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# Analgesic Potential of Sesquiterpenes Derived from Agarwood in Recurrent Aphthous Ulcer

Si-Yu Tao<sup>1,†</sup>, Jing-Kai Fu<sup>1,†</sup>, Sunchuri Diwas<sup>2</sup>, Yi-Nan Zhang<sup>1</sup>, Nan Wang<sup>1</sup>, Yao Yao<sup>1</sup>, Fan-Di Xu<sup>1</sup>, Yang Lin<sup>1</sup>, Zhu-Ling Guo<sup>1,3,\*</sup>

<sup>1</sup>School of Dentistry, Hainan Medical University, Haikou, PR China

<sup>2</sup>School of International Education, Hainan Medical University, Haikou, PR China

<sup>3</sup>Department of Health Management Center, The First Affiliated Hospital of Hainan Medical University, Haikou, PR China

## Email address:

604569033@qq.com (Zhu Ling Guo)

\*Corresponding author

† Si-Yu Tao and Jing-Kai Fu are co-first authors.

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**Abstract:** Background: Oral Aphthous ulcer (RAU) is a common oral mucosal disease, often accompanied by pain affecting eating. In the past, the treatment of RAU has focused on pain relief, but there is no specific drug to treat RAU. Agarwood is one of the most commonly used traditional Chinese medicinal materials in clinic. Pharmacological studies have confirmed that the active ingredient sesquiterpene of agarwood has the effect of relieving pain. Objectives: To explore the mechanism of agarwood in relieving pain of RAU. Methods: The research progress of agarwood in relieving pain was reviewed by referring to the relevant literatures at home and abroad in recent years. Results: The active ingredient sesquiterpene of agarwood relieved the pain symptoms of RAU by affecting the expression of neurotransmitters. The sesquiterpenoids of agarwood can affect the expression of neurotransmitters by regulating the expression of  $\gamma$ -Aminobutyric Acid (GABA), Serotonin (5-HT) and Nitric Oxide (NO) in the nervous system. Based on these, agarwood sesquiterpene has good analgesic effect. Conclusion: Agarwood sesquiterpenoids can relieve pain symptoms of RAU. The role of sesquiterpene in the regulation of neurotransmitters makes it promising to be used as a special drug to relieve the pain and promote the healing of RAU.

**Keywords:** Agarwood, Recurrent Aphthous Ulcer, Sesquiterpene, Pain, Neurotransmitter

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## 1. Introduction

Recurrent aphthous ulcer (RAU), also known as recurrent oral ulcers and recurrent stomatitis, is recognized as the most common oral mucosal disease. A large number of literatures point out that the pathogenesis of recurrent aphthous ulcer may be closely related to viral and bacterial infections, cellular immune dysfunction, abnormal gene expression, genetic factors, food allergy, mental burden and other factors [1]. RAU is usually found on the lips, cheeks and tongue margins. It is usually characterized by the formation of an oval, well-defined ulcer in the oral mucosa over a short period of time, covered with a yellowish false membrane. The mucous membrane around the ulcer is congested, often accompanied

by a strong burning sensation. The disease is recurrent, periodic and self-limiting, and generally heals gradually without scars in about 7 to 10 days. However, it can recur after different intervals, so it has a serious impact on the normal life and work of patients.

Agarwood, a traditional Chinese medicine, is wood containing resins from *Aquilaria sinensis*, a member of the *Daphne* family [2]. Because of its unique fragrance and precious medicinal value, it has been known as the "first of all fragrances" and "gold in medicine" since ancient times [3]. It has been used for centuries in China as a drug to treat respiratory diseases such as asthma and bronchitis, as well as digestive tract diseases such as loss of appetite, vomiting, and diarrhea, because it can reduce cough, sleep disorders, and

relieve pain. *Aquilaria sinensis* cannot form agarwood under natural growth conditions, and only when the plant is traumatized by external stimuli, the resin secreted by *Aquilaria sinensis* near the wound will deposit around the wound or decaying part of the trunk within a few years, resulting in the accumulation of volatile compounds and ultimately the formation of agarwood [4]. Modern studies have shown that the chemical constituents contained in agarwood are mainly sesquiterpenes, 2- (2-phenylethyl) chromone, flavonoids and aromatic compounds [5]. The related pharmacological results showed that agarwood has analgesic and sedative, antibacterial and anti-inflammatory, neuroprotective, antioxidant, antidiarrheal and other pharmacological activities. In this paper, the pharmacological mechanism and analgesic research progress of agarwood were reviewed. This provides a reference for the application prospect of aloes in relieving the pain symptoms of RAU.

