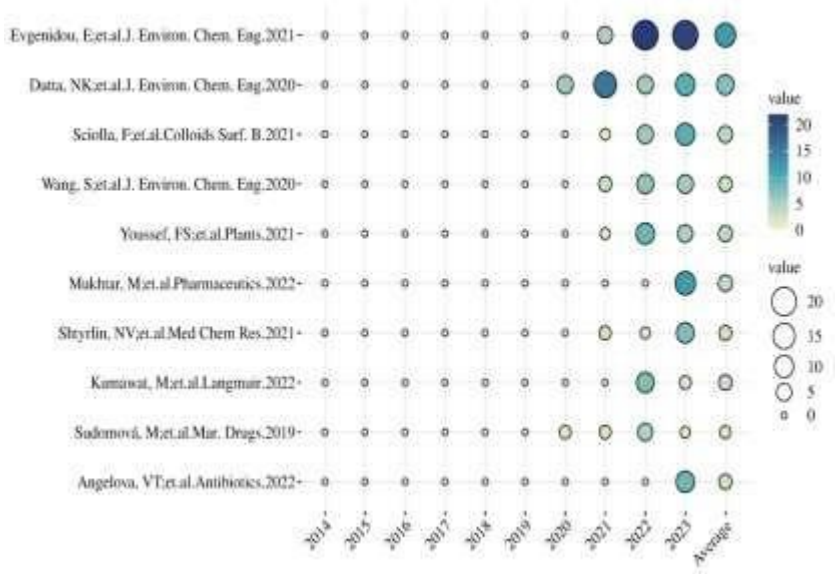
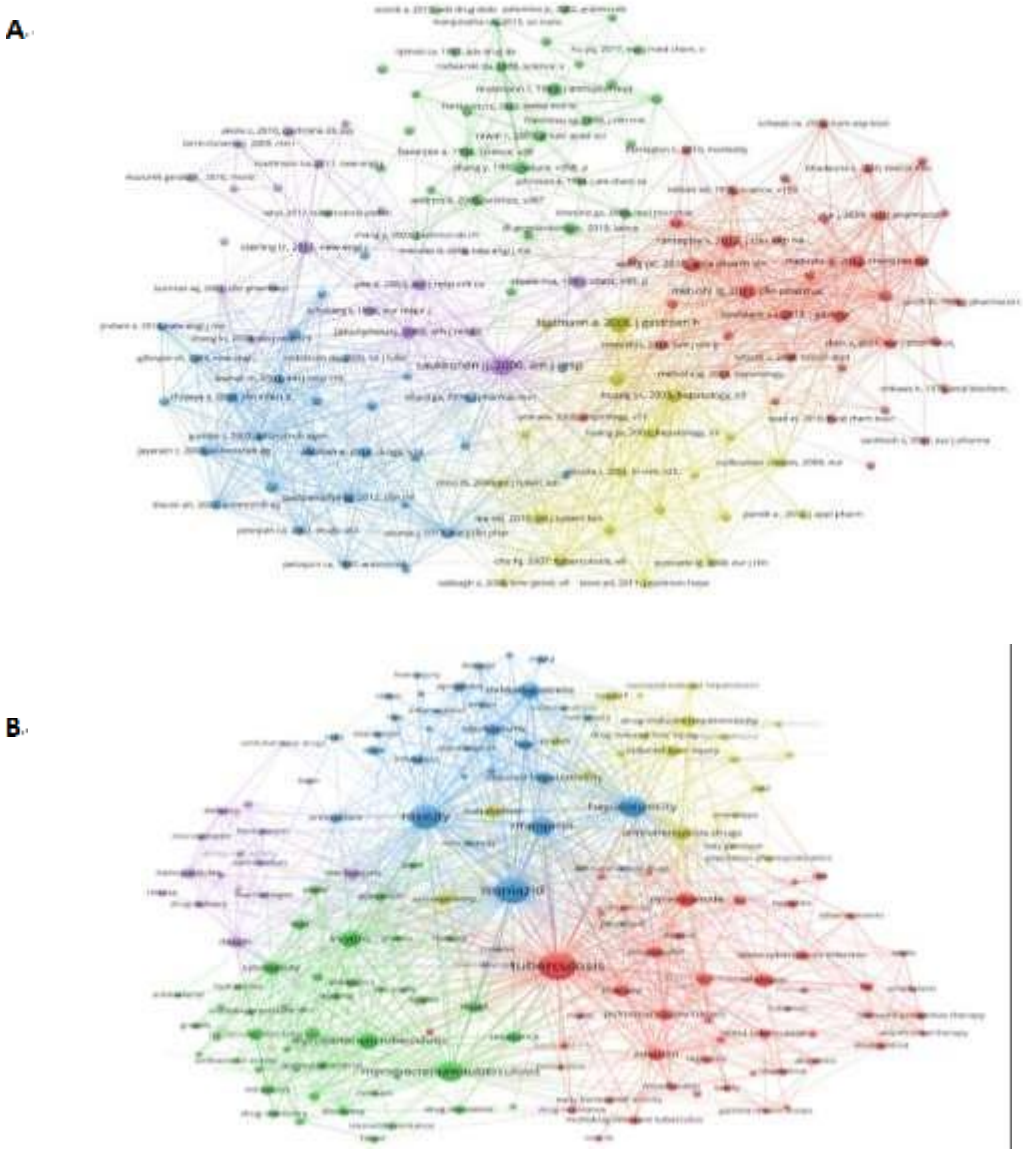


Figure 2.3 – Annual self-citation number of highly cited papers (GCS).

The size and color of the circles represent the GCS of the paper

According to the 2021 citation data of the journal J. Environ.Chem. Eng., Evgenidou et al. ranked first in the number of citations, while Dutta et al. published papers in 2020 ranked second.



