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A brief overview of traditional Chinese medicine prescription powered by artificial intelligence

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Highlights

1. This paper presents a brief overview of traditional Chinese medicine (TCM) prescription powered by artificial intelligence, which introduces research progress on three aspects, TCM prescription mining, TCM prescription or herb knowledge base and TCM prescription discovery.
2. Taking the TCM herb recognition as a toy example, we showcase the capability of artificial intelligence in assessing TCM herbs.

REVIEW

Abstract

Traditional Chinese medicine prescription is one of the treasures of traditional Chinese medicine (TCM). There are tens of thousands TCM prescriptions accumulated in the past thousands of years, corresponding to different diseases, symptoms and therapeutic goals. The correspondences are so complicated that there is an urgent need to leverage new technologies such as artificial intelligence (AI) to analyze, understand and utilize them effectively. In this paper, we present a brief overview of this direction, where current research progress on TCM prescription powered by AI is summarized. Our summarization focuses on three aspects, TCM prescription mining that aims at understanding the TCM prescription, TCM prescription or herb knowledge base construction that aims at extracting knowledge to support the TCM prescription-related study, and TCM prescription discovery that aims at utilizing AI technologies to further energize TCM. It is encouraging to see that steady progress in this direction has been made recently. Besides, a toy experiment on image-based TCM herb recognition by using convolutional neural networks is also conducted. It basically verifies that it is promising to use AI technologies to address challenging tasks in TCM. We also point out several research topics that could be cooperatively performed by researchers from the two disciplines.

Keywords: Traditional Chinese medicine prescription, Artificial intelligence, Knowledge base, Convolutional neural network, Herb recognition

Abbreviations: TCM, Traditional Chinese medicine; COVID-19, coronavirus disease 2019; AI, artificial intelligence; SVM, Support Vector Machine; CNNs, convolutional neural networks; RNNs, recurrent neural networks; NLP, Natural Language Processing; SGD, stochastic gradient descent; CPU, Central Processing Unit; GPU, Graphics Processing Unit.

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Background

Traditional Chinese medicine prescription is an important part of the traditional Chinese medicine (TCM) diagnosis and treatment. It plays a significant role in the prevention and treatment of diseases for thousands of years, even acted as a unique and indispensable role in many scenarios. For example, Longkui (*Solanum nigrum L.*) can control cancer cell proliferation and cancer progression by inducing autophagic and apoptotic cell death [1]. Recently in the battle with COVID-19, Chinese medicine prescription also has shown its effectiveness in preventing patients from becoming serious worldwide [2,3]. However, TCM prescription is also facing some challenges and opportunities as following.

First, TCM prescription is made up of certain herbs with different doses. Their formation depends on not only the personal thinking of the doctors' diagnosis and treatment, but also the rich practical experiences. In other words, the effectiveness of treatment of diseases in TCM is largely influenced by the experience of TCM practitioners. Therefore, the inheritance of TCM prescriptions from ancient prescriptions and some famous TCM doctors which is named "the knowledge inheritance of seasoned doctors" is of great significance. In addition, TCM prescription follows TCM prescription composition rules to the "monarch-minister-assistant-guide" (Jun-cheng-zuo-shi) composition. But the interpretation of the different disease syndrome treated with formula corresponding to disease syndromes is abstract and intricate, single analysis is difficult to accurately obtain the relationship between the TCM prescription and disease.

Second, there are ten thousands TCM herbs, and every TCM herb has many different attributes. In particular, two TCM herbs with similar names may have quite different type of effect. Taking Daxueteng (*Sargentodoxa cuneata (Oliv.) Rehd. et Wils.*) and Jixueteng (*Spatholobi Caulis*) for example, The Daxueteng has an effect of creating circulation and dispelling pathogenic wind, which is used when the patient suffers tortures from rheumatism or cramps. However, Jixueteng has an effect of supplementing blood and dredging collateral, which is used when the patient suffers numbness and paralysis. Moreover, the same herb with different doses may have the opposite effect. For instance, routine use of Baizhu (*Rhizoma Atractylodis Macrocephalae*) can treat diarrhoea, and large doses can relieve defecation. Therefore, it is necessary to establish a herb knowledge graph to help TCM doctors checking leakage and fill the vacancy.

