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Research Article

Exploration of the Effects of Agarwood Extract on the Inflammtory Microbiota in the Oral-Gut Axis

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Abstract

Agarwood, as a precious medicinal material with distinctive characteristics from Hainan, has been shown in recent studies to possess significant anti-inflammatory and antibacterial properties. With the rapid growth in public recognition of health concepts, oral health has garnered increased attention. The main focus of this study is the impact of agarwood extracts on the oral-gut axis microbiota. The relationship between the oral and gut microbiota is closely intertwined, where oral microbiota can directly colonize the intestine via saliva and other means, altering the original microbial composition of the gut and leading to dysbiosis. For instance, Porphyromonas gingivalis significantly increases in patients with gingivitis and periodontitis, as it can tolerate the acidic environment of the stomach and colonize the intestines through the gastric barrier. Therefore, oral health can affect intestinal health. Additionally, oral lesions are evident in patients with intestinal inflammation; such patients, like those with IBD, exhibit a significant accumulation of oral bacteria in the intestines. Although IBD primarily affects the intestines, its extraintestinal symptoms, often prominently displayed, include oral manifestations. Hence, intestinal health can also influence oral health. Agarwood extracts inhibit pathogenic oral microbiota, impedes their colonization in the intestine, and consequently reduces the likelihood of inflammatory bowel disease.. This article, by introducing the microbiota of periodontitis and the pathogenesis of inflammatory bowel disease, along with extraintestinal symptoms, the preventive and inhibitory mechanisms of agarwood extract on the associated microbiota are analyzed, providing new insights for the treatment of such patients. It underscores the importance of maintaining oral hygiene and preventing oral diseases as well.

Keywords

Agarwood, Oral-Gut Axis Microbiota, Inflammation, Periodontitis, Inflammatory Bowel Disease

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1. Introduction

During periodontitis, various factors such as swallowing mechanism and diet lead to the accumulation of oral bacteria in the intestinal contents and mucosal tissues of patients with intestinal diseases [1]. The aggregation of oral microbiota alters the original microbial population in the intestine, resulting in dysbiosis. According to the literature, compared to individuals with periodontal health, patients with periodontitis exhibit reduced diversity and changed composition of gut microbiota, characterized by an increased ratio of Firmicutes to Bacteroidetes, and enrichment of bacterial phyla such as Fusobacteria and Proteobacteria [2]. Similar results were obtained in animal experiments, where after oral gavage with Porphyromonas gingivalis for ten cycles in mice, sequencing of the ileal contents showed that the proportion of Firmicutes was 55.4% and Bacteroidetes was 38.7% in the P. gingivalis-treated mice, while in the control group, Firmicutes accounted for 72.8% and Bacteroidetes accounted for 17.0%, with statistically significant differences [3]. The major pathways and reasons for the appearance of oral microbiota in the intestine may include:

1.1. Influence of Periodontitis on Gut Microbiota

1.1.1. Intraintestinal Pathway

Under physiological conditions, oral microbiota rarely enter the intestine due to protection by gastric acid and alkaline bile. However, the oral microbiota of patients with periodontitis differ significantly from those of orally healthy individuals. Certain types of oral pathogens, such as P. gingivalis, are significantly elevated in patients with gingivitis and periodontitis. This bacterium can tolerate the acidic environment of the stomach and traverse the gastric barrier. Additionally, patients taking certain antibiotics (such as vancomycin) experience expansion of oral bacteria in the body [4].

1.1.2. Hematogenous Pathway

After an increase in intestinal barrier permeability, oral bacteria can directly transfer from the mouth to the systemic circulation. Simultaneously, oral pathogenic bacteria in the blood of patients with periodontitis can also colonize the intestine through a compromised intestinal barrier. Literature review has found that ligature-induced periodontitis in rats leads to the dissemination of oral bacteria to the liver and spleen, indicating that the dissemination of oral bacteria can be determined by the oral disease status [5]. Furthermore, oral bacteria (Porphyromonas gingivalis: P. gingivalis) have been collected from the blood of patients with periodontal disease, and it has been demonstrated that strains of oral Fusobacterium inoculated hematogenously are more successful in tumor colonization, indicating the importance of the circulatory system as a pathway for oral bacteria transmission [6].

Therefore, in certain situations (such as antibiotic-induced dysbiosis or intestinal inflammation and diet), the intestine can provide a niche for ingested oral bacteria, leading to opportunistic intestinal colonization by oral bacteria. Once oral microbiota successfully colonize the intestine, they can become pathogenic factors, inducing immune responses. It has been reported that several resident oral bacteria are potential factors contributing to intestinal inflammation, such as certain members of the oral pathogen family Fusobacteriaceae: Fusobacterium varium and Fusobacterium nucleatum, which are enriched in the intestines of inflammatory bowel disease (IBD) patients, with significantly increased abundance during disease activity rather than remission. Thirty-four strains of Fusobacterium found in the intestines of IBD patients may originate from the oral cavity [6].

1.2. Impact of Gut Dysbiosis on the Oral Cavity

Oral lesions are common in IBD, and literature review reveals that both are closely associated with host immune responses and local dysbiosis-mediated inflammatory reactions [7]. Studies have also clearly shown that patients with intestinal inflammation, such as IBD, exhibit a significant enrichment of oral bacteria in the intestine [8, 9]. Although IBD primarily affects the intestines, the extraintestinal symptoms of this disease are often prominent, and the oral cavity is one of the major affected sites, with involvement rates reaching up to 50% in cases and up to 80% in pediatric IBD cases. Patients with IBD often present with nonspecific inflammatory manifestations such as oral ulcers, gingivitis, and periodontitis, and microbial examinations can reveal relevant pathogens. Compared to healthy individuals, IBD patients have an increased prevalence of oral microbiota and periodontitis.