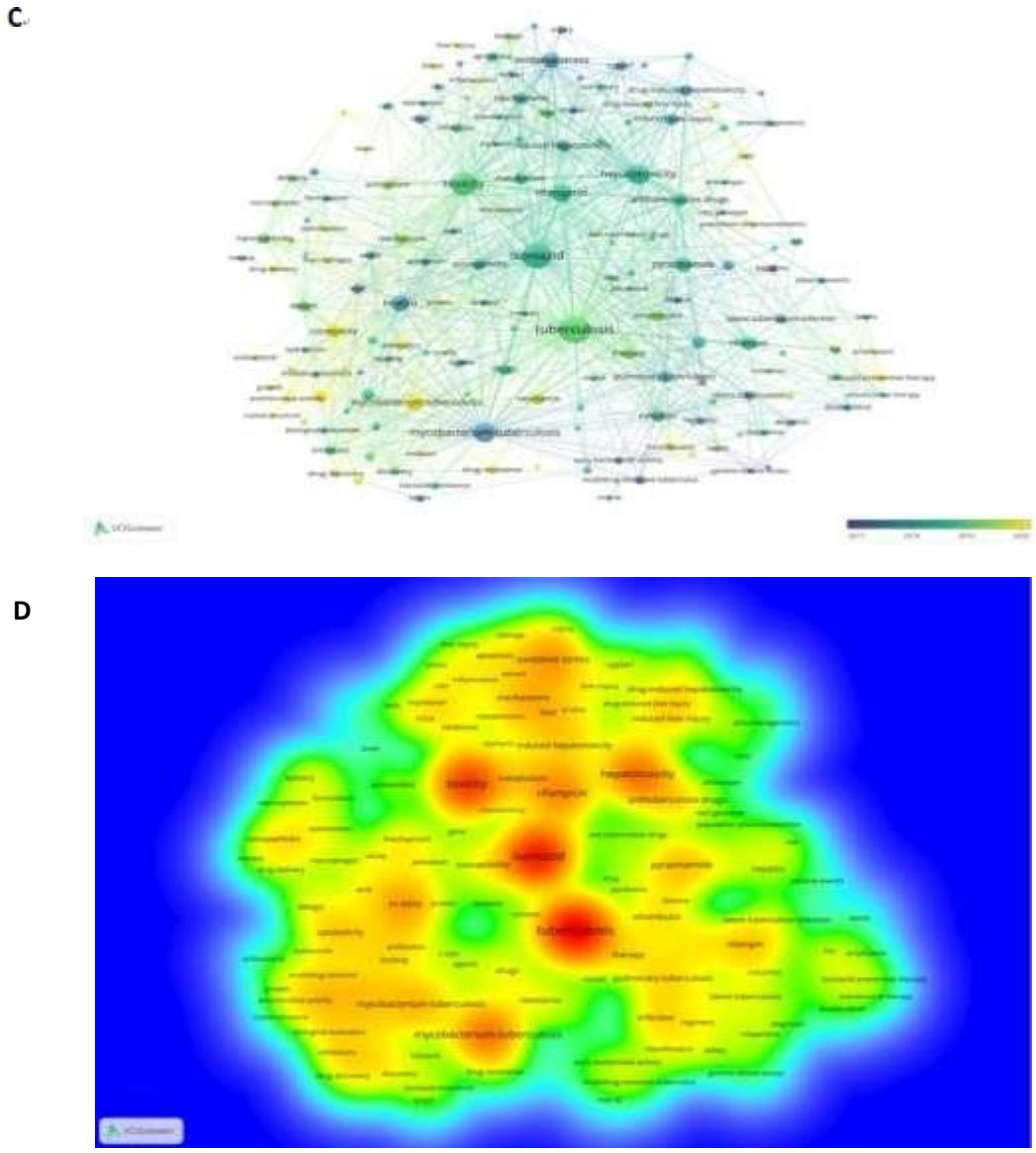


Figure 2.4 – Visual analysis of co-cited article association and keyword association. (A) Cluster analysis of co-cited literature; (B) The 165 keywords that appeared no less than 5 times were divided into five clusters according to different colors: cluster 1 was red, cluster 2 was green, cluster 3 was blue, cluster 4 was yellow, and cluster 5 was purple. Node size represents frequency; (C) Visualization of the occurrence time of keywords. The yellow keywords appeared later than the blue keywords. The yellower the node color in the graph, the more new the keyword was. (D) visualization of keyword density. Keywords in each density visualization are colored to indicate their density, with red indicating higher frequency of occurrence and green indicating lower frequency of occurrence.

After investigation, the related studies on isoniazid mainly refer to the American Journal of Respiratory Sciences published by Saukkonen JJ in 2006 and the Journal of Gastroenterology published by Tostmann A in 2008.

As a visualization method of research hotspots, keyword co-occurrence analysis helps to reveal the core research content of this paper. The keywords of the paper are the author's refinement of the theme of the full paper, which reflect the overall research scope and focus of the paper [1]. Through the analysis of keywords, the core research status of a certain field can be understood to a certain extent [29].

For the research on the co-occurrence relationship of articles, the selection of keywords mainly focuses on the elements closely related to the specific field [30]. After taking into account the number of cited articles, the minimum number of co-occurrences per reference was set to 5. Of the 2636 retrieved papers, 165 keywords were included and analyzed (FIGURE 2-4B). In the figure, the lines between two nodes represent the correlation between keywords, and the short lines indicate that the two keywords are more closely related. Node size reflects the total link strength, which is the number of occurrences of keywords.

VOS viewer divides papers into different clusters by using nodes with different color[31]. Cluster 1 (red) contained 49 keywords, mainly related to treatment methods and inflammation detection; Cluster 2 (green) contained 46 key words, focusing on cytotoxicity and binding with mycobacteria. Cluster 3 (blue) contained 32 key words, mainly focusing on isoniazid and its toxicity; Cluster 4 (yellow) contained 20 keywords, focusing on drug-induced hepatotoxicity and liver injury; Cluster five (purple) contains 18 keywords focused on drug design and optimization (shown in Figures 2-4B).

Through the thematic evolution analysis of keywords, the study found that the isoniazid toxicity research mainly focused on "liver injury" in the early stage. However, with the continuous maturity of the research field, the research scope of isoniazid toxicity has expanded to "neurotoxicity", "antibacterial toxicity" and "cytotoxicity". In the key analysis, a total of 165 keywords were extracted, with "isoniazid" and "toxicity"

being particularly prominent in their outbreak intensity. In addition, the study found that "neurotoxicity", "antimicrobial toxicity" and "cytotoxicity" were emerging keywords in the last three years (FIGURE 2-4C).