Third, it is difficult to analytically mine the TCM prescription. Because of the characteristics of the TCM's theoretical system and the complexity of TCM herbs, the material basis and the action mechanism and its metabolic process of the TCM prescription are somewhat inadequate. At present, less than 1% of the TCM herbs have been studied on their chemical composition. It is difficult to make a purposeful choice because of no clear one-to-one correspondence between the pharmaceutical composition and pharmacological action.

To overcome the challenges aforementioned, one of the most appropriate ways perhaps is by using the rapid developed artificial intelligence (AI) technologies. In recent years, AI technologies have made remarkable progress and have been successfully applied to many fields. With the successful applications of deep learning, AI especially perceptual intelligence has an impressive record of achievement and has been more and more powerful. For example, image recognition technology is used in many areas, such as clinical pathological analysis [4], TCM inspection of tongue diagnosis [5], herbal medicine identification [6] and so on. The AI technologies can be broadly classified as traditional machine learning and deep learning technologies, which is mainly based on multi-layer neural network. While traditional machine learning algorithms include classification algorithms such as decision tree, Support Vector Machine (SVM), Naive Bayes, random forests [7], algorithms for correlation analysis such as Apriori and FP-Growth [8], algorithms for clustering such as k-means and Clara [9], and algorithms for data estimation such as the EM algorithm [10]. The TCM participants also introduce AI into the research of the TCM prescription, where some important progress has been made in several aspects.

Both TCM and artificial intelligence are rapidly developed disciplines in the past years. This paper focuses on a specific field in TCM, namely TCM prescription. It is different from ref. [11] which has a review about quantitative knowledge presentation models of TCM, instead we aim at presenting a brief overview of research efforts on the TCM prescription powered by artificial intelligence. The paper is organized as follows. Firstly, we present a short overview of artificial intelligence, including its development history and present situation. Then, we introduce current progress of TCM prescription by utilizing AI technologies. In the following, a toy experiment on TCM herb recognition is given. At last, we summarize this paper and give a few directions worthy of further investigation in future.

Brief overview of artificial intelligence

As a definition given by IBM, AI enables computers and machines to mimic the perception, learning, problem-solving, and decision-making capabilities of the human mind. The concept is firstly proposed in the year 1956 at the Dartmouth conference. Over the past six decades, the development of AI technologies experiences several ups and downs as follows.

The first upsurge is from the year 1956 to the early 1970s. During the times, logic operation, deductive reasoning, syllogism and prolog logic programming language become the representative ways and methods. Despite progress on these field made, the capability of AI is very limited such that it even could not correctly perform the bitwise exclusive operation. Thus, the pessimistic view gradually dominates AI-based research.

With the development of computer algorithms, AI quickly becomes hot again and enter its second research boom. The most representative outcome during this period is the invention of the back propagation algorithm, which enables the learning capability of artificial neural networks. Meanwhile, developing an expert system for a specific field is becoming a popular means for embedding intelligence into practical systems. A lot of research progress has been made in this direction. However, in their application, it is observed that the human world is so complicated that it is difficult to develop an expert system to cover all the possible cases and clearly distinguish them even for a narrow field. AI then become cold again in the late 1980s.

From the 1990s to middle of the 2000s, statistical machine learning methods gain a significant improvement. Many classification-based, clustering-based and regression-based methods have been proposed and applied to many fields. More and more attention has paid to AI technologies again. Since the year 2006, the invention of deep neural network initializes a new wave of artificial intelligence boom. Thanks to the availability of big data and the improvement of computer hardware, deep neural networks, or saying artificial neural networks with many hidden layers, exhibit its superiority in approximating complex machine learning and pattern recognition tasks. The performance of large-scale classification, detection, segmentation has been largely improved [12,13]. Typical deep neural network models include convolutional neural networks (CNNs) that are good at processing visual tasks, and recurrent neural networks (RNNs) that is suitable for handle sequential tasks including NLP and speech recognition. Besides, AI infrastructures such as large-scale dataset, knowledge bases or graphs are all received much development. These outcomes would have a broad application prospect in TCM.

Brief overview of AI-based TCM prescription

In this section, we introduce current progress of TCM prescription by utilizing AI technologies. It includes: 1) TCM prescription mining. 2) TCM prescription or herb knowledge base construction. 3) TCM prescription discovery.

