Knowledge Graph-Based JingFang Granules Efficacy Analysis for Influenza-Like Illness

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***Abstract*—This study presents a novel approach to evaluate the efficacy of JingFang granules in treating influenza-like illness by integrating knowledge graph technology with clinical trial data. We developed an innovative knowledge graph-based pharmacological analysis method and validated its effectiveness through a randomized controlled clinical trial. A knowledge graph was constructed by extracting drug-disease entities and their relationships from the literature using a machine learning workflow. Deep mining of the knowledge graph was performed using a graph convolutional network and T5 mini-model to analyze the association between JingFang and various diseases. Subsequently, a randomized controlled clinical trial involving 106 patients was conducted. Results showed that the cure rate in the JingFang combined treatment group (92.5%) was significantly higher than in the control group (81.1%), especially among the middle-aged and elderly population. Subgroup analysis revealed that JingFang had a more pronounced therapeutic effect on patients aged 34 and above, consistent with the knowledge graph analysis results. The innovation of this study lies in proposing a novel framework for evaluating therapeutic efficacy by combining knowledge graphs with clinical trial results. This approach not only provides new analytical tools for similar drug development but also improves the efficiency and accuracy of drug development by systematically validating literature efficacy data and integrating it with actual clinical trial results. Furthermore, applying a knowledge graph to evaluate the therapeutic effects of traditional Chinese medicines like JingFang is an innovative and unique approach, bringing new perspectives to this under-explored field. This method holds potential for broad application in drug development and repurposing, particularly in the context of Traditional Chinese Medicine.**

***Keywords*—Knowledge graph; clinical trial; influenza-like illness; jingfang; drug efficacy analysis**

I. INTRODUCTION

A biomedical network can be conceptualized as a knowledge graph (KG) [1], where nodes represent various types of bio-entities such as proteins, drugs, chemicals, diseases, and species, and edges denote relationships between these entities. A KG can be broken down into a series of <head entity, tail entity, predicate> triples, where the predicate links the head and tail entities, indicating their relationship. For example, <drug A, protein B, affect> can illustrate the regulatory relationship between a drug and a protein. Additionally, each node and edge in a KG can have a set of attributes providing further details, such as the sources of the research articles from which the relationship is derived. Through literature mining and deep learning models, numerous KGs have been constructed and applied to various prominent fields in bio-science, including drug discovery and repurposing [2], protein-protein interactions [3,4], chemical-protein interactions [5], disease mechanism identification [6], and disease biomarker networks [7].

Drug efficacy prediction and analysis are critical tasks in computational pharmacology [8]. In recent years, a variety of KG-based methods have been developed for drug efficacy analytics [9, 10]. These methods primarily focus on evaluating the similarity between drugs and their treatment efficacy on diseases [11], based on the assumption that two similar drugs may exhibit similar efficacy for the same diseases. For pharmaceutical companies, understanding the efficacy of a particular drug on various diseases throughout its market presence is crucial. This information can often be found in clinical trials reported in research articles. Therefore, it is essential to develop a system that can track and compile relevant clinical trials involving the drug, enabling comprehensive efficacy analysis.

We present a novel methodology for demonstrating knowledge graph-based drug efficacy analysis, validated by a randomized controlled clinical trial conducted for JingFang [12]. To provide a comprehensive understanding of JingFang's treatment effects and functions, we developed a machine learning-based pipeline to extract drug-disease entities and relationships from the literature. These extracted relationships are used to construct a knowledge graph, which is then utilized for clustering-based drug efficacy analysis. With a given drug, our tool can report the inferred relatedness between the drug and disease, indicating the degree of efficacy for the drug-disease pair.

We propose a literature-based measure to assess the "impact of drug composition on efficacy". The increasing costs of drug research, combined with a notable decline in new pharmaceutical approvals, have heightened the need for innovative tools for target identification and effectiveness prediction. Here, we introduce a measure that quantifies the interaction between a drug component and a disease by analyzing literature data. This measure adjusts for known biases in interaction groups, using proximity to detect a drug's therapeutic impact and distinguish between unsuccessful and effective therapies. Our analysis identifies JingFang as effective in treating flu and colds. To further validate this finding, we conducted a randomized controlled clinical trial to

evaluate JingFang's efficacy on Influenza-like illness, a subtype of cold.

Influenza-like illness refers to symptoms similar to the common cold, including chills, fever, limb aches, nasal congestion, runny nose, headache, and cough, especially when exposed to air conditioning for extended periods. It is also known as Influenza-like illness syndrome. Treatment focuses on symptomatic relief and includes rest, proper hydration, and ensuring good indoor air circulation.