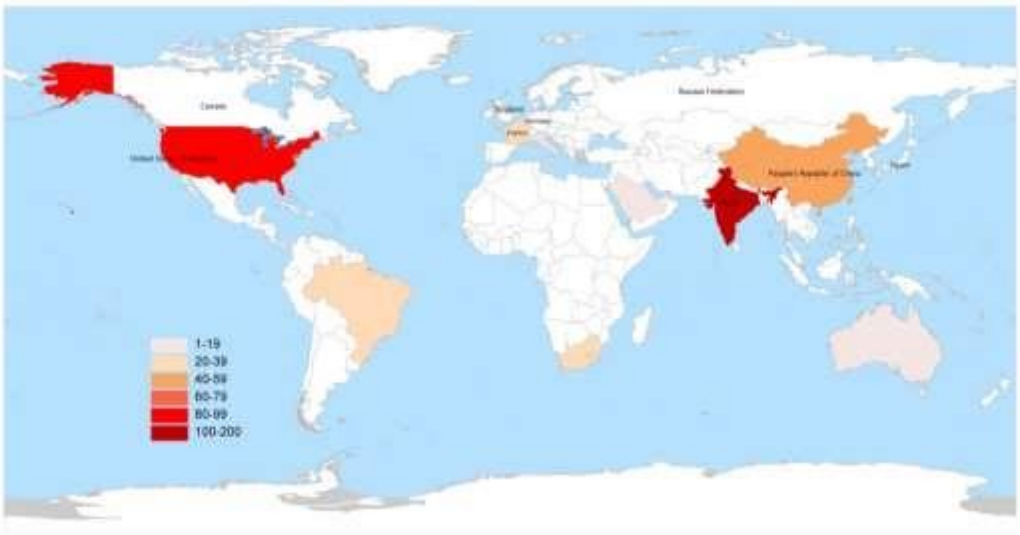


Figure 2.5 – Geographical distribution of countries engaged in isoniazid research worldwide

Visual analysis was carried out for the top ten countries and regions with the highest number of publications, with darker colors representing more publications, as shown in Figure 2-5. India topped the list, followed by the United States and China. It can be clearly observed from the figure that relevant research is mainly concentrated in India, the United States and China, while the research in other countries is relatively less popular.

Table 2.1 – **Top 10 countries/regions for the number of articles on isoniazid toxicity**

Rank	Country	Np	Nc	H-index	Average per item
1	INDIA	102	1296	19	13.92
2	UNITED STATES	93	2227	24	25.83
3	CHINA	56	691	18	13.48
4	SOUTH AFRICA	35	622	14	18.54
5	ENGLAND	28	695	14	27.68
6	BRAZIL	21	406	11	20.05
7	FRANCE	20	283	10	14.85
8	ITALY	17	281	11	17.59
9	SAUDI ARABIA	17	152	8	9.12
10	AUSTRALIA	16	204	10	13.19

Effective international cooperation is of great significance to promote academic exchanges. According to the ranking of the 10 high-producing countries/regions for all authors (Table 2-1), India has the highest number of articles published (102), followed by the United States (93) and China (56). India and the United States dominate the research field, and the degree of cooperation between them is far greater than that of other countries. In terms of total citations, the US topped the list with 2,227 citations, followed by India (1,296) and England (695). Meanwhile, the US has the highest H-index (24), which is three times higher than that of Saudi Arabia (8). Although Australia has a slightly lower NP compared to Saudi Arabia, its H index and Nc are significantly higher.

Table 2.2 – **Top 10 authors in the number of publications related to isoniazid toxicity**

Rank	Author	Np	Nc	H-index	Average per item
1	Grenha, Ana M	6	70	5	15.83
2	McHugh, Timothy	5	280	4	57.4
3	Rosa Da Costa, Ana	5	71	5	19
4	Wiesner, Lubbe	5	46	4	9.4
5	McIlleron, H.	4	42	3	10.75
6	Reves, Randall	4	81	4	20.25
7	Peng, Shuangqing	4	82	3	20.75
8	Buttini, Francesca	4	51	4	17
9	Belknap, Robert	4	74	4	18.5
10	Diacon, Andreas H.	4	279	4	71.25

Table 2-2 presents the analysis of the top 10 authors in terms of publication volume. In the field of research, Grenha and Ana M ranked first in the number of publications, followed by McHugh, Timothy and Rosa Da Costa, Ana. Notably, Diacon, Andreas Hh and McHugh, Timothy had high Nc values.

Table 2.3 – **Top 10 institutions in the number of publications related to isoniazid toxicity**

Rank	Affiliations	Country	Np	Nc	H-index	Average per item
1	UNIVERSITY OF CAPE TOWN	SOUTH AFRICAN	15	390	10	27.07
2	COUNCIL OF SCIENTIFIC INDUSTRIAL RESEARCH CSIR INDIA	INDIA	13	316	10	24.69
3	UNIVERSITY OF CALIFORNIA SYSTEM	USA	11	107	5	10
4	DEPARTMENT OF BIOTECHNOLOGY DBT INDIA	INDIA	10	244	7	25.8
5	EGYPTIAN KNOWLEDGE BANK EKB	EGYPT	10	163	7	16.6
6	JOHNS HOPKINS UNIVERSITY	USA	9	154	6	17.22
7	CENTRE NATIONAL DE LA RECHERCHE SCIENTIFIQUE CNRS	FRANCE	8	73	6	9.13
8	KING SAUD UNIVERSITY	SAUDI ARABIA	8	76	5	9.5
9	UNIVERSITY OF CALIFORNIA SAN FRANCISCO	USA	8	30	4	4
10	UNIVERSITY OF LONDON	UNITED KINDOM	8	334	7	45

Tables 2-3 show the ranking of the top 10 institutions with the highest number of publications. The University of Cape Town in South Africa tops the list, followed by CSIR INDIA and the University of California in the US. In terms of total publications, US institutions rank first and South Africa second in terms of output. It is no accident that the United States has the highest number of publications, as it is home to three institutions (including universities and research institutions) in the field. The results reveal that American research institutions are more active in this field than other countries.

Table 2.4 – **Top 10 source journals for the number of articles on isoniazid toxicity**

Rank	Journal	Np	Nc	IF(2020)	H-index	Average per item
1	EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY	11	385	5.81	9	36.36
2	ANTIMICROBIAL AGENTS AND CHEMOTHERAPY	9	129	5.938	6	14.78
3	INTERNATIONAL JOURNAL OF TUBERCULOSIS AND LUNG DISEASE	9	108	4.873	7	12.67
4	MOLECULES	8	87	3.319	4	10.88
5	MEDICINAL CHEMISTRY RESEARCH	7	99	1.783	5	14.71
6	FRONTIERS IN PHARMACOLOGY	6	60	5.988	4	10.67
7	PLOS ONE	6	153	3.709	5	25.5
8	TUBERCULOSIS	6	71	3.561	3	11.83
9	CLINICAL INFECTIOUS DISEASES	4	71	7.841	3	17.75
10	ENVIRONMENTAL TOXICOLOGY AND PHARMACOLOGY	4	182	4.860	4	45.5

Tables 2-4 present the rankings of the top 10 journals with the highest number of publications. At the top OF the list was the EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY, followed by ANTIMICROBIAL AGENTS AND CHEMOTHERAPY)

2.4 Discussion

2.4.1 Problems exist

This study used bibliometrics to conduct an in-depth analysis of publications in the field of isoniazid and toxicity. Overall, the number of publications in this field is on the rise. By using VOS viewer and other literature analysis software, cluster analysis and co-occurrence analysis were conducted to reveal the research focus and development trend in this field in the past decade. The results of the analysis showed that the problem of hepatotoxicity caused by isoniazid was the focus of concern in the field. However, the specific mechanism of its hepatotoxicity is not clear.