Mining the TCM prescription

Mainstream studies mainly focus on detecting the correlation among herbs from ancient books, as well as finding the relationship between the TCM prescriptions and the diseases or the symptoms from the literature and medical records. Those studies aim to assist TCM doctors to compose prescriptions. The methods of mining the TCM participants whose core is leveraging term co-occurrence are including association rules, probabilistic model, classification model, clustering algorithm and so on. For example, the authors used the improved Apriori algorithm to find 18 high-frequency herbs including Gancao (*Licorice*), Jueminzi (*Cassia Twig*), Zao (*Jujube*) and Rensen (*Ginseng*), etc. and 52 herbs combinations such as *Licorice-Cassia Twig*, *Jujube-Ginger* and *Ginger-Licorice*, etc [14]. Ref. [15] used frequent itemsets to get statics of herbs from "*Treatise on Febrile Diseases*" (Zhubing Yuanhoulun) and "*Synopsis of prescriptions of the Golden Chamber*" (Jinkui Yaolue), where 43 typical herbs including Gancaogen (*Glycyrrhizae Radix Rhizome*), Shengjiang (*Zinggiberis Rhizome Recens*), Suanzao (*Jujubae Fructus*), etc. and 35 traditional herb pairs were obtained. In [16], the Apriori algorithm was employed for producing association rules of "*Shennong Classic of Materia Medica*" (Shennong Bencaojing) and the confirmed 120 resulting rules that described the intrinsic relationships between herbal property. Dan et al. [17] collected a lot of medical records and adopted the SVM classification model to classify all the data to construct the relationship between TCM prescriptions and diseases. The authors of ref. [18] proposed a novel probabilistic model to jointly analyze symptoms, diseases, and herbs. With this model, we could obtain the typical symptom groups associated with disease conditions, the typical herb groups associated with disease conditions and the relation of symptom groups and herb groups.

The multi-target therapy theory of TCM, characterized by uncertainty and ambiguity, is essentially different from the "one-target" precision treatment of modern medicine. Following the "monarch-minister-assistant-guide" composition, the authors of ref. [19] proposed a ranking-based clustering algorithm to mining the symptoms of four types of herbs. Ruan et al. [20] developed a bipartite embedding model to detect relations of herb-herb and herb-

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symptom with the help of a heterogeneous network. In [21], the authors built the platform FangNet which used the PageRank algorithm to ranks all herbs on their relative topological importance to the prescription. These research efforts have shown promising results by using AI technologies to analyze the off-the-shelf TCM records and prescriptions.

Constructing TCM prescription or herb knowledge base

Noting TCM knowledge consolidation is the first step for applying AI technologies, there are some studies on building a knowledge base of prescriptions or herbs. For example in [22], the authors proposed an item for describing the herbal origin, including basic herbal category (e.g. English name, Latin name, and family), effective parts, and clinical effects of the herbs. Miao et al. [23] shown the steps and tools for building the prescription ontology. It is implemented by extracting the core concepts, concept descriptions, relations between the two entities and the constraints of the relationship in the field of TCM.

With the continuous efforts made, there are some TCM prescription knowledge bases available. For example, knowledge base of TCM prescriptions (http://kb.tcm.cnki.net/TCM/TCM/Index?dbcode=ZYFF) which includes more than 20,000 prescriptions extracted from nearly one hundred ancient and modern medical books (such as Prescriptions, Tangtou Gejue, and so on). The knowledge base provides many properties, e.g., name, source, function, preparation method, etc. Wei et al. [24] proposed a deep learning-based model to obtain the distributed embedding of TCM herbs, which was helpful to facilitating doctors composing prescriptions. The prescriptions were from TCM medical records and prescription knowledge base consisting of 85166 prescriptions. Meanwhile, there also are some herbs knowledge bases. For example, knowledge base of TCM herbs (http://kb.tcm.cnki.net/TCM/TCM/Index?dbcode=ZCYF), it describes every herb in detail on its map, nature and flavor, meridian, efficacy, form, traits, usage, dosage, origin, the chemical formula of ingredients, pharmacological effects, toxic and side effects, representative prescriptions, classic compatibility, storage methods and so on. These infrastructures would be critical when using computer-aided methods to analyze TCM.

