

# Visual Analysis of Application and Development Trend of Agarwood Based on CiteSpace

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**Abstract** The Chinese traditional medicine, agarwood, is a commonly used medicine for regulating qi, which has many clinical applications because of its unique curative effect. In this study, CiteSpace software was used to visually analyze the application and development trend of agarwood in the literature from CNKI website in the period of 2007–2022. The analysis results showed that the research on agarwood has basically formed core groups of authors, and universities and their affiliated hospitals are main publishing institutions. Moreover, in this study, several research directions of agarwood were also summarized, including clinical research, chemical composition, structural identification and quality standards, showing that agarwood has rich and flexible application prospects in many aspects. On this basis, several suggestions were put forward: strengthening the cooperation between universities and research institutes and building a scientific research cooperation community, and promoting the combination of clinical research and laboratory research.

**Key words** Agarwood; CiteSpace; Knowledge graph; Visual analysis; Chinese medicine; Traditional Chinese Medicine (TCM)

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The Chinese traditional medicine, Agarwood, also known as Mixiang, refers to the medicinal wood of *Aquilaria sinensis*, a plant of Thymelaeaceae<sup>[1]</sup>, has a good reputation of "the first of all incense" and "gold in medicine". Agarwood has always been valued by doctors. As a common clinical medicine, its application history has been thousands of years. The clinical application of Agarwood was first seen in the medical book of the Liang Dynasty in China, *Supplementary Records of Famous Physicians*, and its author Tao Hongjing listed it as a top grade in the Volume of Wood<sup>[2]</sup>. Agarwood is spicy, warm, and can promote qi circulation and relieve pain, nausea and asthma. In ancient times, it was commonly used to treat symptoms such as abdominal distension, stomach coldness, nausea, and difficulty breathing<sup>[3]</sup>.

## Current Research Status of Agarwood

Modern research on agarwood can be traced back to 1955, when Li Weipu used agarwood in combination with other medicinal herbs to treat chronic myeloid leukemia<sup>[4]</sup>, opening a chapter in agarwood research since the founding of New China. For decades, scholars have studied agarwood in various aspects. Before 2007, the research direction mainly focused on clinical application, such as observing the curative effect of agarwood preparation on diseases and summarizing the clinical prescriptions of famous and old Chinese medicine practitioners. Based on the therapeutic charac-

teristics of agarwood, the therapeutic methods for diseases such as spleen and stomach diseases<sup>[5-6]</sup>, hiccup<sup>[7]</sup>, coronary heart disease<sup>[8]</sup> and insomnia<sup>[9]</sup> were put forward. Meanwhile, the physical and chemical properties of agarwood were preliminarily explored from the chemical point of view, and it was found that agarwood had antioxidant activity<sup>[10]</sup>, antibacterial activity<sup>[11]</sup> and inhibition of central system activity<sup>[12]</sup>.

## Visualized Analysis of Scientometric Analysis of Agarwood

In order to explore the new trend and direction of agarwood research, we made a scientific review of the scientific literature on agarwood in recent 15 years (2007–2022).

Bibliometric analysis methods and information visualization analysis were applied to study related published documents. Bibliometric research can evaluate the research in specific fields obtained in a period of time<sup>[13]</sup>. Information visualization analysis is a tool for detecting and displaying the bibliometric results. It is a good choice to employ information visualization text analysis software to visualize bibliometric results<sup>[14]</sup>. CiteSpace is one of the most popular knowledge mapping tools, which can present relevant information of literature in a clear and intuitive knowledge map<sup>[16]</sup>. All the research documents of agarwood in this study were published by CNKI database. Based on the results of CiteSpace analysis, according to different analysis parts, four aspects were obtained: growth trend analysis, keywords and keyword clustering analysis, author analysis and institutional analysis.