In China, researchers have paid much attention to the study of liver injury, because cases of liver injury caused by isoniazid are common in patients with tuberculosis. In clinical practice, doctors have noticed that although liver injury is the most serious adverse reaction of isoniazid, its impact in the field of encephalopathy and neurological diseases has not received enough attention [32].

This phenomenon may be attributed, in part, to the more pronounced clinical manifestations of liver injury, as compared with the more insidious manifestations of toxic injury in the domains of encephalopathy and neurologic disorders. In addition, the study of encephalopathy and neurological diseases is complex and difficult, which also makes the relevant research limited to a certain extent. However, with the continuous development of science and technology, researchers have gradually realized that the impact of isoniazid in the field of encephalopathy and neurological diseases cannot be ignored.

2.4.2 Suggested directions for development

As a widely used anti-tuberculosis drug, isoniazid's neurotoxicity and hepatotoxic injury have been widely concerned [33]. This study was based on a bibliometric analysis of the history and current status of isoniazid toxicity research,

aiming to explore the possible future development direction. Researchers are advised to pay close attention to the following research directions in the coming years:

1. Focus on the role of mitochondrial dysfunction in isoniazid-induced liver injury: mitochondrial dysfunction is regarded as one of the key mechanisms inducing various liver injury diseases (such as liver failure, cirrhosis, fatty liver, etc.), and mitochondria also play an important role in the development of drug-induced liver injury [34]. Therefore, it is important to explore how isoniazid causes hepatotoxicity by affecting mitochondrial function, and how to develop new protective drugs based on this mechanism.

2. In-depth study on the mechanism of isoniazid hepatotoxicity: The hepatotoxicity of isoniazid may be related to oxidative stress produced by CYP2E1 metabolism [35]. Future studies can further explore the mechanism, including how isoniazid affects the expression and activity of CYP2E1, and how isoniazid can alleviate or eliminate hepatotoxicity by inhibiting oxidative stress or other methods.

3. Focus on synergistic effects of isoniazid with other drugs: Isoniazid may interact with other drugs to exacerbate its hepatotoxicity and neurotoxicity. For example, the combination of isoniazid and some drugs, such as acetaminophen, may aggravate their hepatotoxicity, which may be due to the fact that isoniazid can induce hepatic cytochrome P-450, thereby increasing the amount of toxic metabolites produced by the former, thereby increasing hepatotoxicity and nephrotoxicity [36]. In addition, the combination of isoniazid with other neurotoxic agents may further increase neurotoxicity. Therefore, the study of these interactions provides a theoretical basis for the rational use of isoniazid in clinical practice.

4. Research and development of hepatoprotective drugs: In recent years, a series of achievements have been made in the research of isoniazid in liver protection. At present, some isoniazid derivatives have been put into use as hepatoprotective drugs on the market, such as azathioprine [37], glutathione [38], etc. However, the current hepatoprotective drugs of isoniazid on the market are mainly traditional formulations and lack innovation. Moreover, the existing studies are mainly for the hepatoprotective

treatment of diseases such as viral hepatitis, and the therapeutic effect on other types of liver diseases is not clear. In the future, the new route of administration and pharmacokinetic characteristics of isoniazid can be improved to improve its bioavailability in vivo and reduce side effects.

Conclusions to chapter 2

1. As an interdisciplinary subject, bibliometrics uses mathematics, statistics, philology and other methods to quantitatively describe academic information, and then combines statistical analysis to reveal the quantitative characteristics and potential rules of literature. To date, bibliometric analysis has emerged as an effective tool for mapping data on published articles and is important in assessing and predicting trends in research development on specific topics.

2. Isoniazid, the mainstay of the treatment for tuberculosis (TB), has saved countless lives since its introduction in the 1950s. However, with its widespread use, research on its toxicity has gradually attracted attention, especially the problem of liver damage. Clustering and co-occurrence analysis of VOS viewer and other analysis tools showed that isoniazid toxicity studies became the focus of attention from 2013 to 2023 and showed a rapid development trend. The results of the analysis revealed that the problem of liver toxicity caused by isoniazid is the focus of the research field. Despite this, the specific mechanism of its hepatotoxicity remains unclear.

3. International cooperation is of great value in promoting academic exchanges, and research cooperation between India, the United States and China is particularly significant in this field

4. Isoniazid toxicity research is gradually becoming the focus of attention and entering a stage of rapid development. Visual analysis of highly cited and co-cited articles revealed that Evgenidou et al. 's work was the most cited, while Dutta et al.' s 2020 paper was the second most cited. Keyword co-occurrence analysis revealed the research hotspots of isoniazid toxicity, including "liver injury", "neurotoxicity",

"antibacterial toxicity" and "cytotoxicity", and it was found that "neurotoxicity", "antibacterial toxicity" and "cytotoxicity" were the research hotspots in recent years.

5. Future research directions are recommended as follows: further study on the role of mitochondrial dysfunction in isoniazid-induced liver injury; To explore the mechanism of isoniazid hepatotoxicity. Attention should be paid to the synergistic effect of isoniazid with other drugs. And research and development of medicines to protect the liver.

CHAPTER 3
EXPERIMENTAL PART

3.1 Introduction

Artificial intelligence has been widely used in the field of traditional Chinese medicine research and development. A comprehensive and complex data foundation has been constructed in network pharmacology research, which provides convenience for the application of artificial intelligence technology in this field. Network pharmacology relies on rich database platforms in biology, pharmacology and other fields to reveal the interaction mechanism between drugs and organisms through the study of molecular interaction networks in human biological systems. Network pharmacology can systematically collect the multiple components of traditional Chinese medicine and their corresponding targets, and then construct the network relationship between components and targets [15], so as to understand the pharmacological effects of traditional Chinese medicine more comprehensively. In addition, network pharmacology, by combining with genomics, proteomics, transcriptomics and other research methods, has deeply explored the material basis of the effect of traditional Chinese medicine. As a new research method of traditional Chinese medicine, network pharmacology has increasingly shown great application prospects and value in modern society.