TCM prescription discovery

The significance of TCM prescription discovery is twofold. First, it broadens the notion of what existing TCM prescription can do. Second, it could be a feasible way to detect novel prescriptions. Herb recommendation can be a part of TCM prescription discovery. In [25], the authors utilized graph convolution networks (GCNs) on symptom-symptom, symptom-herb, herb-herb graphs to construct the symptom embedding and herb embedding, from which herb recommendation can be established. Wang et al. [26] shown an herb recommendation system. It was based on a Linear Discriminant Analysis (LDA) based model for the herb representation by considering co-occurrence and the relation between the symptoms and herbs. This data-driven herb recommendation method can help TCM participants make scientific treatment prescriptions. Such as in [27], the authors proposed a topic model which generates a new prescription by mining TCM theories from 33,765 prescriptions. Other researchers also [28] built symptom-herbs sequences based on a number of therapy records and treatment guidelines in the TCM classics composed by outstanding TCM practitioners, and adopt an end-to-end paradigm to generate TCM prescriptions based on textual symptom.

The concept of “network pharmacology” was proposed by Hopkins et al [29]. It is transferred from the “one target, one drug” paradigm to the “network target, multi-component drug” strategy, which is suitable for “monarch-minister-assistant-guide” composition of TCM prescription. In network Pharmacology, Li et al. [30] developed a TCM-NP platform, where a network target is constructed to illustrate the associations between the herbal formulae and specific diseases. The TCM-NP platform is helpful in clarifying the mechanism of TCM prescription. Li et al. [31] shown a network target-based strategy to illustrate the significant progress made in TCM, with artemisinin and arsenic trioxide being two of the outstanding representatives of these achievements. However, to date the mechanism of widely used TCM herbal formulae still remains an open question. Network target-based approaches have been determined to integrate ingredient contents and their interactions with corresponding targets, which can assist in clarifying the traditional uses, as well as the exploration of the pharmacological activities and modern indications of TCM. There are researchers who used the network pharmacology to investigate the relation of the interventions and different symptoms. Yang et al. used network pharmacological methods to investigate the underlying molecular mechanisms of LianXia NingXin formula to treat coronary heart disease and disease phenotypes [32].

A toy experiment on TCM herb recognition

To showcase the capability of artificial intelligence in assisting TCM prescription, in this section we present a simple and easy-to-understand toy experiment on TCM herb recognition. In the experiment, we use the TCM herb image and its name category as input and output, respectively. Several typical convolutional neural networks (CNNs), one of the most popular kinds of artificial intelligence models, are chosen as recognizers. Our objective is to simulate the human ability in recognizing typical TCM herbs.

We briefly introduce the dataset used in the experiment at first. It is the Paddle Chinese herbal medicine dataset, which consists of 902 colored images of five classes, i.e., Jinyinhua (*Flos Lonicerae Japonicae*), Huaihua (*Sophora japonica L.*) Gouqi (*Lycium barbarum L.*), Dangshen (*Codonopsis radix*) and Baihe (*Bulbus LiLii*), as shown in Figure 1. The images cover different views and capturing conditions such that even in the same class, some images also exhibit significant differences. We split the dataset into training and validation sets, respectively for model training and preliminary verification. There are 771 and 131 images in the training and validation sets. The dataset is publicly available via the link (https://aistudio.baidu.com/aistudio/datasetdetail/70575).

Six popular CNN models are chosen to perform the classification task. They are VGG-16, GoogleNet, ResNet-50, MobileNetV1, MobileNetV2 and ShuffleNetV2. Readers can refer to [33] for details of the CNN architectures. Before fed into the network, we resize all the image to 256*256 and divide the pixel values of each image by 255 so they are in the [0, 1] range. To train the models accommodated to this specific task, we use stochastic gradient descent (SGD) for 200 epochs. The learning rate is fixed to 0.001 and the batch size is set to 16. We use random flipping and random changing of brightness as the data augmentation strategy. The model with the highest validation accuracy during training is picked out as the accuracy. All the experiments are conducted using PaddlePaddle, an open-source deep learning platform. The code can be accessed via the link (https://aistudio.baidu.com/aistudio/projectdetail/17762).

The experimental results are presented in Table 1. As can be seen, each of the six models can report satisfactory accuracy in the validation set, where approximately 90% of images can be corrected identified. It is also seen that running the inference on GPU is much faster than on CPU, indicating that GPU is suitable for executing artificial intelligence programs. On the other hand, different models have quite different model parameters (Params), memory cost (Memory) and computational cost (FLOPs). We can flexibly deploy this artificial intelligence service to different scenarios according to their resource condition.

