International Journal of Homeopathy & Natural Medicines
2022; 8(2): 29-33
http://www.sciencepublishinggroup.com/j/ijhnm
doi: 10.11648/j.ijhnm.20220802.12
ISSN: 2472-2308 (Print); ISSN: 2472-2316 (Online)

Therapeutic Potential of Agarwood in Oral Chronic Inflammatory Diseases Management

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To cite this article:

Si-Yu Tao, Nan Zhou, Jin-Qi Chen, Yue-Li Zhou, Xiao-Ju Wu, Di Chen, Muhammad Zia Ullah Shahid, Zhu-Ling Guo. Therapeutic Potential of Agarwood in Oral Chronic Inflammatory Diseases Management. *International Journal of Homeopathy & Natural Medicines*. Vol. 8, No. 2, 2022, pp. 29-33. doi: 10.11648/j.ijhnm.20220802.12

Received: November 10, 2022; **Accepted**: November 18, 2022; **Published**: December 8, 2022

Abstract: Almost all people may suffer from gingivitis of varying degrees. As a kind of periodontal disease, gingivitis is mainly caused by many factors such as poor oral hygiene habits or immune dysfunction. Untreated gingivitis may develop into irreversible periodontitis. An important research direction of gingivitis is to find a drug that can reduce inflammation and has fewer side effects instead of traditional anti-inflammatory drugs. Agarwood is a kind of traditional Chinese medicine with high medicinal value. Previous studies on the chemical components and pharmacological activities of agarwood showed that the active components of agarwood, such as sesquiterpene and quercetin, have positive effects on the relief of inflammation. However, there is not much research on the use of agarwood to treat oral chronic inflammation such as gingivitis. In order to summarize the possible mechanism of the effect of agarwood on gingivitis, this paper reviewed and summarized domestic and foreign literatures. By reviewing the anti-inflammatory, antioxidant, antibacterial, analgesic and immune activities of the active components of agarwood in gingivitis respectively, the possible mechanism of agarwood in alleviating oral chronic inflammation was demonstrated. This review will provide theoretical reference value for the application of agarwood and its secondary products in the treatment of oral inflammation.

Keywords: Agarwood, Gingivitis, Anti Inflammation, Bacteriostasis, Analgesia

1. Introduction

Agarwood is the resinous heartwood formed by the trees of the genus Aquilaria Lam. It belongs to the Daphne family in taxonomy. The agaricus produced in China is mainly composed of Aquilaria Sinensis, named as Aquilariasinensis (Lou.) Gilg [1]. It is mainly produced in Hainan Island, Taiwan, Guangdong and Guangxi [2]. Agarwood has been used as a folk medicine since ancient times, mainly for the treatment of circulatory disorders, abdominal pain, vomiting and dyspnea [3]. Agarwood also plays a fundamental role in traditional chinese medicine. It has both sedative and anthelmintic effects. It is also used to relieve stomach problems, cough, vomiting, rheumatism and high fever [4, 5]. Agarwood essential oil is the essence obtained after refining and concentrating the original aroma components of agarwood. Through research, it is found that it is mainly composed of sesquiterpenes, aromatics, chromones, fatty acids and other substances, which inhibit the occurrence of many diseases. It has been developed to have multiple pharmacological effects [6]. Gingivitis is an inflammation caused by substances accumulated in or near the gingival groove by microbial plaque. If not treated in time, it may progress to periodontitis. As a local specialty, agarwood has extremely high research value for its medicinal potential. We should explore its development and application, and add it to

various products in various forms for its role.