Dracocephalum moldavuca L., as a traditional Chinese medicine of Uygur and Mongolian, has been widely used in the treatment of cardiovascular and cerebrovascular diseases in folk medicine [39]. In this study, we used network pharmacology method to predict and analyze the hepatoprotective activity of Dracocephalum moldavuca L.. The results showed that Dracocephalum moldavuca L. had potential hepatoprotective effect, which provided scientific basis for effective exploration and development of the pharmacodynamic value of Dracocephalum moldavuca L., and provided new ideas and methods for the treatment of liver injury diseases in clinical practice.

3.2 Database and software

In data processing, Cytoscape_v3.10.0 software [40] as used in the study. As a popular open source software at present, it has outstanding performance in target visualization and processing, has powerful functions, and can integrate the selected target interaction network into a unified conceptual framework. With this software, users can easily perform network construction, visual analysis, re-layout, pathway tagging, and identification of key targets, which is suitable for handling any system involving molecular components and interactions. In this study, the software was used to successfully realize the visualization of protein interaction and target network.

Table 3.1 – **The database used in**

Name	Uniform Resource Locator
Bioinformatics (WeiShengXin)	https://www.bioinformatics.com.cn/
HERB	http://herb.ac.cn
OMIM	https://www.omim.org/
TCMSP	https://tcmsp-e.com/
DAVID	https://david.nciferf.gov
STRING	https://string-db.org
Gene Cards	https://www.genecards.org
Swiss Target Prediction	http://www.swisstargetprediction.ch

3.3 Active ingredient prediction and target screening of Dracocephalum moldavuca L.

The main components and action targets of Dracocephalum moldavuca L. were obtained from HERB database (http://herb.ac.cn) [41], TCMSP database (https://tcmsp-e.com/) [42] and other databases.

The main active ingredients of cyan were obtained by searching the database, and according to the five principles of Lipinski [43], the molecular weight (MW) is less than 500, the number of hydrogen bond donors is less than 5, the number of hydrogen bond recipients is less than 10, and the number of hydrogen bond donors is less than 5. Fat-water partition coefficient (AlogP) less than 5, Oral bioavailability (OB) ⩾30% and Drug likeness (DL)⩾0.18 were selected as index parameters, and six main active ingredients of Dracocephalum moldavuca L. were screened: Thymol, Neral, Nerol, Tilianin, Thymonin, (2E)-3-(4-hydroxy-3-methoxyphenyl)propyl-2-enoate. The 3D structure and Smiles format of compounds were obtained from HERB database, and then imported into Swiss Target database [44] to obtain the corresponding predicted targets. The data were exported to re-screen 381 targets of active ingredients of cyan.

3.4 Disease target prediction

"Isoniazid-induced liver injury" and "INH-ILI" were used as keywords in Gene cards (https://www. Gene cards.org /) [45], OMIM (https://www. omim. org/about) [46] and other databases, collected the targets of "Isoniazid-induced liver injury" and "INH-ILI" diseases in the above databases, and exported the Excel file of target genes in the search results. The two groups of result gene ids were merged into the same Excel to remove duplicates, and 124 human related disease targets were obtained after removing duplicates.

The obtained active ingredients of Dracocephalum moldavuca L. and the disease targets of "Isoniazid-induced liver injury" and "INH-ILI" were uploaded to the Bioinformatics platform [47], the intersection of drug components and disease targets was obtained, and the relevant Venn diagram was drawn. There are a total of 11 targets at the intersection of its components and disease targets, as shown in Figure 3-2. The detailed screening technical route is shown in Figure 3-1.