The purpose of this study was to establish a method for measuring pharmacological effectiveness using knowledge graphs, integrating data from the literature, and validating the results through a randomized controlled clinical trial on JingFang granules. By combining the findings from knowledge graphs and clinical trials, we can more accurately assess the efficacy of JingFang granules against Influenza-like illness (see Fig. 1).

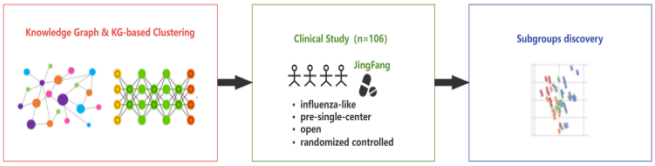

Fig. 1. The evaluation framework of knowledge graph and influenza-like illness clinical trials. Combining the results of the knowledge graph and clinical trials, JingFang's efficacy is accurately evaluated.

II. Related Work

In recent years, there has been growing interest in applying knowledge graph (KG) techniques and machine learning approaches to drug discovery, efficacy analysis, and adverse reaction prediction. This section reviews related studies in these areas, with a focus on methods relevant to our work on JingFang granules and influenza-like illness.

A. Knowledge Graph-based Drug Analysis

Knowledge graphs have emerged as a powerful tool for representing and analyzing complex biomedical information. For instance, Arnold K. Nyamabo et al. [13] developed a novel method called Gated Message Passing Neural Network (GMPNN) for predicting drug-drug interactions (DDIs). GMPNN learns chemical substructures of varying sizes and shapes from molecular graph representations of drugs. In this approach, edges act as gates controlling message flow, effectively learning and delimiting substructures. The final DDI prediction is based on the interactions between these learned substructures, each weighted by a relevance score. GMPNN-CS, their proposed model, demonstrated competitive and improved performance on real-world datasets compared to previous methods.

Similarly, Fangping Wan et al. [14] proposed a knowledge graph embedding approach named NeoDTI for drug-target interaction (DTI) prediction. NeoDTI integrates diverse information from heterogeneous network data, learning topology-preserving representations of drugs and targets. This method significantly improves prediction performance over state-of-the-art DTI prediction methods and has been validated by novel DTI predictions supported by previous studies. NeoDTI's robustness to a wide range of hyperparameters and its ability to integrate additional drug and target-related information, such as compound-protein binding affinity data, highlight its potential as a powerful and robust tool for drug development and drug repositioning.

B. Machine Learning for Drug Efficacy Prediction

Machine learning techniques have been widely applied in drug efficacy prediction. Jessica Vamathevan et al. [15] provided a comprehensive review of AI applications in drug discovery and development, highlighting various stages where machine learning can be utilized. Their review discusses the potential of deep learning models in predicting drug efficacy, validating targets, identifying prognostic biomarkers, and analyzing digital pathology data in clinical trials. Despite challenges such as lack of interpretability and repeatability, the authors emphasize that with systematic and comprehensive high-dimensional data, machine learning can significantly enhance data-driven decision-making, accelerate the drug discovery process, and reduce failure rates.

In a more specific application, Wenxuan Wu et al. [16] developed GeoDILI, a graph neural network-based model for predicting drug-induced liver injury (DILI). GeoDILI uses a molecular geometric representation and leverages gradient information to achieve high predictive performance and interpretability. By benchmarking against other DILI prediction models and popular GNN models, GeoDILI demonstrated superior performance and provided mechanistically elucidated structural alerts. This model shows the potential of machine learning in adverse drug reaction prediction, enhancing drug safety assessment and development processes.

C. Traditional Chinese Medicine (TCM) Efficacy Evaluation

Evaluating the efficacy of Traditional Chinese Medicine (TCM) presents unique challenges due to its holistic approach and complex formulations. Zhao et al. [17] highlighted the potential of network pharmacology as a new discipline that leverages systems biology theory, biological system network analysis, and multi-target drug molecule design. Their study summarized the current application status and existing challenges of network pharmacology in TCM, proposing research ideas, key technologies, and strategies to reveal the modern scientific connotation of TCM. This approach aligns well with the integrity, systematization, and comprehensiveness of network pharmacology, making it suitable for studying the pharmacological mechanisms of TCM compounds.