## 2. RAU Pain-Causing Mechanism

RAU can often make patients feel severe pain, which is related to the special physiological structure of the oral mucosa. Because there is rich blood supply below the oral mucosa and dense nerve endings are scattered, the oral mucosa has a relatively keen perception of temperature, touch and pain. When ulcers occur, the integrity and continuity of the mucosal epithelium are destroyed, and nerve endings will be partially exposed to the oral cavity. At this time, if cold and heat stimuli and mechanical stimuli of external food debris are encountered, they will be transmitted to the nerve center, thus causing severe pain. Especially in patients with severe ulcers accompanied by infection, oral mucosa nerve endings will be more exposed. The inflammatory response is a core aspect of the body's immune system, a defense mechanism that protects the body from infection and injury. But dysregulated inflammatory responses can disturb homeostasis balance in the body and lead to many chronic inflammatory diseases. Ulcers are a type of inflammatory disorders. In the process of ulcer development, tissues defend against the stimulation produced by various damage factors, but excessive inflammatory response will also cause damage to the body, such as IL-1, IL-6, TNF can cause symptoms of fever, PGE<sub>2</sub>, bradykinin, substance P are related to the production of pain, oxygen free radicals, lysosomal enzymes, NO will cause damage to the body tissues. Pain is further exacerbated by these inflammatory mediators. Therefore, in this case, it is essential to help the body resist the occurrence and spread of inflammation through extrinsic treatments.

Stress and acute psychological factors are well-known to cause stress ulcers. Clinical observations have found that in chronic ulcers, people with long-term mental stress, anxiety, irritability or high mood swings are more susceptible to recurrent aphthous ulcers, and the mechanism may be through the vagus nerve mechanism affecting the secretion of glands, mucosal blood flow regulation. Therefore, relieving the symptoms of wound pain in RAU patients can be mainly considered from analgesic sedation, anti-inflammatory,

anti-infective and promoting healing. Due to the complex etiological mechanism of RAU, there is a lack of unified treatment in clinical practice, but through the continuous exploration of clinical treatment of RAU at home and abroad, it is found that the local treatment, systemic therapy, laser therapy and diet control adopted for patients have a certain effect [6-7]. At present, there are many successful cases of using Chinese herbal medicine to treat RAU and achieve efficacy in clinical practice.

## 3. Agarwood Analgesic Effect

Agarwood is used as analgesic in traditional Chinese medicine. Animal experiments have confirmed that volatile oil of Agarwood can significantly increase the pain threshold of mice and reduce the number of writhing reactions induced by acetic acid in mice, and the results show that Agarwood herbs have a significant analgesic effect [8]. On the other hand, there were significant differences in anti-inflammatory and analgesic effects among different methods of agarwood, and the effect of agarwood produced by natural agarwood method was the strongest. At the same time, in terms of the technique of artificial incense, agarwood obtained by fire drilling incense has the best anti-inflammatory effect, while agarwood obtained by drilling incense has the best analgesic effect [9]. Therefore, agarwood may selectively inhibit and relieve pain to a certain extent, thereby reducing the anxiety and restlessness caused by pain in patients with ulcers, and promoting the healing of ulcer wounds while fully improving the quality of life of patients. In order to screen the effective analgesic parts of agarwood, Xiong used hot plate method and acetic acid-induced writhing method to investigate the effects of each part on the analgesic effect of mice, and screened the effective analgesic parts of agarwood; UPLC method was used to analyze the blood components of the effective analgesic parts of agarwood and explore the material basis of its analgesic effect. The results showed that the petroleum ether fraction and n-butanol fraction of ethanol extract of agarwood were the effective parts of analgesic effect of agarwood. It indirectly reflects that the drug agarwood has an inhibitory effect on both central and peripheral pain. Therefore, agarwood is effective for both severe and dull pain [10].

Modern pharmacological studies have shown that extracts, volatile oils, and sesquiterpenes and their derivatives [11-16] of agarwood have sedative, hypnotic, antidepressant, and antineuritic effects on the central nervous system. Through KEGG pathway analysis, it was found that the pathways related to neuromodulation in agarwood volatile oil were neuroactive ligand-receptor interaction pathway, cAMP signaling pathway, serotonergic neural pathway, cholinergic neural pathway, and dopaminergic neural pathway [17].

