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Empirical Research on the Anti-Inflammatory, Antibacterial, and Mucosal Protective Effects of Agarwood Based on the Oral and Intestinal Microenvironment

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Abstract: Objective: To investigate the effects of chemical substances contained in agarwood on the body's inflammatory response, oxidative stress, oral and intestinal micro-ecology, as well as their role in various mucosal diseases, such as recurrent aphthous ulcer (RAU) and inflammatory bowel disease (IBD). Materials and Methods: By reviewing and summarizing literature from the past decade on agarwood and its related chemical components composition, as well as their effects on RAU and IBD, we explore the role of agarwood in the body and its relationship with mucosal-related diseases. Results: The Specific components in agarwood, such as sesquiterpenes, flavonoids, etc., can regulate the body's inflammatory response and oxidative stress levels through various signaling pathways, thereby affecting the mucosal status of the oral and intestinal cavity, such as influencing the expression of tight junction proteins between epithelial cells to restore mucosal barrier permeability. Conclusion: Agarwood can down-regulate the inflammatory response by inhibiting various signaling pathways, mainly NF-κB, reduce oxidative stress by decreasing ROS expression, improve the mucosal barrier in the oral and intestinal cavity, and simultaneously impact the improvement of oral and intestinal micro-ecology. It plays a certain controlling role in mucosal-damaged diseases such as IBD and RAU, laying the foundation for the transformation, development, and upgrading of the agarwood industry.

Keywords: Agarwood, Anti-Inflammatory, Flavonoids

1. Introduction

Recurrent aphthous ulcer (RAU), also known as oral ulcer, is a common inflammatory ulcerative disease affecting the oral mucosa. Its main features include recurrent painful episodes that affect eating. The exact pathogenesis of oral ulcers is still unclear; however, research suggests a close association of its etiology with microorganisms, infections, and immune factors [1]. Inflammatory diseases in the oral cavity lead to an imbalance in the local microbiota and immune homeostasis, characterized by elevated levels of inflammatory indicators in the oral mucosa and saliva. This imbalance can contribute to the progression of the disease and even exacerbate or trigger other systemic conditions, such as chronic inflammatory diseases of the gastrointestinal tract [2]. Inflammatory bowel disease (IBD) is a common chronic relapsing inflammatory disorder of the gastrointestinal tract, with an increasing incidence and affecting millions of people

worldwide [3]. The rapid development of high-throughput metagenomic sequencing technologies, increasing evidence suggests a correlation between IBD and dysbiosis or alteration of the gut microbiota. The commensal gut microbiota has a significant impact on pathogen colonization and drug resistance, as well as the induction of primary immunity. Once an ecological imbalance occurs, it can impair the defense of the intestinal mucosal epithelium, thereby accelerates the pathological process. Recent researches have demonstrated the critical interplay and fine-tuning between the gut microbiota, immune cells, and the epithelium in maintenance of normal immune responses [4]. Furthermore, emerging evidences indicate that disturbances in the mucosal microbiota can regulate innate and adaptive immune responses, while a reduction in commensal microbial abundance and/or an increase in pathogenic microbial burden may lead to systemic inflammatory reactions [5]. Agarwood is a valuable medicinal plant in China, and has a history of its use spanning thousands of years worldwide. Recent studies have revealed out that active compounds in agarwood possess broad anti-inflammatory and antibacterial activities [6]. Agarwood exhibits inhibitory effects on a range of bacteria and fungi, including methicillin-resistant Staphylococcus aureus, Escherichia coli, Candida albicans, and Staphylococcus aureus [7, 8]. This article primarily reviews the mechanisms through which agarwood alleviates oral mucosal ulcerative diseases, aiming to explore the anti-ulcer effects of agarwood's active compounds by relieving inflammation, modulating the microbiota, and strengthening the mucosal barrier. It aims to provide new insights for the improvement of oral mucosal ulcerative diseases.