### Analysis on the characteristics of annual number of published papers

The analysis on retrieved documents for the annual number of published papers can help understand the development status of a certain field<sup>[17]</sup>. Documents were retrieved from CNKI with the theme of "agarwood" and a time range of 2007–2022. Only

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"academic journals" and "theses" were selected, while conferences, newspapers, and books were ignored, and unrelated papers were manually reviewed and deleted. In the end, 1 174 valid Chinese literatures were retrieved. The analysis of the annual number of published papers, as shown in Fig. 1, exhibited that the evolution of the annual number of published papers related to agarwood mainly experienced three stages. The first stage was from 2007 to 2009, with a relatively low number of 42 papers per year, and the research related to agarwood was still in the exploratory stage. The second stage was from 2010 to 2011, with a significant increase in the number of published papers on agarwood, showing a compound growth rate of 36.4%. The research on agarwood continued to heat up, and more and more scholars entered the field of agarwood. The third stage was from 2012 to 2022, with an average annual number of published papers reaching 82.6 papers, about twice that of the first stage. In this stage, the number of papers published in each year was over 65, and there was a sudden increase in some years. In 2017, it reached a statistical peak of 101 papers, and agarwood has gradually become one of the research hotspots. Overall, the annual number of published papers on agarwood shows an upward trend, with the most significant increase since 2010. The research on agarwood has gradually attracted the attention of many scholars.

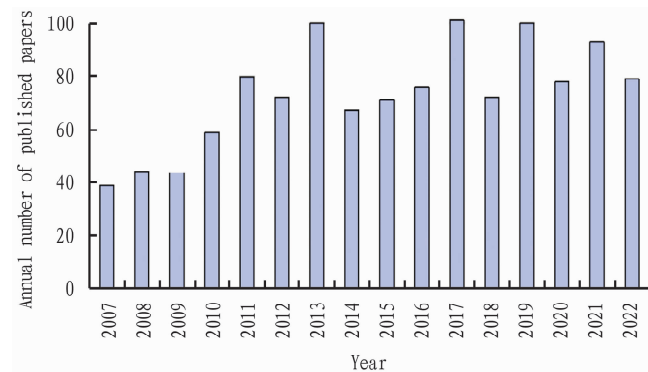


Fig. 1 The number of papers published on Chinese medicine agarwood in CNKI from 2007 to 2022

### Keyword co-occurrence analysis

Keywords are the core essence of an article. By collecting keywords from all documents within a time slice, we can analyze the research hotspots in this field during the period, and thus predict future research directions<sup>[18]</sup>. When analyzing keywords, Fig. 2 was obtained by selecting "By Degree" for Keyword Term Overlay Labels and setting the Threshold to "7". There were 192 nodes (N) and 225 lines (E), and the network density was 0.012 3. Each individual node represented a keyword, and the frequency of keyword occurrence was proportional to the size of the node, and the lines represented the connection between keywords. Large nodes represented their importance in the research field, and tight connection symbolized a higher frequency of co-reference.

### Keyword clustering analysis

In order to perform clustering analysis on keywords, CiteSpace clustering function was adopted to cluster the keywords

of agarwood, and nine clusters are shown in Fig. 3. The automatically generated groups were integrated, and the nine clusters were further divided into following categories:

- (1) Clinical research; including the clinical application and observation of agarwood and the research of ethnic medicine.
- (2) Material extraction; including chemical component extraction, structure analysis and structure identification, and component quality standards.
- (3) Structural identification; mainly involving techniques for identifying the quality of agarwood.
- (4) Quality standard; mainly related to the formulation of prescription quality standards.