Similarly, Liu et al. [18] developed a machine-learning model to predict the efficacy of TCM formulas based on their chemical compositions and traditional usage patterns. Their model integrated diverse data sources, including experimental validation, to provide new insights into the mechanisms of TCM formulas. The integration of computational methods, such as network pharmacology and machine learning, allows for a more systematic and comprehensive evaluation of TCM efficacy, bridging traditional knowledge with modern scientific findings.

D. Integration of Computational Methods and Clinical Trials

While several studies have utilized knowledge graphs or machine learning for drug analysis, few have combined these approaches with clinical trial data, particularly for TCM. For instance, Wang et al. [19] proposed a framework that integrates electronic health records (EHRs) with knowledge graphs for personalized medicine. Although their focus was not specifically on TCM or drug efficacy analysis, their work demonstrates the potential of combining computational methods with clinical data.

Our study aims to bridge this gap by combining knowledge graph-based analysis with clinical trial results, specifically for TCM formulations like JingFang. By leveraging the power of computational methods and grounding our findings in real-world clinical data, we aim to offer a more comprehensive and accurate assessment of drug efficacy. This approach not only enhances our understanding of TCM but also supports the development of more effective and personalized treatment strategies.

III. METHODS

A. Knowledge Graph-based Analytics

We utilized a self-developed tool for web scraping. As shown in Table I, a total of 19,053 paper abstracts were collected using four different keywords: "JingFang", "荆防" (Chinese for JingFang), "Flu", and "Influenza-like illness". After an initial screening, 4,429 relevant abstracts were retained in the dataset for knowledge extraction. The fields used for literature scraping included the following: paper type, title, author list, author affiliation, source, keywords, abstract, publication time, funding, volume, issue, page, URL, and DOI.

TABLE I. STATS OF LITERATURE COLLECTION

Keyword	# abstracts	# Abstracts after cleaning
JingFang	642	221
JingFang (Chinese)	2,324	578
Flu	8,592	1,327
Influenza-like illness	7,495	2,303
Total	19,053	4,429

Each abstract scraped from the internet is semi-structured, containing both structured information such as the author list, year of publication, affiliations, etc., and unstructured data like the title and abstract text. Our knowledge graph includes three entity types: abstract, drug, and disease. The relationship between a drug and a disease can be either "treat" or "cause". As shown in Fig. 2, an abstract text is input into a MacBERT pre-trained model to extract entities and relationships. Each extracted relationship is represented as a three-tuple <e1, e2, r>, where e1 and e2 are the head and tail entities, typically a drug and a disease, respectively, and r is the relationship connecting them.

Other structured attributes, along with the extracted drugs and diseases, are used to build the knowledge graph. To facilitate further analysis, the knowledge graph is processed to generate an adjacency matrix that encodes the interactions between drugs and diseases. Specifically, if a drug can treat a disease and this relationship appears in n abstracts, the value of the corresponding cell in the matrix for that drug and disease is set to n.

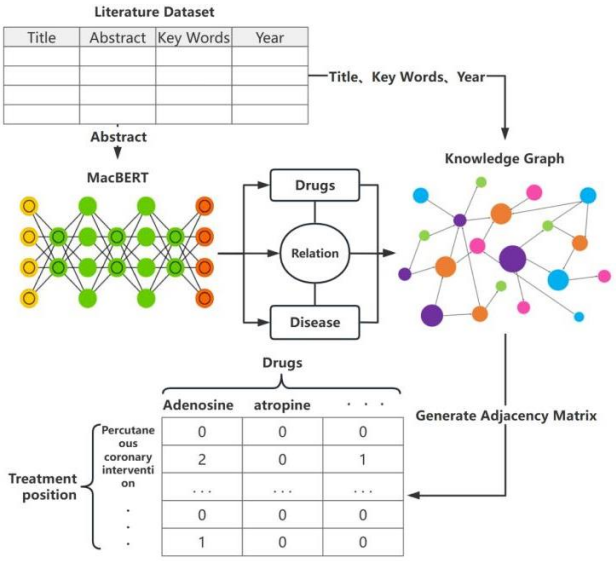

Fig. 2. Workflow of building the drug-condition knowledge graph.

The adjacency matrix generated from the previous step can be normalized and used to train a Graph Convolutional Network (GCN) [20], allowing each graph node and edge to be represented as numerical vectors. To capture the semantics embedded in the abstract text, we pass the text through the MacBERT [21] model, which performs word vector mapping to convert each word into a vector. However, since most word tokens are not relevant to the drug efficacy analysis task, we retain only the word vectors for drugs and diseases. Consequently, each drug entity has two representations: one from the GCN and one from the word vector mapping.