2. Agarwood's Anti-Inflammatory Effects

2.1. Mechanisms of Flavonoid Compounds in Anti-Inflammation

In the inflammatory response, macrophages play a crucial role by secreting various pro-inflammatory mediators, including tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), interleukin-1beta (IL-1β), prostaglandin E2 (PGE2), etc. Interleukins (IL) are lymphokines that mediate interactions between leukocytes or immune cells. ILs play important roles in cell communication, activation, and regulation of immune cells, as well as T and B cell activation, proliferation, differentiation, and inflammation [9]. Research has shown that interleukins associated with inflammation primarily include interleukin-1 (IL-1), interleukin-6 (IL-6), interleukin-8 (IL-8), interleukin-10 (IL-10), among others. IL-1 can stimulate the expression of genes associated with inflammation, induce the expression of cyclooxygenase-2 (COX-2), phospholipase A2 (PLA2), inducible nitric oxide synthase (iNOS), and other effector proteins are playing a significant role in the inflammatory process. IL-6 can act as a stimulating factor, induces the production of inflammation-related proteins in acute inflammatory reactions which is caused by infection or trauma [10]. IL-8, when released upon contact with neutrophils, releases a series of active substances that can lead to local inflammatory reactions in the body. IL-10 can promote the expression of TNF-α and also inhibit the production of pro-inflammatory cytokines [11]. Therefore, inhibiting the generation of IL-1, IL-6, IL-8, or increasing the content of IL-10 can reduce the occurrence of inflammation. Agarwood's active components, flavonoid compounds, are a potential class of drugs with wide-ranging pharmacological activities. Agarwood flavonoid compounds have been proven to be long-acting anti-inflammatory agents with good anti-inflammatory and analgesic effects. Researches have found that the analgesic mechanism of quercetin (a plant pigment-Flavonoid) is related to the down-regulation of expression and regulation of inflammatory factors and mediators in inflammatory-related signaling pathways [12]. Numerous in vitro studies have shown that flavonoid compounds can prevent the occurrence of LPS-mediated TNF-α in macrophages and inhibit the production of inflammatory cytokines such as IL-6, TNF-α, and IL-1β by up-regulating Toll-like receptor 4 and peroxisome proliferator-activated receptor gamma [13].

2.2. Mechanism of Action of 1.2-Dihydroxybiflavonoids in Anti-Inflammation

Recurrent Aphthous Ulcer (RAU) inflammation response persists throughout the entire process. In the early stages of both diseases, inflammatory damage stimulates the release of cytokines such as TNF-α, IL-1β, IL-4 (Interleukin 4, IL-4), etc. From oral mucosal epithelial cells, inducing an immune-inflammatory reaction and recruiting inflammatory and immune cells to the damaged site for repair. Subsequent chronic inflammation leads to inflammatory infiltration, inducing excessive secretion of cytokines by macrophages and neutrophils, such as TNF-α, interferon-γ (IFN-γ), triggering oral inflammation. The NF-κB signaling pathway has been considered the classical pro-inflammatory signal transduction pathway. Under the activation of IKK, IκB is phosphorylated, ubiquitinated, and subsequently degraded by proteases, releasing the NF-κB dimer which enters the cell nucleus. Activation of the NF-κB signaling pathway increases the transcription of genes such as TNF-α, thereby increasing the release of inflammatory mediators, activating the body's inflammatory response, and promoting its amplification and persistence [14, 15]. Spiroaquilarenes A-E (1-5) [16] are semi-synthetic polymers obtained from agarwood, characterized by a unique furan ring connecting the semi-synthetic monomers. Their structures have been determined through spectroscopy and computational methods. Compound 3, in LPS-induced RAW264.7 cells, dose-dependently inhibits the generation of TNF-α, IL-6, and nitrites, thus attenuating the inflammatory response. Compounds 2 and 3 significantly inhibit the activation of NF-κB (primarily reducing G and H protein levels) and down-regulate iNOS content. Activated NF-κB promotes the

expression of chemokines and cytokines, thereby facilitating inflammation and immune reactions [17].

3. Agarwood Inhibits Oxidative Stress

3.1. Flavonoids and Their Antioxidative Mechanisms

Oxidative stress is the imbalance between reactive oxygen species (ROS) levels and endogenous antioxidative capacity in cells, leading to cellular oxidative-reductive imbalance beyond its regulatory range and causing damage to the body. When the body is subjected to oxidative stress damage, it accelerates the formation of free radicals and ROS, which alters the cell membrane permeability, triggers free radical chain reactions, induces cell apoptosis, and reduces cell survival. Research has shown that the over-activation of macrophages plays a crucial role in the pathogenesis of acute and chronic inflammatory diseases and many cells can produce a large amount of ROS through LPS/ROS pathway acting on the NLRP3 receptor induced by LPS, leading to oxidative stress reactions and causing inflammatory damage [18]. Therefore, inhibiting the activation of macrophages can result in the down-regulation of inflammatory damage and alleviation of inflammatory diseases. Studies have shown that the oxidative stress index values in patients with RAU are significantly higher than those in normal individuals, and DNA damage is significantly higher as well [19]. Furthermore, RAU patients have elevated levels of malondialdehyde (MDA) in their serum, and reduced levels of glutathione (GSH) and superoxide dismutase (SOD) [19]. The changes in MDA, GSH, and SOD expression may indicate the activation of the peroxidation reaction in the extracellular fluid due to damage to the antioxidant defense system, leading to abnormalities in the cytokine mechanism. Research has found that agarwood flavonoids have strong abilities to scavenge DPPH and ABTS free radicals [20]. They can slow down oxidative damage to the cell membrane system, maintain the integrity of cell structure and function, strengthen the defense capacity of the antioxidant system, eliminate excessive ROS in the body, and protection against cellular oxidative damage. Agarwood flavonoids have a significant inhibitory effect on free radical generation when their concentration is 40.14±0.0192μL/mL, thereby inhibiting cellular oxidative stress reactions [21].