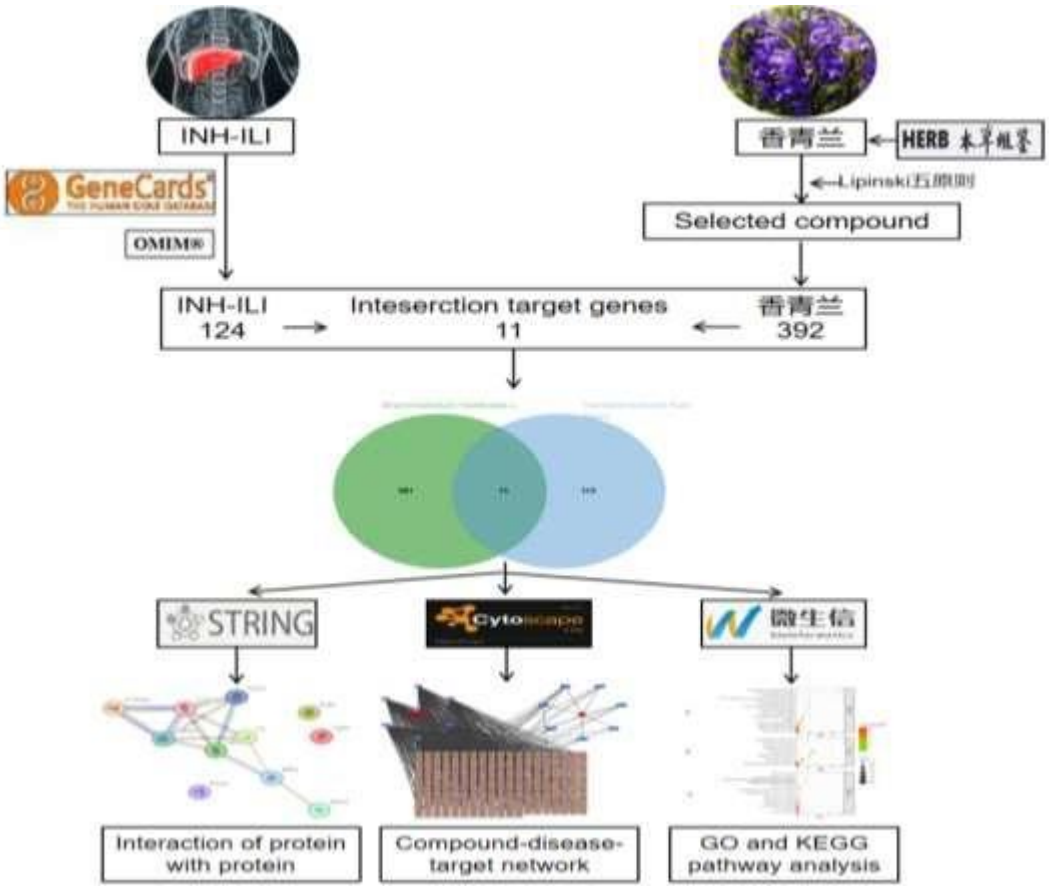


Figure 3.1 – Flow chart of active ingredients and target screening

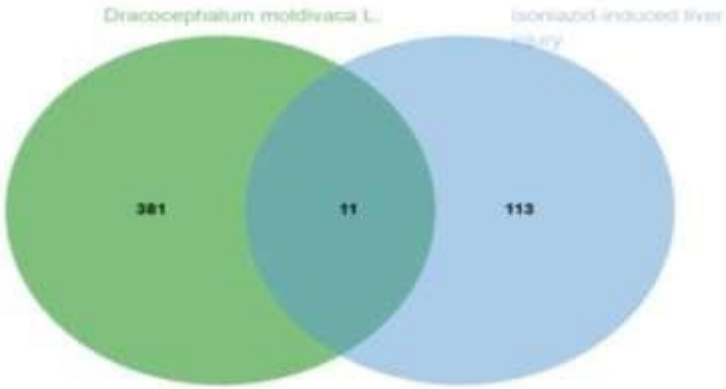


Figure 3.2 – Vann diagram of Dracocephalum moldavuca L.-liver injury target induced by isoniazid

3.5 Protein interaction network construction

The obtained ID of Dracocephalum moldavuca L. and 11 common target genes of "Isoniazid-induced liver injury" and "INH-ILI" were uploaded to the STRING database [48], and the species was set as "Homo sapiens". The 11 selected targets were introduced into the STRING database (https://string-db.org/) for interaction analysis. The nodes represent 11 intersection targets, which are: CYP2A6, CYP3A4, CES2, ALPL, CYP2C9, CES1, F2, TSPO, MPO, PYGL, ARG1, the lines show the interaction between the targets. Among them, there are interactions between the targets CYP2A6, CYP3A4, CES2, CYP2C9, CES1, F2, MPO, ARG1, and there is no interaction between ALPL, TSPO, PYGL targets and other intersection targets. See Figure 3-3 for details.

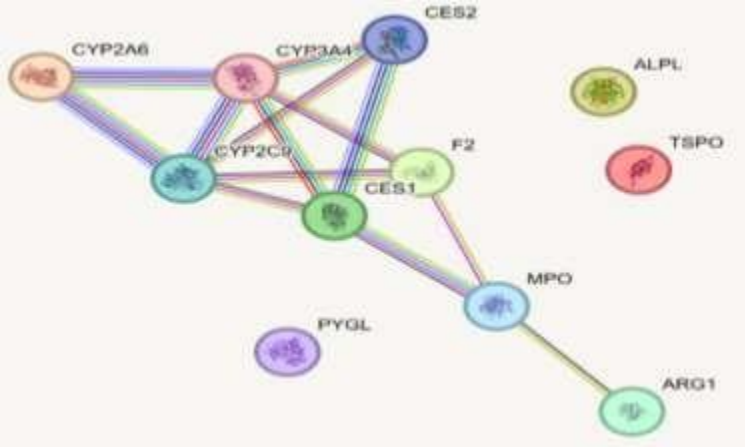
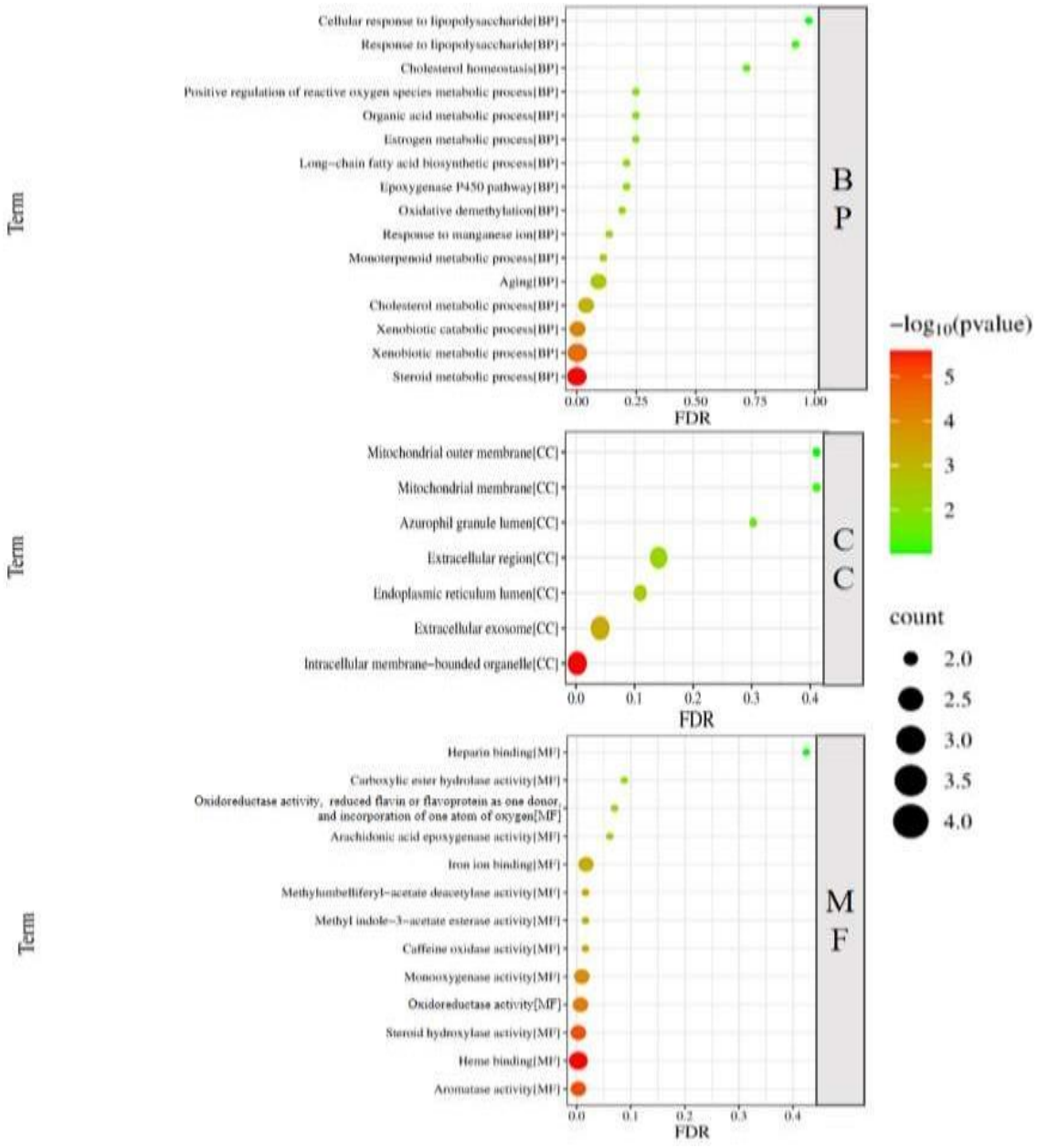