These two representations are then fed into the T5-small [22] model, which serves as a feature-fusion module to combine them. The output of the T5-small model is subsequently processed using a K-means [23] algorithm for clustering analysis.

Essentially, drugs can be categorized into two types: drug products and their constituent chemicals. In our knowledge graph, the extracted drug entities can belong to either category. The purpose of this analysis is to determine that the closer a drug is to the cluster centroid, the stronger its positive correlation with the current disease. The overall process is illustrated in Fig. 3.

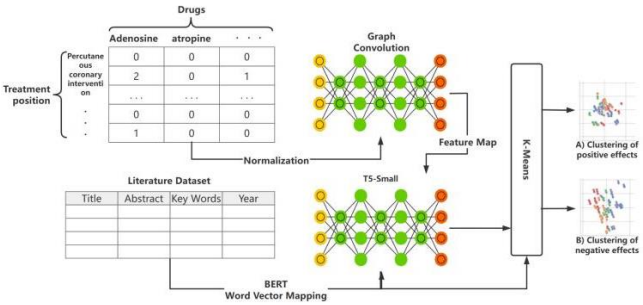

Fig. 3. Workflow of KG-based clustering for drug efficacy analysis.

B. A Randomized Controlled Clinical Study

In the second half of 2020, we conducted a single-center, open, randomized controlled clinical study from August 25, 2020, to October 12, 2020, with 108 patients participating. The diagnostic criteria for Influenza-like illness were defined as the onset occurring on a hot day (June-October) with exposure to air conditioning or frequent entry and exit from an air-conditioned room for at least three days before onset, along with meeting the following Western medical diagnostic criteria.

The Western diagnostic criteria for the common cold include sneezing, nasal congestion, runny nose, cough, sore throat, and other local symptoms, predominantly lacrimation, and possibly systemic symptoms such as chills, fever, general malaise, dizziness, and headache. The white blood cell count is either normal or low.

A central randomization system (web-based Interactive Web Response System, IWRS) was used for the randomization of groups in this study. Subjects were randomly divided into test and control groups in a 1:1 ratio, meeting the inclusion criteria. Subjects in the control group took only Neocontrol (Blue) (Sino-Medical), while subjects in the trial group took Neocontrol (Blue) plus JingFang (Shandong New Age Pharmaceutical Co., Ltd.). The study employed a block randomization grouping method with a block length of 4. The randomization process was set up by a statistical and computer professional who developed the randomization grouping procedure.

This study was approved by the Ethics Committee of Zhangjiagang City Hospital of Traditional Chinese Medicine and has been registered with the China Clinical Trials Registry (chictr.org.cn) under the registration number ChiCTR2000036543.

Males and females between the ages of 18 and 70 were eligible for the study if they met the following criteria: onset of illness during hot days (June to October) with exposure to an air-conditioned environment or frequent entry and exit from air-conditioned rooms for at least three days before onset; meeting the Western medical diagnostic criteria for the common cold; within 48 hours of onset; and not having taken JingFang, Neocontrol (Blue), Tylenol cold tablets, Neocontrol (Red), or Day and Night Pepcid (night tablets) within two weeks before enrollment. Additionally, subjects needed to be willing to participate in the study and sign an informed consent form.

Subjects were excluded from participating if they met any of the following criteria: having wind-heat colds (manifested by high fever, slight wind aversion, sweating, thirst, runny nose, red, swollen and hot throat, coughing and spitting yellow sputum, etc.); having pharyngoconjunctivitis, acute attacks of chronic bronchitis, purulent tonsillitis, or infectious upper respiratory tract infection; having uncontrolled cardiovascular disease, diabetes, hypertension, thyroid disease, asthma, glaucoma, emphysema, chronic lung disease, dyspnea, or prostatic hypertrophy; having pneumonia diagnosed by chest imaging; having used drugs for the treatment of this disease since the onset; having active liver disease or uncontrollable liver disease; having uncontrollable kidney disease or being on kidney dialysis; having an axillary temperature ≥ 40 degrees Celsius, a total white blood cell count of 10 × 10^9/L or neutrophil classification > 80%; being allergic to the drugs used in this study; having mental or neurological disorders that prevent correct expression of their will; being pregnant, lactating, or women of childbearing age not using contraception; currently participating in clinical trials of other drugs or medical devices; and being considered unsuitable for inclusion by the investigator.