2. Anti-Inflammatory Activity

Gingivitis is a chronic inflammatory disease, manifested as gingival swelling, bleeding and pain. Agarwood has anti-inflammatory effect, chromone and sesquiterpene are the main anti-inflammatory related active components isolated from agarwood essential oil [7]. The anti-inflammatory active components of agarwood can play an anti-inflammatory role by inhibiting the synthesis of inflammatory mediators such as 5-hydroxytryptamine, histamine and prostaglandin [8]. In molecular docking and ADME studies, it was found that several major sesquiterpenoids in agarwood essential oil have strong affinity for major anti-inflammatory receptors and immunoregulatory receptors [9]. Some sesquiterpenoid monomers also inhibit the release of NO induced by lipopolysaccharide in the anti inflammatory activity screening model of mouse monocyte macrophages RAW 264.7 in vitro [10, 11]. It was found that sesquiterpenoids in agarwood essential oil inhibit the expression of p-STAT3, thereby reducing the production of proinflammatory cytokine IL-1 β and IL-6, releasing anti-inflammatory mediators [12]. In addition, some scholars confirmed through experiments that 2 - (2-phenylethyl) chromone derivatives in agarwood can inhibit STAT1/3 and NF- κ B signal pathway showed significant anti-inflammatory effect [2]. Tryptone derivatives can also inhibit the production of carbon monoxide in macrophages induced by lipopolysaccharide [1]. In addition, the alcohol extracts of the flowers, seeds, pericarp and leaves of agarwood contain n-hexadecanoic acid and squalene [1]. Hexadecanoic acid can inhibit phospholipase A2 by binding to the active site of phospholipase A2 to control inflammation [9]. Some researches have found that agarwood essential oil has significant anti-inflammatory activity when administered by gavage. The anti-inflammatory activity of agarwood essential oil has been confirmed. The incidence of periodontal tissue inflammation is high in systemic inflammation. At present, there is no precedent for the treatment of periodontitis with agarwood composition. The anti-inflammatory function of agarwood extract provides a theoretical basis for its application in the treatment of gingivitis.

3. Antioxidant Effects

A large number of studies have shown that oxidative stress is caused by the imbalance between the excessive production of reactive oxygen species (ROS) and the relative lack of antioxidants, and oxidative stress is also one of the pathophysiological mechanisms of periodontal tissue inflammation [13]. ROS can change the periodontal microenvironment by activating inflammatory factors, nuclear factor KB (NF-KB), c-Jun amino terminal kinases (JNKs) and autophagy, causing indirect serious damage to periodontal tissue, leading to periodontitis [14]. Some people measured the antioxidant activity of agarwood essential oil by 1,1-diphenyl-2-trinitrophenylhydrazine (DPPH) radical scavenging and iron ion reduction / antioxidant capacity method (FRAP), proving that it has a good antioxidant capacity in vitro [15]. Its essential oil extract β- Caryophyllene shows strong antioxidant effect [16]. Its antioxidation can reduce the level of intracellular reactive oxygen species to a certain extent, and significantly enhance the cellular antioxidation. The activity of enzyme SOD and GSH Px can protect PC12 cells from oxidative damage induced by H_2O_2 [17]. There is also a flavonoid compound in the agarwood extract that can provide antioxidant effect by preventing the formation of ROS, directly capturing ROS, protecting lipophilic antioxidants and stimulating the increase of enzymatic antioxidants [18]. In addition, different concentrations of agarwood essential oil have scavenging effects on DPPH free radicals, hydroxyl free radicals and superoxide anion free radicals, and with the increase of the concentration of agarwood essential oil, the antioxidant capacity gradually increases, with obvious correlation [19]. The analysis results also showed that both young leaves and mature leaves of agarwood have strong antioxidant activity, and the two kinds of leaves have the same use value in terms of chemical content and antioxidant capacity, which can reduce inflammatory reaction to a certain extent [20]. Agarwood essential oil shows certain antioxidant capacity in various systems, can reverse the imbalance between reactive oxygen species and antioxidants, and has the potential to be applied to gingivitis. Therefore, agarwood is a natural antioxidant, which can resist oxidative stress and alleviate gingivitis.