In summary, the oral and gut microbiota are interrelated and mutually influential: the inflammatory state of the oral cavity can cause gut microbiota dysbiosis through swallowing actions; while inflammation in the gut can also correspondingly affect oral environment and conditions.

2. Results and Analysis

Agarwood, a common name for species of the Aquilaria and Gyrinops genera, is a precious traditional Chinese medicinal material primarily grown in tropical and subtropical regions. Agarwood contains several active substances that exhibit antibacterial and anti-inflammatory effects and has preservative and deodorizing effects in food. Its component efficacy mainly include stopping emesis by warming the stomach, calming the whoop by bring the pneuma to kindey, and stopping the pains by unclogging the pneuma [10].

Therefore, there are also many agarwood-related health products on the market. Moreover, the essential oil of domestic agarwood has been found to inhibit the activity of Staphylococcus aureus, and the essential oils of artificial or natural agarwood exhibit significantly greater inhibitory activity against Gram-positive bacterial strains (Staphylococcus aureus and Bacillus subtilis) than Gram-negative bacterial strains (Escherichia coli) [11, 12].

2.1. Terpenoids

1) Monoterpene compounds: Only (-)-bornyl ferulate has been isolated domestically [13, 14]. Diterpenoid compounds possess characteristics such as easy absorption and good biological activity [15]. Triterpenoid compounds can be extracted with ethanol, with 3-oxo-22-hydroxyhopane being the most extensively studied [16].

2) Sesquiterpenoid compounds are one of the primary chemical components of agarwood, which are categorized into six types in domestically and internationally [17]. Both chromone compounds and sesquiterpenoid compounds in agarwood have significant anti-inflammatory effects [18, 19]. In terms of inflammation, inflammatory responses can activate complex signaling pathways, among which STAT3, as a key transcription factor, participates in the signaling of multiple cytokines and is considered a therapeutic target for inhibiting the inflammatory process. Additionally, it has been found that sesquiterpenoid compounds (68.83%) in agarwood essential oil (Chinese eaglewood essential oil, CEEO) can alleviate inflammation by inhibiting the phosphorylation of STAT3 signaling transduction and suppressing the production and release of IL-1β and IL-6 [20].

The main pathways are as follows: The phosphorylation of tyrosine (Tyr705) on STAT3 and its entry into the nucleus produce transcriptional responses, promoting the transcription and expression of inflammatory cytokines, while inhibiting its phosphorylation alleviates inflammation and increases the survival rate of sepsis. During inflammation, activated inflammatory cells such as neutrophils, eosinophils, monocytes, and macrophages secrete large amounts of pro-inflammatory cytokines such as IL-1β, IL-6, TNFα, and NO. Among these, IL-1β, as one of the important pro-inflammatory factors involved in inflammation, is upstream of the inflammatory response and can induce the production of various inflammatory cytokines and effector molecules (such as IL-6). IL-6 is one of the most important mediators of fever and acute-phase response, and it is the strongest endogenous inflammatory factor that triggers systemic inflammatory responses, catalyzing and amplifying the inflammatory response. Research has found that the STAT3 pathway can be activated by the inflammatory factor IL-1β. Activated STAT3 forms homodimers or heterodimers, rapidly enters the nucleus, and can induce the transcription and expression of pro-inflammatory factors IL-6 and IL-1β. Inhibiting the phosphorylation of STAT3 tyrosine can reduce the production of pro-inflammatory factors.

2.2. Chromone

Another major chemical component of agarwood is chalcones, which are generally divided into four types: 5,6,7,8-dioxo-2-(2-phenylethyl)chalcones (THPECs), 5,6-epoxy-2-(2-phenylethyl)chalcones(EPECs), 5,6,7,8-tetrahydro-2-(2-phenylethyl)chalcones(DEPECs) and 2-(2-phenylethyl)chalcones (FTPECs) [21, 22].

3. Discussion

A research team from Peking University isolated and identified 17 compounds from the ethanol extract of cultivated agarwood produced by artificial tapping of the"No.2 Tropical science" Aquilaria sinensis. Anti-inflammatory activity testing results showed that the compounds exhibited anti-inflammatory activity, with the median inhibition concentration (IC50) value of (27.81±2.34) μmol/L [23]. In addition, chromones isolated from ethyl acetate extracts exhibited strong inhibitory activity against Staphylococcus aureus, as well as good inhibitory activity against methicillin-resistant Staphylococcus aureus [24]; Some extracts also showed inhibitory activity against Xanthomonas oryzae [25].

4. Conclusion

IBD and periodontitis can be linked through microbiota. At the same time, antimicrobial components in agarwood leaves have high medicinal and development value, for example, inhibiting the growth of bacteria such as Staphylococcus aureus and reducing the production of inflammatory factors to alleviate inflammatory reactions as well. Therefore, agarwood extract can influence the microbiota connection between periodontitis and IBD to some extent, and in the future, it may be used in the form of sprays or capsules for preventive measures and adjustments to microbiota dysbiosis in the oral cavity and gastrointestinal tract.

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Conflicts of Interest

The authors declare no conflicts of interest.

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