JingFang is produced by Shandong New Times Pharmaceutical Co., Ltd. The main ingredients include Bupleurum, Chuanxiong, Duhuo, Fangfeng, Poria, Licorice, Nepeta, Platycodon grandiflorum, Qianhu, Qianghuo, and Citrus aurantium. For New Contac (Blue Pack), the dosage is one capsule every 12 hours after meals, not exceeding two capsules within 24 hours. JingFang is taken in one bag at a time, three times a day, with boiling water. The therapy duration is seven days. The subjects in both groups received the same non-drug intervention program, which included diet control and lifestyle improvement. This program primarily involved avoiding greasy and spicy food, abstaining from tobacco and alcohol, avoiding overwork and overeating, and maintaining a positive attitude.

The primary endpoint was the rate of healing within seven days. Clinical cure: clinical symptoms and signs vanished or almost vanished, and the symptom score was decreased by 95%; efficacy: clinical symptoms and signs considerably improved, and the symptom score was lowered by 70%.

Clinical symptoms and indicators improved, and the symptom score was lowered by more than 30%. Clinical symptoms and indicators did not improve considerably, if at all, and the symptom score was lowered by less than 30%. Healing rate (%) = (number of clinically healed cases + number of apparent effect cases) ÷ total cases ×100%. The secondary endpoint was the incidence of adverse events.

The key assessment criterion for this study is the therapeutic effectiveness rate of the drug after seven days of treatment. This study adopts the hypothesis of superiority. Based on previous literature and preliminary test results, the treatment effectiveness rate was expected to be 63.3% in the control group and 90% in the experimental group. The superiority margin between the two groups was set at 3%, with α=0.025 (one-sided) and β=0.2, and a 1:1 sample size ratio. A total of 45 patients were initially calculated for each group. Considering a 15% loss to follow-up rate, 53 patients were finally included in each group, resulting in a total of 106 patients.

Statistical analysis was performed using SAS 9.4 software. Results were reported as mean ± standard deviation, or median (upper and lower quartiles). Measurement data comparisons were first tested for normality. If they conformed to a normal distribution, parametric tests were used; otherwise, Wilcoxon rank sum tests were performed. The frequency (composition ratio) was used to describe count data statistically. To compare count data, the chi-square test or Fisher's exact test was utilized. A p-value of <0.05 was considered significant.

Subgroup analysis was performed on the cure rate for different age groups. Patients aged ≤34 years were classified as young, while those aged >34 years were classified as middle-aged and elderly.

IV. RESULTS

The experiments for this study were conducted using Python 3.7.0. PyCaret was employed to implement the learning algorithms [24]. Microsoft Office 365 Excel, Matplotlib 3.4.2, and Seaborn 0.11 were used to create the charts. BAIX (https://github.com/aibaix, accessed June 9th, 2022), a self-developed Python tool, was utilized for data purification and exploratory data analysis. Results of Knowledge Graph Analysis

A. Discovery of Knowledge Graph-based Drug-Disease Relationships

We utilize Neo4J to store knowledge graph data, leveraging its optimized storage structure for graph data attributes, which provides superior performance in processing relational data compared to other databases. Fig. 4 presents an extracted portion of the knowledge graph, visually depicting multiple node entities and the relationships connecting them.

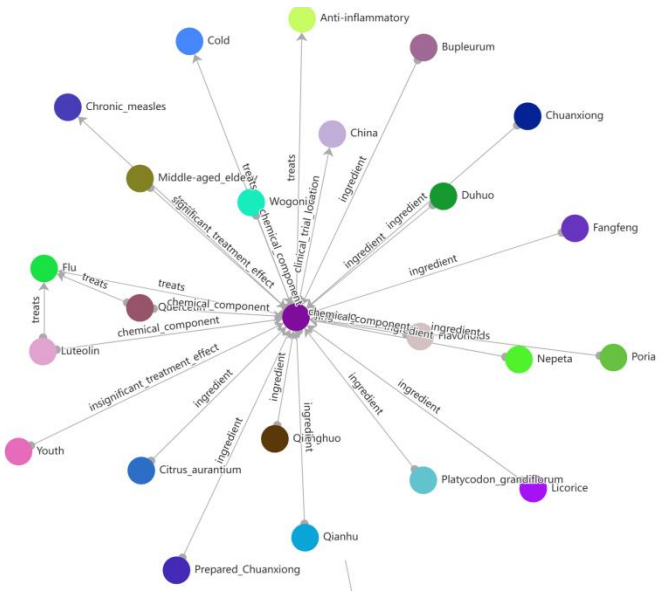

Fig. 4. An example of the generated drug-condition knowledge graph.