Note that the models have no knowledge about TCM herbs before. All the recognition capabilities are purely learned from the training set. That is, we teach the models by using the training images and their category labels. When merely 771 samples are seen, each model is able to correctly distinguish most of them, showing its superiority in learning from the experience. We believe if there are more labeled data available, an even better accuracy would be obtained. The code is also available at the Baidu AI studio platform. Readers can follow the pipeline above the built their own recognition models, or create models dedicated to their personal data and tasks.

Jinyinhua (金银花) *Flos Lonicerae Japonicae* | Huaihua (槐花) *Sophora japonica L.* | Gouqi (枸杞) *Lycium barbarum L.* | Dangshen (党参) *Codonopsis radix* | Baihe (百合) *Bulbus LiLii*

Figure 1. Images of the five classes in the Paddle Chinese herbal medicine dataset

Table 1. Performance comparison of different CNN models as well as their inference speed and resources consumption

Model	Speed (FPS)		Resource Consumption			Accuracy on Validation Set
	GPU	CPU	Params(M)	Memory(MB)	FLOPs(M)	
VGG-16 (2014)	60.5	4.9	134.28	109.39	15479	0.875
GoogleNet (2014)	157.4	8.9	5.61	30.03	1503	0.893
ResNet-50 (2016)	78.7	5.7	23.51	109.68	4109	0.915
MobileNetV1 (2017)	157.4	17.4	3.21	57.71	582.9	0.903
MobileNetV2 (2018)	112.4	4.03	2.23	74.25	312.8	0.892
ShuffleNetV2 (2018)	93.8	24	1.26	20.85	149.63	0.886

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Summary and future directions

In this paper, we briefly summarize the TCM and AI combined research efforts. It is mainly on three aspects: TCM prescription mining, TCM prescription or herb knowledge base construction, and TCM prescription discovery. It is worthy to note that our summarization only covers a small portion of research efforts connecting the two disciplines. As stated at the six hundred and seventy-fourth Xiangshan Scientific Conference held on Sept. 2020, TCM shares many commonalities with AI in thinking mode. Both can be viewed as data-driven methods. TCM diagnosis and prescription are built upon clinical data accumulated. The quality of data plays a crucial role with respect to the outcome of medical activities. Besides, AI has been proved to be able to improve the effectiveness and reduce the cost of medical activities, provide accurate decision support, etc. More importantly, it can provide unbiased and reproducible results in many circumstances. To this point, AI would be an effective means to further improve the clinical decision-making capabilities of TCM. It is not surprising that more and more work in this direction would appear in the near future.

Looking back on the past years, the research of TCM prescription has made remarkable progress. On one hand, it is owing to the support of national policy, based on which many TCM projects are performed. On the other hand, it benefits from the rapid development of AI technologies. Generally speaking, current studies of TCM prescription powered by AI technologies are mainly focused on two aspects: the first is using NLP and data mining technologies to extract knowledge from the experience of TCM practitioners including classical works and medical records, which would generate tools that can facilitate computer-aided analysis of TCM. One typical outcome is different kinds of knowledge graphs, e.g., TCM prescription -- diseases knowledge graph, TCM prescription knowledge graph and herb knowledge graph. The other is the application of network pharmacology in TCM prescription to assist new TCM prescription discovery, which is shown to be an effective means in the literature.

Along with the advancement of TCM prescription research made, we deem that there are two directions worthy of paying attention to in future.

Quantitative research on the does of herbs and their functions

As mentioned in the introduction, the function of the same medicinal material varies with different doses. In current herb knowledge graph, the knowledge of the function change with different does is far from enough. According to the patients' follow-up records, it is an open issue to discover the relationship between the herb dosage and its effect on patients. A number of machine learning or deep learning technologies can contribute to this task. For instance, causal inference based on graph neural networks (GNN) would be a feasible way.

The change of herb pharmacology with different properties

As natural crops, one herb may have different clinical properties because of the differences in sunshine duration, the place of origin, handling methods and so on. For the same herb with different properties, whether there are some changes of the material basis, the action mechanism and its metabolic process and how to quantitate their influences upon the patients. It still remains an open issue on network pharmacology that requires researchers from the two fields studies cooperatively.

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