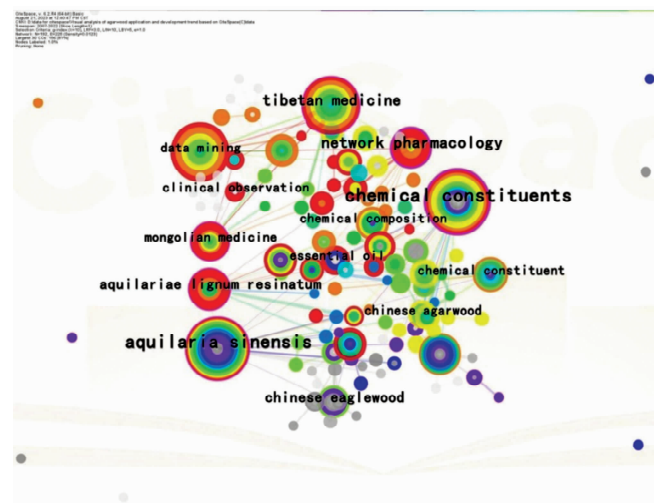


Fig. 2 Keyword co-occurrence

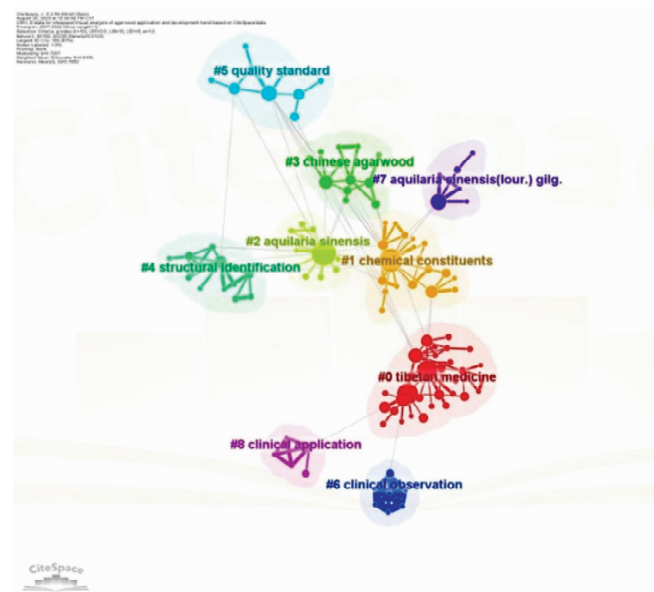


Fig. 3 Keyword clustering

## General Situation Analysis of Research in the Field of Agarwood

Based on Citespace6.2. R4 software and bibliometric method,

this study made a visual analysis on the characteristics, keywords, keyword clustering, authors and institutions of agarwood documents from 2007 to 2022.

### Clinical research

Agarwood is spicy, warm, and serves as an essential medicine for promoting qi circulation, which is widely used in clinical practice. From the co-occurrence analysis of keywords, the keywords "Tibetan medicine", "Mongolian medicine" and "Bawei Chenxiang Powder" could be seen. From keyword clustering, the clustering of "#0 tibetan medicine" could be seen. On the whole, there were not many clinical studies on agarwood from 2007 to 2022, but new treatment methods were also explored. Tibetan and Mongolian medical scholars have made great progress in the study of agarwood, and their research focus is clinical observation and research on prescriptions. From the analysis of related papers, it is known that myocardial ischemia, insomnia, spleen and stomach diseases and stroke (and sequelae) are the diseases that have been studied more.

Myocardial ischemia refers to a pathological state in which the blood perfusion of the heart is reduced, which leads to the decrease of oxygen supply to the heart and abnormal myocardial energy metabolism, which cannot support the normal work of the heart. In the application of myocardial ischemia, Tibetan medicine scholars have made in-depth analysis of many prescriptions. Bawei Chenxiang Powder, a Tibetan medicine, is one of the traditional Tibetan medicines (prescription: agarwood, Semen Myristicae, Fructus Choerospondiatis, travertine, Olibanum, Radix Aucklandiae, Fructus Chebulae, Gossampini Flos)<sup>[9]</sup>, which was recorded in the 1995 edition of *Drug Standard of Ministry of Public Health of the Peoples Republic of China · Tibetan Medicine*. Studies have shown that Bawei Chenxiang Powder can significantly improve the myocardial contraction and relaxation function of acute myocardial ischemia<sup>[20]</sup>, reduce the levels of LDH and CK caused by isoproterenol<sup>[21]</sup>, and has a protective effect on myocardial ischemia caused by pituitrin<sup>[22]</sup>. In addition, the Tibetan prescription, Siwei Lagencaitang Powder has been found to have protective effect on myocardial ischemia reperfusion injury<sup>[23]</sup>, and the Tibetan prescription, Sanshiwuwei Chenxiang Pill has myocardial protective function and slows down the adverse effects of myocardial ischemia on the body<sup>[24]</sup>. These two Tibetan prescriptions are also worthy of attention.