4. Antibacterial Activity

The antibacterial and anti-inflammatory effects of agarwood are the main mechanisms to alleviate gingivitis. Gingivitis is caused by substances accumulated in or near the gingival sulcus by microbial plaque. Dental plaque is the main cause related to the development of gingivitis. It can aggravate inflammatory reaction by enhancing plaque accumulation or enhancing the susceptibility of gingival tissue to microbial attack. In recent years, it has been reported that agarwood has antibacterial activity and can inhibit some bacteria in oral cavity. Bacteria in the mouth mainly include Streptococcus mutans, Porphyromonas gingivalis, Staphylococcus, etc. The antibacterial activity test shows that agarwood essential oil has a good inhibitory effect on Gram-negative bacteria and Gram-positive bacteria, and has a more obvious antibacterial effect on Gram-positive bacteria. Because the cell wall of the external gram-negative bacteria contains a layer of lipopolysaccharide, which prevents hydrophobic compounds from entering the cells, thereby reducing the bacteriostatic effect [21]. In the process of agarwood formation, the infection of pathogenic bacteria causes the defense system of the Aquilaria Sinensis to resist external damage. It can prevent further infection of the pathogenic bacteria by generating local allergic reaction, that is, blocking the damage site [22]. This indicates that antibacterial activity has been carried out in the process of

agarwood formation, so agarwood itself may have antibacterial activity. In previous studies, Mei showed that Chinese agarwood essential oil has anti MRSA activity [23]. Wetwitayaklung found that agarwood essential oil (A. crassna) has antibacterial activity against Candida albicans [24]. Filter paper method was used to test the antibacterial ability of agarwood essential oil by measuring the antibacterial circle. With the increase of the concentration of agarwood essential oil, the inhibition rate against bacteria increased. The inhibition rate of agarwood essential oil against bacteria is in the following order: Staphylococcus aureus > Bacillus subtilis > Escherichia coli [25]. The antibacterial effect of agarwood essential oil is related to sesquiterpenes and chromones in agarwood. Sesquiterpenes usually have antibacterial activity. Studies have found that sesquiterpenes in the volatile oil of agarwood β-Caryophyllene has significant antioxidant and antibacterial properties. Its antibacterial activity is attributed to its strong antioxidant activity [26]. Flavone widely exist in the plant kingdom, and are one of the main components of agarwood. The pharmacological activities of flavonoids include anti-inflammatory activity, anti allergic activity, antioxidant activity, anti-tumor activity, antifungal and antibacterial activity, which can inhibit a variety of bacterial virulence factors [27].

5. Analgesic and Sedative Effects

Most plant herbs have antipyretic and analgesic effects. The analgesic and sedative effects of agarwood can alleviate the clinical manifestations of gingivitis, such as swelling and pain. The agarwood contains a variety of analgesic and sedative substances, and valerenic acid has obvious sedative activity, α- Sandalyl alcohol and agarospirol have the same chlorpromazine like stabilizing effect as agallospirol. Through animal experiments, researchers found that agarwood oil has a sedative effect on mice, which is manifested in that the autonomous motor activity of mice inhaled agarwood oil gradually decreases with the increase of medication time [28]. In addition, some scholars evaluated the pharmacodynamic effects of different parts of agarwood on sedation and hypnosis through the hypnosis experiment with pentobarbital sodium and the autonomous activity experiment. They found that the volatile oil of agarwood could significantly prolong the sleep time and increase the proportion of mice entering sleep. Based on the experimental results, the active molecules with sedative and hypnotic effects in the volatile oil of agarwood were further inferred [29]. In addition, they evaluated the sedative and hypnotic effects of agarwood essential oil through animal behavior experiments and explored the potential mechanism of action on GABA ergic system. The results showed that agarwood volatile oil has a versatile sedative and hypnotic effect, and its mechanism of action may be related to regulating the gene expression of GABAA receptor, enhancing the function of GABAA receptor, and promoting the influx of CL^{-1} [30]. Researches have compared the analgesic effects of different years of agallodendron, and deduce that the volatile oil of agallodendron can significantly increase the pain threshold of mice and reduce the number of writhing induced by acetic acid in mice, proving that it has a clear analgesic effect [31]. The nonsteroidal anti-inflammatory drug diclofenac is a commonly used anti-inflammatory drug with analgesic and anti-inflammatory effects. The anti-inflammatory activity of agarwood essential oil in vivo and in vitro is comparable to that of standard diclofenac [9]. The analgesic and sedative effects of agarwood essential oil can be applied to gingivitis to alleviate the pain reaction caused by gingivitis and the active inflammation and immune reaction in the gums.