3.2. Sesquiterpenes' Antioxidative Mechanisms

Sesquiterpene lactones are sesquiterpene-derived polymers abundant in plants, and they are the main active components of agarwood, exhibiting a wide range of antioxidative biological activities. Imbalance in the generation of reactive oxygen species can lead to increased oxidative stress, resulting in oxidative damage to cells and tissues, ultimately leading to the development or worsening of certain diseases such as RAU and inflammatory bowel disease (IBD) with mucosal ulcers [22]. Research has found that agarwood sesquiterpene polymers, in the form of extracts (aqueous, alcoholic, and hydro-alcoholic), essential oils, and isolated compounds, have extensive antioxidative and free radical scavenging properties, improving oxidative stress and exhibiting anti-inflammatory effects [23]. Additionally, other studies have indicated that sesquiterpene lactones can inhibit oxidative stress reactions by activating the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway [24]. The pathogenesis of oral ulcers is closely related to local oxidative stress, and an imbalance in the oxidative-antioxidative system hinders ulcer healing. Nrf2 is a crucial intracellular antioxidant transcription factor that plays an important role in the body's defense system against oxidative stress, thereby inhibiting the oxidative stress reactions of ulcer lesions and alleviating oxidative stress damage to the oral mucosa [24].

4. Agarwood Protects the Mucosal Barrier

4.1. Flavonoids Protect the Mucosal Barrier

Recurrent aphthous ulcer (RAU) is an oral mucosal ulcer disease that mainly affects the oral mucosa and soft tissues. The oral mucosa is the lining tissue of the oral cavity and serves as the primary defense against potential pathogens and exogenous chemicals. It consists of two major components: a physical barrier composed of stratified epithelial cells and cell-cell connections, and a microbial immune barrier that maintains the internal environment in a balanced state [25]. The epithelial tissue not only separates vital internal organ systems from the outside world but also promotes communication with the microbial community and nutrient uptake [26]. The loss of epithelial barrier integrity can exacerbate the progression of diseases. The latest advancement in microbiology and immunology emphasize the importance of mucosal barrier integrity in homeostatic mechanisms. Changes in environmental conditions that disrupt the stability of the oral microbial community can lead to inflammation and the development of oral mucosal diseases such as RAU [27, 28]. Studies have shown that agarwood flavonoids can enhance intercellular tight junctions, regulate the body's immune response, maintain the stability of the internal environment's micro-ecology, and thereby maintain the function of the mucosal barrier [29]. Intercellular tight junctions are mainly composed of occludin, claudin, zonula occludens (ZO) adherens junction proteins, and junctional adhesion molecules (JAMs), which play a crucial role in maintaining the integrity of the mucosal barrier. Agarwood flavonoids can enhance integrity and strengthen tight junction function by regulating the expression and assembly of tight junction-forming proteins. Previous research has found that flavonoids can reduce the secretion of inflammatory cytokines by macrophages and inhibit the extracellular regulated protein kinases/mitogen-activated protein kinase (ERK/MAPK) pathway [29]. It has also been suggested that MAPK plays a central role in permeability regulation, and inhibiting ERK phosphorylation activation

can up-regulate the expression of tight junction proteins, down-regulate the secretion of inflammatory cytokines, improve epithelial barrier permeability, and protect the mucosal barrier [30].

4.2. Fold Sesquiterpene Polymer Protects Mucosal Barrier

Oral ulcers and ulcerative colitis (UC) belong to the category of mucosal ulcerative diseases. Research has shown that the tyrosine kinase/signal transducers and activators of transcription (JAK/STAT) pathway plays an important role in inflammation and mucosal barrier damage [31]. STAT3 is a key factor in mucosal wound repair, particularly in the JAK2/STAT3/NF-κB molecular pathway [32, 33]. Studies have found that when the levels of JAK2 and STAT3 decrease in mucosal tissue, mucosal damage is reduced, and most of the mucosal tissue undergoes repair. Sesquiterpene derivatives present in agarwood can improve mucosal damage by inhibiting the STAT signaling pathway or reducing NF-κB activity and subsequently down-regulating the inflammatory response [33].

5. Conclusion

Agarwood is a traditional precious medicinal herb in China, containing active ingredients such as sesquiterpenes and flavonoids. It possesses favorable pharmacological activities such as anti-inflammatory, antibacterial, antioxidant, anti-ulcer, and mucosal barrier protection, thus it is being used in the treatment of digestive system-related diseases. This article summarizes the chemical components of agarwood and their potential effects on inflammatory response and mucosal ulcerative diseases, briefly introducing the pharmacological effects of active ingredients in agarwood, providing a scientifically rational reference for the subsequent development and industrial standardization of agarwood.

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