Insomnia is a kind of sleep disorder disease, and long-term sleep disorder can cause serious diseases such as depression, coronary heart disease and hypertension<sup>[25]</sup>. In the application of insomnia, aromatherapy has become a research hotspot. The aromatherapy of agarwood is a kind of therapy that makes agarwood volatilize and absorb into human body to play its role. The aroma of agarwood plays its role through indirect absorption through skin, ear canal inhalation and nasal inhalation<sup>[26]</sup>. The Medication methods can be roughly divided into the methods of aroma sachet, aroma pillow, aromatherapy and aroma bath<sup>[27]</sup>. At present, scientific research shows that agarwood aromatherapy has anti-anxiety and anti-depression effects<sup>[28]</sup>, and its mechanism is related to regulating the balance of multiple nerve pathways and neurotransmitter secretion<sup>[29]</sup>. Lei *et al.*<sup>[30]</sup> treated 120 insomnia patients

with agarwood aromatherapy. The results showed that the total score of PSQI decreased by about 5 points, the sleep efficiency increased by about 15% and the sleep latency was shortened by about 15 min, after three weeks of continuous intervention. Tibetan medicine scholar Miemiecili *et al.*<sup>[31]</sup> made innovations on the basis of single agarwood, and tried to treat primary insomnia by aromatherapy using Tibetan prescription Sanyiwei Chenxiang Powder, and achieved good therapeutic effects.

Stroke is an acute cerebrovascular disease caused by sudden rupture of blood vessels in the brain or blockage of blood vessels that prevents blood from flowing into the brain, resulting in brain tissue damage. Its sequelae also cause great harm to the human body. At present, there is no research focus on the application of agarwood in stroke (and its sequelae). Scholars have explored various treatment methods. For example, according to the rules of accumulation, development and rest based on the three causes of Tibetan medicine, Qinglam, treated post-stroke sequelae using Qishiwei Zhenzhu Pills in the early morning (6:00–8:00), Ruyi Zhenbao Pills in the morning (8:00–10:00), Shibawei Dujian Pills in the afternoon (12:00–14:00), and Ershiwei Chenxiang Pills in the evening (18:00–20:00), with an effective rate of 91.4%<sup>[32]</sup>. In addition, some scholars also used Mongolian prescription Zhachong Shisanwei Pills to treat stroke<sup>[33]</sup>, Jiangni Decoction to treat intractable hiccup of stroke<sup>[34]</sup>, Huoluo Pills to treat hemiplegia<sup>[35]</sup> and Xiaoshuan Zaizao Pills to treat stroke<sup>[36]</sup>.

Generally speaking, the clinical research of agarwood is mostly aimed at a certain prescription/treatment, but there is still a lack of research on physical and chemical effects. Therefore, the analysis of the physical and chemical effects of prescriptions/treatment may be a research direction in the future.

### Chemical composition

Because of the various components and complex components of traditional herbs, the exploration of effective components of traditional Chinese medicine has always been a hot spot in the research of traditional Chinese medicine<sup>[37]</sup>. Many scholars in China and abroad have extracted and analyzed the therapeutic factors of agarwood, and this study selected research which is more valuable to make a statement.

Wang *et al.*<sup>[38]</sup> found a series of key factors of gastric ulcer, including quercetin,  $\beta$  sitosterol, 6, 7-dimethoxy-2-phenethylchromone, 6, 7-dimethoxy-2-[2-(4-methoxyphenyl) ethyl] chromone, and boldine. Feng *et al.*<sup>[39]</sup> found that the extract of peeled stem of agarwood has protective effect on myocardial ischemia through p53-mediated apoptosis pathway. Cao *et al.*<sup>[40]</sup> found that agarwood inhibited cyclooxygenase-1 and -2 in animal myocardial tissue to play an anti-myocardial ischemia role. Li<sup>[41]</sup> found that key factors for treating myocardial ischemia included zingiberone. Meryem *et al.*<sup>[42]</sup> found that agarwood extract (AWE) could heal the anxiety-like behavior and disordered circadian rhythm caused by stress in animals. Bao *et al.*<sup>[43]</sup> found that the anti-anxiety and antidepressant mechanisms of agarwood might be related to the expression of hippocampal neurotransmitters, GluR1, and VGluT1. Lai *et al.*<sup>[44]</sup> found that agarwood extract AA could improve animal depression to a certain extent. Huang<sup>[45]</sup> reported that a series of eudesmane sesquiterpene polymers linked by