6. Immune Activity of Agarwood

The development of gingivitis is mostly due to the chronic inflammatory process caused by long-term microbial stimulation of the gums. Gingivitis involves a series of immune reactions, such as the accumulation of lymphocytes, macrophages and plasma cells in the place where inflammation occurs. Overinduction, prolongation or imbalance of immune response will lead to immune diseases. Gingivitis is also an immune disease. Agarwood is not only able to enhance the cellular and humoral immune functions of the body, but also inhibit the immune function and reduce the release of inflammatory factors. This two-way immune regulation reflects the theory of "holism" and "balance between yin and yang" emphasized by traditional Chinese medicine [32]. Through modern pharmacological research, it has been found that agarwood and its essential oil have a variety of pharmacological activities, which may be related to their strong immune regulatory function. Inflammation, as the most basic immune reaction of the body, makes it possible to find new anti-inflammatory drugs from agarwood essential oil. Because of the correlation between immune reaction and inflammation, it was isolated from agarwood. Tryptone and sesquiterpene are not only the main anti-inflammatory substances, but also the main immunoactive substances. Compound CYF-2 is an epoxide 2 - (2-phenylethyl) - chromone derivative isolated from agarwood, which can significantly inhibit the activation of microglia, dendritic cells and neutrophils, which play an important role in innate immunity. In addition, GYF-21 significantly inhibits the transformation of adaptive immune+T cells into helper T cell 1 (Th1) and helper T cell 17 (Th17) by inhibiting the differentiation of primitive CD4, and inhibits the activation, proliferation and IFN of CD8- γ Secreting+t cells. Mechanism study showed that GYF-21 significantly inhibited STAT1/3 and NF in microglia- κ Activation of B signal path. In conclusion, GYF-21 can inhibit STAT1/3 and NF- κ B signal pathway significantly inhibits innate immunity and acquired immunity [7]. In addition, compound HHX-5 is a sesquiterpene derivative from agarwood. HHX-5 significantly inhibits the activation of macrophages and neutrophils, which plays an important role in innate immunity. In addition, HHX-5 strongly

inhibits the transformation of adaptive immune +t cells into Th1, Th2 and Th17 cells by inhibiting the differentiation of original CD4, and inhibits the activation, proliferation and differentiation of CD8+t cells and B cells. Inhibits innate and adaptive immunity by inhibiting STAT signaling pathway [33]. The excesive immunity of macrophages and neutrophils in inflammatory reaction is the main immune mechanism that causes gingivitis. Because the chromone and sesquiterpene in agarwood can inhibit the relevant signal pathway and immune response respectively, in conclusion, agarwood has the possibility to alleviate the overimmunity of gingivitis.

7. Conclusion

The active components of the traditional Chinese medicine, Agaricus formosana, are sesquiterpenoids, flavonoids, quercetin and other compounds. The active ingredients of agarwood have anti-inflammatory, antioxidant, bacteriostatic, analgesic, sedative, immune and other pharmacological activities. Gingivitis is a chronic inflammation caused by plaque accumulation on the gingival margin. An important research direction of gingivitis is to find a drug with small side effects and can alleviate inflammation to replace traditional anti-inflammatory drugs. Agarwood has less side effects than commonly used chemical synthetic drugs. However, the application of agarwood in gingivitis is rare. This paper expounds the possible mechanism of agarwood to alleviate periodontal tissue inflammation by demonstrating the above effects of agarwood. It provides a theoretical basis for the transformation of agarwood industry.

Acknowledgements

This research was funded by Health Science Research Project of Hainan Province (22A200041), Teaching Achievement Award Cultivation Project of Hainan Medical University (HYjcpx202217), High-level Talents Project of Hainan Natural Science Foundation (821RC687), Higher Education and Teaching Reform Research Project of Hainan Province (Hnjg2021-60), Course Construction Project of Hainan Medical University (HYZD202215), Education Research Project of Hainan Medical University (HYJW202117), Innovative Entrepreneurial Training Program of Hainan Medical University (S20211810012).

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