Fig. 5 and Fig. 6 illustrate the results of the KG-based clustering analysis. Fig. 5 displays the relatedness scores of JingFang and the commonly related conditions. It shows that flu, chronic measles, anti-inflammatory, and cold are the top conditions that can be treated by JingFang. Specifically, flu has the highest score of 0.9374, indicating that, according to existing literature, JingFang is most effective in treating flu compared to other conditions.

Fig. 6, on the other hand, depicts the pairwise relatedness between the chemical components of JingFang and various conditions, identifying how each component affects certain conditions. The figure highlights only the top 8 ranked chemical components: quercetin, luteolin, kaempferol, wogonin, beta-sitosterol, naringenin, acacetin, and tanshinone IIA. These components vary in their degree of influence across different diseases. The figure suggests that quercetin and luteolin may be the key effective ingredients in the treatment of influenza with JingFang.

- Use either SI (MKS) or CGS as primary units. (SI units are encouraged.) English units may be used as secondary units (in parentheses). An exception would be the use of English units as identifiers in trade, such as “3.5-inch disk drive”.
- Avoid combining SI and CGS units, such as current in amperes and magnetic field in oersteds. This often leads to confusion because equations do not balance dimensionally. If you must use mixed units, clearly state the units for each quantity that you use in an equation.
- Do not mix complete spellings and abbreviations of units: “Wb/m2” or “webers per square meter”, not “webers/m2”. Spell out units when they appear in text: “. . . a few henries”, not “. . . a few H”.
- Use a zero before decimal points: “0.25”, not “.25”. Use “cm3”, not “cc”. (*bullet list*).

Condition	Relatedness
Flu	0.9374
Chronic measles	0.6818
Anti-inflammatory	0.5539
Cold	0.3409
Anti-allergy	0.2983
Upper respiratory tract infection	0.2983
Flat wart	0.2557
Acute lung injury	0.2131
Mumps	0.2131
Atopic dermatitis	0.2131
White fresh skin	0.1704
Eczema	0.1704
Psoriasis	0.1704
Allergic dermatitis	0.1278
Pruritus	0.1278
Diabetic nephropathy	0.1278

Fig. 5. Relatedness scores of JingFang and the commonly-related conditions.

	Cold	Chronic Measles	Upper Respiratory Tract Infection	Atopic Dermatitis
quercetin	0.4857	0.2429	0.7286	0.6072
luteolin	0.6072	0.3642	0.4857	0.4857
kaempferol	0.3642	0.3642	0.2429	0.1214
wogonin	0.3642	0	0.2429	0.1214
beta-sitosterol	0.2429	0.1214	0.4857	0.2429
naringenin	0.2429	0.2429	0.1214	0.2429
acacetin	0.2429	0.1214	0.2429	0.1214
tanshinone IIA	0.2429	0	0.2429	0.3642

Fig. 6. Pair-wise relatedness between the composed chemicals of JingFang and conditions.

B. Results of Clinical Trials

A total of 108 patients were recruited from August 25, 2020, to October 12, 2020, and finally, 106 patients were enrolled and randomized to receive JingFang and Neocontrol (53 patients in the treatment group) or Neocontrol only (53 patients in the control group). The ages of patients in the treatment and control groups were 41.8 ± 15.8 years and 43.5 ± 13.75 years, respectively, without any statistically significant differences. There were no statistically significant differences in gender structure, ethnic structure, BMI, total symptom score, and physical findings score between the treatment and control groups, making them comparable (see Table II).

TABLE II. BASELINE CHARACTERISTICS OF ENROLLED PATIENTS

	Test group (N=53)	Control group (N=53)	p-value
Mean age (SD)	41.8 (15.18)	43.5 (13.75)	0.58
# male patients (%)	19 (35.8)	12 (22.6)	0.14
BMI (SD)	23.09 (2.999)	23.41 (3.258)	0.61
Overall symptom score (SD)	5.5 (2.11)	5.7 (2.24)	0.81
Physical examination score (SD)	0.8 (0.55)	0.9 (0.48)	0.67

The healing rate within seven days was 92.5% (49 cases) in the test group and 81.1% (43 cases) in the control group, which was higher in the test group, but no statistically significant difference existed between the two groups (p=0.0852, 95% CI: 11.3 (-2.0, 25.3)). The very effective rate within seven days was 98.1% (52 cases) in the test group and 92.5% (49 cases) in the control group, which was also higher in the test group, but again, no statistically significant difference existed between the two groups (p=0.3692, 95% CI: 5.7 (-3.5, 16.5)) (Table III).