furanone spiro could effectively resist inflammation, and chromone-sesquiterpene heteropolymers had anti-renal fibrosis activity. Yang *et al.*<sup>[46]</sup> found that eight 2-(2-phenylethyl) chromone derivatives had anti-inflammatory activity. Pang KokLun *et al.*<sup>[47]</sup> found that agarwood extract ALE could promote the immune response of macrophages by upregulating the levels of pro-inflammatory cytokines and the expression of COX2, which might enhance the innate immune system's resistance to infection. Vasudevan *et al.*<sup>[48]</sup> found that methanol agarwood seeds had a protective effect on nerves and could treat memory impairment and neuroinflammation. Tao *et al.*<sup>[49]</sup> found that agarwood sesquiterpenes could affect the expression of neurotransmitters by regulating the expressions of  $\gamma$ -aminobutyric acid (GABA), 5-hydroxytryptamine (5-HT) and nitric oxide (NO) in the nervous system, thus alleviating oral ulcers. Thi *et al.*<sup>[50]</sup> found that the leaves and stems of agarwood had the characteristics of significantly inhibiting *Staphylococcus aureus*.

It is worth mentioning that studies have shown that agarwood also has therapeutic effects on cancer<sup>[51]</sup>. Nahar *et al.*<sup>[52]</sup> found that agarwood extract had a protective effect on lung cancer. Dahham *et al.*<sup>[53]</sup> found that agarwood essential oil had anti-pancreatic cancer effect. Nurhanan *et al.*<sup>[54]</sup> found that agarwood extract mangiferin had anti-cancer effects. Antonio *et al.*<sup>[55]</sup> reported that agarwood fructan had a protective effect on animal colon cancer. Zainurin *et al.* and Hye Young Park *et al.*<sup>[56–57]</sup> found that the essential oil of agarwood leaves and the alcohol extract of agarwood had therapeutic effects on breast cancer.

Network pharmacology is a discipline that uses bioinformatics and network analysis methods to analyze biological systems, comprehensively elucidate drug action mechanisms, and design multi-target drug molecules<sup>[58]</sup>. Molecular docking technique is a method of drug design that utilizes the characteristics of receptors and the interaction between receptors and drug molecules<sup>[59]</sup>. Combined with the analysis of papers, it is found that the application of network pharmacology and molecular docking technique in the research of chemical constituents of agarwood is very rich, and many papers are based on them. Meanwhile, it is also found that most of the research on chemical constituents of agarwood is to explore and extract therapeutic factors of agarwood. Related research has made gratifying progress, but it only stays in the laboratory research stage, and has not yet formed clinical treatment plans through the research results. It may be a future research direction to construct clinical treatment schemes using the results of chemical composition research.

### Structural identification

Structural identification is mainly about the identification of the quality of agarwood. Fingerprint is a relatively new quality identification method of agarwood. Fingerprints refer to chromatograms or spectrograms that are obtained from certain complex substances, such as traditional Chinese medicine, and DNA and proteins of certain organisms or tissues or cells, after appropriate processing, using certain analytical methods and can indicate their chemical characteristics<sup>[60]</sup>. The fingerprint of high-quality agarwood can be established based on the content of specific components in it, and the fingerprint of low-quality agarwood is different

from that of high-quality agarwood, so the quality of agarwood can be effectively evaluated and high-quality agarwood can be identified. Gao *et al.*<sup>[61]</sup> used gas chromatography-mass spectrometry combined with chemometrics to construct reliable standards including the correlation coefficient of GC-MS fingerprint of natural laminwood and 22 metabolic markers of natural and artificial laminwood, and found that the chemical composition of artificial agarwood obtained by comprehensive excitation method (formic acid + fungal inoculation) was closer to that of natural agarwood than that obtained by chemical excitation method (formic acid), which provides important reference for the quality identification of agarwood and the selection of medicinal agarwood varieties. Wu *et al.*<sup>[62]</sup> constructed a new method of digital chromatography-mass spectrometry fingerprint of agarwood by using HPLC-Q-TOF-MS technique. Agarwood was extracted with ethanol, and determined by HPLC-Q-TOF-MS, and the HPLC-Q-TOF-MS and liquid chromatography-ultraviolet data were collected at the same time, and the chromatogram of liquid chromatography-ultraviolet detection (HPLC-UV) and the total ion chromatogram of high-resolution time-of-flight mass spectrometry (TOF-MS) were obtained. Each chromatographic peak in the chromatogram was identified by accurate mass number, and a digital fingerprint was established, and unique digital information was given for each chromatographic peak. Further, its chemical composition was reflected in a digital form, and the molecular formula was calculated according to the accurate mass and isotope to identify the chemical composition. Tan *et al.*<sup>[63]</sup> identified the quality of agarwood by using hydrogen nuclear magnetic resonance mode, and established the 1H-NMR fingerprint of agarwood, and used a decision-making tree model (AdaBoost-DT) optimized by cluster analysis (HCA), principal component analysis (PCA), partial least squares discriminant analysis (PLS-DA), decision tree (DT) in machine learning identification and adaptive boosting iterative algorithm AdaBoost to perform data analysis and performance comparison.