Figure 3.3 – PPI network of target proteins

3.6 GO and KEGG enrichment analysis

The potential target genes of "Isoniazid-induced liver injury" and "INH-ILI" were imported into the DAVID database [49], and the GO function enrichment analysis and KEGG signaling pathway enrichment analysis were performed, and the KEGG pathway bubble map was made using the Bioinformatics website. The analysis results were visualized and bubble charts were made, as shown in Figure 3-4.



Figures 3.4 – GO analysis bubble plots

KEGG analysis was mainly used to screen the signaling pathways of "Isoniazid-induced liver injury" and "INH-ILI" treated by Dracocephalum moldavuca L.. The ordinate of the bubble chart represents the enriched entries, and the abscissa represents the weight. Through GO enrichment analysis, Biological Process(BP)including Cholesterol metabolic process, Xenobiotic metabolic process, Steroid metabolic process, etc. Cell Component (CC) includes Extracellular exosome, Intracellular

membrane-bounded organelle, etc. Molecular Function(MF) includes Oxidoreductase activity, Steroid hydroxylase activity, Aromatase activity, etc.

Through KEGG enrichment analysis, 7 major signaling pathways were screened out. These include Linoleic acid metabolism, Retinol metabolism, Metabolism of xenobiotics by cytochrome P4500, Drug metabolism-other enzymes, etc., are all major pathways, as shown in FIG. 3-5. The analysis showed that the differentially expressed genes were enriched in metabolic pathways, indicating that Dracocephalum moldavuca L. may play a role in drug action by affecting drug metabolism efficiency or pathways.

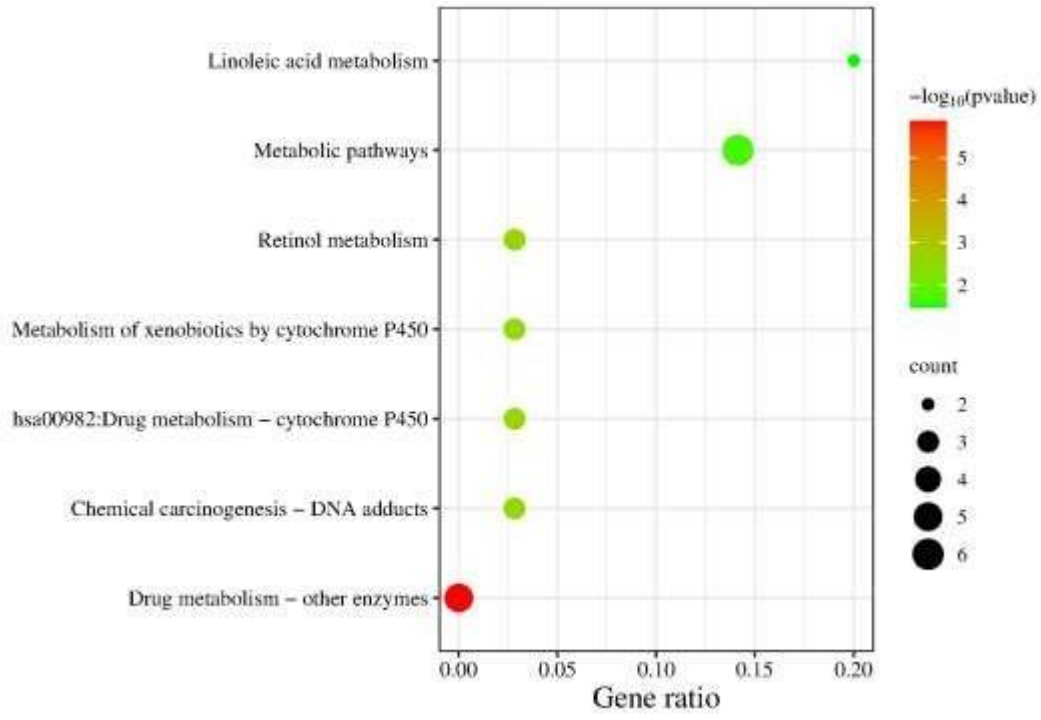


Figure 3.5 – Bubble plot of KEGG enrichment analysis

3.7 Construction of "drug-component-disease-target" network

The corresponding data set of "drug-active ingredients" and "disease-target" of Dracocephalum moldavuca L. was established, and the selected active ingredients and intersection targets were imported into Cytoscape_v3.10.0 software. Six potential active ingredients of cyanine green were screened as follows: Thymol, Neral, Nerol, Tilianin, Thymonin, (2E)-3-(4-hydroxy-3-methoxyphenyl)-propyl-2-enoate. The relationship between key compounds and targets was represented by nodes and lines,

and the "disease-target-component-drug" network was constructed. It reflects the synergistic effect of multiple components and targets of cyanine blue in the treatment of Isoniazid-induced liver injury (INH-ILI), as shown in Figure 3-6.