TABLE III. EFFICACY ANALYSIS

	Test group (N=53)	Control group (N=53)	p-value
Cured	49 (92.5)	43 (81.1)	0.09
Very effective	3 (5.7)	6 (11.3)	-
Effective	1 (1.9)	4 (7.5)	-
Not effective	0	0	-
Cured+very effective (%)	52 (98.1)	49 (92.5)	0.36

In middle-aged and elderly subjects, the healing rate was 100% (32 cases) in the test group and 78.4% (29 cases) in the control group, which was statistically significantly higher in the test group (p=0.0059, 95% CI: 21.6 (8.3, 38.2)) (Table IV). In the youth population, the healing rates were essentially the same in both groups.

This study aims to evaluate the therapeutic efficacy of JingFang for influenza-like illnesses by integrating knowledge graph technology with clinical trial data. We developed an innovative knowledge graph-based pharmacological analysis method and validated its effectiveness through a randomized controlled clinical trial.

First, we constructed a knowledge graph by extracting drug-disease entities and their relationships from literature using a machine learning workflow. Our tool can report drug-disease correlations, indicating the degree of efficacy between drug-disease pairs. Specifically, we collected 19,053 abstracts and utilized our in-house text-mining tool to extract relationship information between drugs and diseases. Each extracted relationship was encoded as an adjacency matrix for subsequent analysis. This knowledge graph not only contains drug and disease entities but also reflects the therapeutic or pathological associations between them.

TABLE IV. EFFICACY ANALYSIS

Age group	Curative effect	Test group (N=53)	Control group (N=53)	p-value
Young	Cured	17(81.0)	14(87.5)	0.6796
	Very effective	3(14.3)	1(6.3)	-
	Effective	1(4.8)	1(6.3)	-
	Not effective	0	0	-
	Cured+very effective	20(95.2)	15(93.8)	1
Middle-aged and elderly	Cured	32 (100.0)	29(78.4)	0.0059
	Very effective	0	5(13.5)	-
	Effective	0	3(8.1)	-
	Not effective	0	0	-
	Cured+very effective	32 (100.0)	34(91.9）	0.243

To deeply mine the information embedded in the knowledge graph, we applied a graph convolutional network (GCN) to normalize the adjacency matrix and used a T5 mini-model to fuse the GCN-obtained representations with word vector graphs. Through this approach, we analyzed the association between JingFang and various diseases and explored the potential therapeutic effects of JingFang for influenza-like illnesses using the K-means clustering algorithm.

To validate the knowledge graph analysis results, we conducted a randomized controlled clinical trial in China. The trial enrolled 106 patients with influenza-like illnesses, and the results showed that the cure rate in the JingFang combined treatment group (92.5%) was significantly higher than that in the control group (81.1%), especially among the middle-aged and elderly population. Subgroup analysis of the clinical data revealed that JingFang had a more pronounced therapeutic effect on middle-aged and elderly patients aged 34 and above, which was consistent with the knowledge graph analysis results. However, the knowledge graph did not capture this age-related difference in efficacy, and future work may consider incorporating demographic information into knowledge representation and analysis.

The innovation of this study lies in proposing a novel framework for evaluating therapeutic efficacy by combining knowledge graphs with clinical trial results, thereby enhancing the understanding of drug treatment effects. This not only provides new analytical tools for similar drug development but also improves the efficiency and accuracy of drug development by systematically validating literature efficacy data and integrating it with actual clinical trial results. Additionally,

applying a knowledge graph to evaluate the therapeutic effects of traditional Chinese medicines like JingFang is an innovative and unique approach, bringing new perspectives to this under-explored field.

In terms of technical implementation, we constructed a multi-layered knowledge graph by extracting relevant data from a vast amount of biomedical literature and using automated text-mining tools to identify key drug and disease entities and their relationships. With the aid of graph convolutional network processing, we could capture complex associations between entities and discover drug combinations with similar therapeutic effects through clustering analysis. This multi-layered knowledge graph comprehensively presents the relationships between drug components and diseases, and reveals the potential therapeutic effects of different components on specific diseases, laying a theoretical foundation for clinical trials and drug development.

However, this study also has some limitations. First, the accuracy of clustering analysis depends on the quality and completeness of the literature data, and biases and omissions in the literature may affect the accuracy of the results. Second, the sample size of the clinical trial is relatively small, which may impact the stability and generalizability of the statistical results. Future work should expand the sample size and utilize more independent data sources to validate and optimize this integrated analysis method.