To sum up, structural identification, especially fingerprint, is still a research hotspot in the field of agarwood because there are a lot of potential technical innovations to be tapped.

### Quality standards

The evaluation of the quality of agarwood preparations is also one of the hot spots. Due to the lack of evaluation methods for a specific preparation, scholars have explored this, in order to improve the quality standards. For example, Zhang *et al.*<sup>[64]</sup> applied thin-layer chromatography (TLC) to identify agarwood, patchouli and *Radix Aucklandiae* in a preparation qualitatively, and used high-performance liquid chromatography (HPLC) to identify agarotetrol in the preparation quantitatively, and an evaluation method of Chenxiang Huaqi Capsules was constructed. The quality standards of some famous agarwood preparations are being explored, such as Xiaoe Zhenbei Powder<sup>[65]</sup>, Tanchuan Banxia Granules<sup>[66]</sup>, Chenxiang Huazhi Pills<sup>[67]</sup>, Quanlu Pills<sup>[68]</sup>, Gongluxiao Capsules<sup>[69]</sup>, Tibetan medicine Jiebai Pills (Capsules)<sup>[70]</sup> and Mongolian medicine Shaosha-7 Pills<sup>[71]</sup>.

To sum up, because there are many prescriptions of traditional Chinese medicine, the components are complex, and a large number of prescriptions of traditional Chinese medicine lack

specific quality standards, it is still a research hotspot in the field of agarwood to predict quality standards in the future.

## Conclusions

Based on bibliometrics, in this study, we searched CNKI Chinese literature and summarized the research progress of Chinese medicine agarwood from 2007 to 2022. The number of papers published by agarwood is generally on the rise. Since 2011, the number of papers published by agarwood has remained above 65, which indicates that the research of agarwood has developed rapidly in the past decade. From the visual analysis, the cooperation between scholars is relatively close, and the embryonic form of core author groups has been formed. The keywords "aquilaria sinensis", "chemical constituents" and "data mining" had a higher frequency. The keyword co-occurrence clustering analysis showed that the research on agarwood focused on four aspects: clinical research, chemical composition, structural identification, and quality standards.

On this basis, the research hotspots in clinical research, chemical composition, structural identification and quality standards were reviewed separately. (1) Myocardial ischemia, insomnia, and stroke are hot topics in agarwood disease research. Ethnic medicine, especially Tibetan and Mongolian medicine, has rich research on the clinical application of agarwood. (2) In terms of chemical research, a considerable number of therapeutic factors have been discovered, greatly enriching the gap in the chemical composition of agarwood, and most of them are based on network pharmacology and the molecular docking technique. (3) Fingerprint has become a widely studied and emerging quality identification method for agarwood, and it will still be a hot research topic in the future. (4) Research scholars have made progress in exploring the construction of quality standards for agarwood prescriptions. Due to the lack of specific quality standards for a large number of traditional Chinese medicine prescriptions, it is expected that quality standards will continue to be a research hotspot in the agarwood field in the future.

Meanwhile, through the review of traditional Chinese medicine agarwood, two problems were summarized. (1) The main force of agarwood publications is universities (and their affiliated hospitals), and the number of paper published by research institutes is significantly lower than that of universities, and the cooperation between research institutes and universities is not close enough. As an important link in the construction of national industry-university-research system, promoting the cooperation between research institutes and universities is conducive to promoting scientific research and technological development. Therefore, future research should consider strengthening the cooperation between research institutes and universities and building a scientific research collaboration community. (2) In clinical research, many prescriptions of traditional Chinese medicine, including Tibetan medicine, Mongolian medicine and some therapies, have been studied, but the mechanism of action has not been deeply analyzed. In terms of chemical composition, new therapeutic characteristics of agarwood have been found, but they have not been used in clinic. Therefore, promoting the combination of clinical research and

laboratory research is the direction that may be considered in the future.

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strengthening and promoting agriculture", and to cultivate a large number of high-quality talents for promoting rural revitalization.

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