## 4. Agarwood Sesquiterpenes Affect the Expression of Neurotransmitters

Gas chromatography mass spectrometry (GC-MS) analyzes

the components of agarwood, in which many active compounds with neuromodulatory functions are found. Sesquiterpenes are the main characteristic compounds in agarwood. GC-MS analysis identified 68 essential oil compounds of agarwood, 51.13% of which were sesquiterpenes, while medicinal chemistry has identified sesquiterpenes as active ingredients with sedative and hypnotic functions in agarwood [13]. Sesquiterpene lactones have been shown to be active components of analgesia and anti-inflammation in a variety of traditional Chinese medicines and have strong anti-inflammatory activity in different pain and inflammation models. However, the molecular mechanisms by which sesquiterpenes in agarwood exert their sedative and hypnotic effects have not been fully elucidated. Neurotransmitters play a critical role in intercellular neurotransmission, and many sedative hypnotics usually exert their pharmacological effects by altering the concentration of neurotransmitters. Experimental studies on the effect of agarwood extract on neurotransmitters have shown that volatile oil and ethanolic extract of agarwood can affect the expression of neurotransmitters and have sedative and tranquilizing active components [18]. It is also suggested that volatile oil and ethanolic extract of agarwood have certain therapeutic effects on insomnia. In addition, the analgesic effect of sesquiterpene lactones in agarwood may be related to the regulation of monoamine neurotransmitters and amino acid neurotransmitters.

#### **4.1. Agarwood Sesquiterpenes Relieve Pain by Regulating $\gamma$ -Aminobutyric Acid (GABA)**

GABA is an important inhibitory neurotransmitter in the central nervous system. Some scholars have combined the alcohol extract and volatile oil of agarwood with pentobarbital sodium for hypnosis experiments, and found that both of them can significantly increase the sleep rate and prolong the sleep time of mice. On this basis, scholars found that agarwood essential oil can significantly increase the expression of GABAA receptor subunits and subtypes in the cerebral cortex, and increase the influx of chloride ions ( $\text{Cl}^-$ ) through GABAA receptors in human neuroblasts. The potential mechanism of agarwood on GABA system was preliminarily elucidated, and it was considered that the sedative and hypnotic effects were related to the regulation of GABAA receptor gene expression by the body [13].

#### **4.2. Agarwood Sesquiterpenes Relieve Pain by Regulating Serotonin (5-HT)**

5-HT is a widely distributed monoamine that has long been considered to have an important role in controlling pain in the peripheral and central nervous systems. Agarwood sesquiterpene lactones significantly down-regulated serum 5-HT levels in C-IBS and D-IBS model rats [13]. The mechanism of sesquiterpene lactones on 5-HT regulation is complex, and the regulation of 5-HT and the therapeutic effect on RAU need to be further developed.

#### **4.3. Agarwood Sesquiterpenes Relieve Pain by Regulating Nitric Oxide (NO)**

NO is considered to be an important inhibitory neurotransmitter, which is mainly found in small and medium-sized neurons in the dorsal root ganglion and trigeminal ganglion, and is the main neuron involved in the transmission of pain information. NO is also an inflammatory factor, and sesquiterpenes of agarwood have a significant anti-inflammatory effect. Sesquiterpenes isolated from Chinese agarwood significantly inhibited NO production by lipopolysaccharide (LPS)-stimulated BV-2 microglia, with up to 96% inhibition at doses of 4.0  $\mu\text{g/mL}$  [15].

## **5. Conclusion**

Agarwood in anti-inflammatory, anti-infective, promote healing have a good effect. Pain is the main symptom of RAU and is the main reason patients seek medical attention. The main active components in the essential oil of agarwood are sesquiterpenes. However, sesquiterpenoids have significant analgesic and sedative effects. Agarwood sesquiterpenoids can affect the expression of neurotransmitters by regulating the expression of GABAA receptor gene, 5-HT and NO in GABA system, and then play a good analgesic effect. Therefore, agarwood essential oil can increase the pain threshold and relieve mucosal pain in patients with RAU. This is undoubtedly of great benefit to patients who suffer from severe pain on the RAU wound affecting work or even sleep. Taken together, agarwood can relieve severe wound pain in RAU patients to a certain extent, and help patients improve their quality of life and sleep, but the specific clinical efficacy still needs further data to confirm.

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