Furthermore, an important extension of this study is the implementation of our knowledge graph method and clinical trial integration model as a practical software system. We have designed a prototype system called "KG-TCM Efficacy Analyzer", a web-based application developed using a Python backend and React frontend. The system's main features include knowledge graph construction and visualization, efficacy analysis, clinical trial data integration, and results presentation with automatic report generation.

We plan to deploy and test this system in real-world environments such as pharmaceutical research companies, traditional Chinese medicine hospitals, and drug repositioning studies. Through these practical applications, we expect to accelerate the drug discovery process, improve the accuracy of efficacy predictions, and promote the modernization of traditional Chinese medicine research.

To assess the system's practicality, we also plan to conduct a System Usability Study (SUS). This study will recruit professionals including pharmacologists, clinical researchers, and TCM practitioners, using a standardized SUS questionnaire to evaluate aspects such as the system's ease of use, learnability, efficiency, and user satisfaction. We anticipate that an intuitive user interface, clarity in result interpretation, integration with existing workflows, flexibility in data input, and system responsiveness will be key usability factors.

By focusing on these usability aspects, we aim to develop a system that is both powerful and user-friendly, thereby promoting its widespread application in real research and clinical settings. This transition from theoretical research to practical application will not only further validate the value of our proposed knowledge graph method in evaluating the efficacy of traditional Chinese medicines, but also enhance our understanding of drug mechanisms of action, providing a robust decision-support tool for future drug development. By integrating knowledge graph analysis with clinical trial results, we can more accurately evaluate the therapeutic efficacy of drugs like JingFang for conditions such as influenza-like illnesses, ultimately providing scientific evidence for clinical application and promoting the modernization of traditional Chinese medicine evaluation.

V. CONCLUSION

This study introduces a novel approach to drug efficacy analysis using a knowledge graph (KG) methodology, complemented by a randomized controlled trial to validate the effectiveness of JingFang in treating influenza-like illness. By extracting and analyzing drug-disease relationships from the literature, a comprehensive KG was constructed, serving as the foundation for the efficacy analysis. The trial results indicated a significantly higher cure rate for the JingFang group, especially among middle-aged and elderly patients, compared to the control group.

This innovative approach not only provides a powerful tool for predicting drug efficacy but also combines traditional clinical trial results with advanced data analysis techniques, thereby enhancing the accuracy and reliability of drug efficacy evaluations. This method holds potential for broad application in drug development and repurposing, particularly in the context of Traditional Chinese Medicine.

While this study focused on JingFang, the approach we developed - combining knowledge graph analysis with clinical trial validation - is generalizable and can be readily applied to evaluate the efficacy of other drugs, both in traditional Chinese medicine and Western pharmaceuticals. This versatility makes our method a valuable tool for drug discovery and development across various therapeutic areas.

Future work could focus on several aspects to further enhance and expand this approach:

1) Incorporating more diverse data sources: Integrating data from electronic health records, genomic databases, and other real-world evidence could enrich the knowledge graph and improve prediction accuracy.

2) Enhancing the machine learning models: Exploring more advanced graph neural network architectures or developing hybrid models that combine different AI techniques could potentially improve the performance of our system.

3) Expanding to multi-drug interactions: Extending the framework to analyze the efficacy of drug combinations and potential drug-drug interactions could provide valuable insights for personalized medicine.

4) Longitudinal studies: Conducting longer-term follow-up studies to assess the long-term efficacy and safety profiles of drugs identified through this approach.

5) Cross-cultural validation: Applying this method to evaluate drug efficacy across different populations and

healthcare systems to ensure its generalizability and identify any cultural or genetic factors that may influence drug responses.

6) Actual development and deployment of the "KG-TCM Efficacy Analyzer" prototype system, followed by a comprehensive usability study based on the outlined plan. We will continuously optimize the system based on user feedback to improve its applicability and efficiency in real-world environments. Additionally, we plan to expand the system's functionality to support more types of drugs and diseases and explore the possibility of integrating it with other existing drug development tools.

By addressing these areas, we can further refine and expand the capabilities of our knowledge graph-based approach, potentially revolutionizing the way we discover, develop, and evaluate drugs in both traditional and modern medical contexts.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

AUTHOR'S CONTRIBUTION

Conceptualization and methodology, Y. L., Z. J., Z. H., W. G., G. C., and Y. J.; software, validation, and original draft preparation, Y. L., Z. J., Z. H., and W. G.; review and editing, G. C. and Y. J.. All authors have read and agreed to the published version of the manuscript.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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