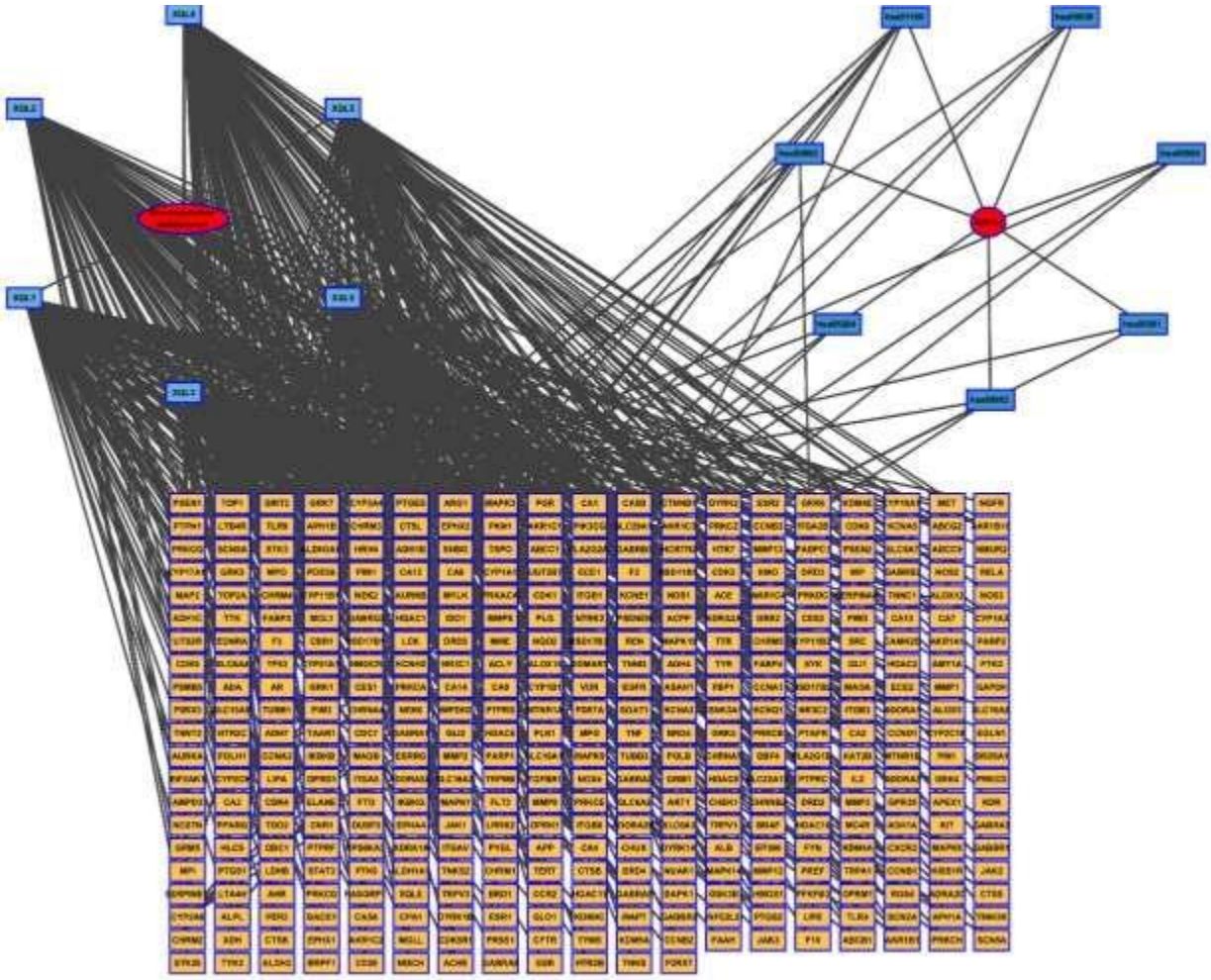


Figure 3.6 – "Drug-component-disease-target" network diagram

Conclusions to chapter 3

1. Artificial intelligence has been widely used in the research field of traditional Chinese medicine, especially in the research of network pharmacology, which has built a comprehensive and complex data base, providing convenience for the application of artificial intelligence technology in this field.

2. Network pharmacology relies on rich database platforms in the fields of biology and pharmacology to reveal the interaction mechanism between drugs and organisms by studying the molecular interaction network in human biological systems.

The present study is the first to predict and analyze Dracocephalum moldavuca L using a network pharmacology approach. The hepatoprotective activity of Dracocephalum moldavuca L. has potential hepatoprotective effects. It provides a scientific basis for the effective development of the pharmacodynamic value of, and provides new ideas and methods for the clinical treatment of liver diseases.

3. A "disease-target-component-drug" network reflecting Dracocephalum moldavuca L was constructed by integrating the "drug-active ingredient" and "disease-target" data sets and visualized using Cytoscape software. Synergistic effect of multiple components and targets in the treatment of isoniazid-induced liver injury.

4. GO and KEGG enrichment analyses were also performed to screen out the signaling pathways associated with isoniazid-induced liver injury, which were visualized by KEGG pathway bubble map. The results of these analyses showed that the differentially expressed genes were enriched in metabolic pathways, indicating Dracocephalum moldavuca L. It may exert its effect by affecting the efficiency or pathway of drug metabolism.

CONCLUSIONS

This article aims to explore the application of artificial intelligence technology in modern scientific research, especially its role in drug activity screening and safety evaluation. Through the use of bibliometric methods, combined with VOS viewer software, in-depth cluster analysis of authors and keywords was carried out. This study focuses on the current status of research on adverse reactions and toxicity of isoniazid, reveals that hepatotoxicity is the main concern in this field, and notes possible future research directions of isoniazid.

This study was the first to successfully predict the hepatoprotective potential of Dracocephalum moldavuca L. and its target by using network pharmacology approach. In addition, the "drug-component-disease-target" network was constructed to deeply analyze the multi-component and multi-pathway action characteristics of Dracocephalum moldavuca L.. Through GO and KEGG enrichment analysis, it was found that the differential genes were enriched in metabolic pathways, suggesting that Dracocephalum moldavuca L. may play a role in anti-isoniazid liver injury by affecting the efficiency or pathway of drug metabolism.

In summary, this study provides a solid theoretical basis for the study of Dracocephalum moldavuca L. in improving liver injury, and provides new ideas and methods for drug development. These research results are of great significance for promoting the application of artificial intelligence technology in drug research and development.

With the development of artificial intelligence in the field of medicine, the field of drug research and development is undergoing unprecedented changes, and drug activity screening and safety evaluation become the key. The application of artificial intelligence will significantly improve the efficiency and success rate of drug research and development, and open up a new way for new drug research and development.

Artificial intelligence technology also plays an important role in drug safety assessment. The research and development of new drugs may have side effects. Artificial intelligence predicts and evaluates the safety of drugs through big data

analysis, and establishes a data-based drug safety assessment model, which can effectively identify the risks in drugs, reduce toxic and side effects, and ensure drug safety.

With the continuous innovation and application of artificial intelligence technology in new drug development, the efficiency of new drug activity screening and safety assessment will be greatly improved. On this basis, through the continuous accumulation of experimental data, the algorithm is further improved to achieve accurate prediction of drug efficacy and safety, which is expected to provide more possibilities for new drug development, accelerate the process of new drug research and development, and benefit the people.

In summary, AI-based drug activity screening and safety evaluation will bring revolutionary changes in drug research and development. The application of intelligent bibliometrics and network pharmacology is expected to make more breakthroughs in the field of drug research and development, provide more effective and safer new drugs, and promote the continuous development of medicine

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