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Review
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Potential Anti-Inflammatory Properties Effect of Myrrh

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Abstract: The natural gum Myrrh, a resinous extrude of genus *Commiphora species*, has found several applications, especially in traditional medicine. Myrrh has been used for treating different diseases, including inflammatory diseases, in diverse communities across the world. Allopathic usage of Myrrh, however, is limited by knowledge deficits regarding pharmacological mechanisms underlying these clinical effects, in particular, its anti-inflammatory role. This review aims to provide up-to-date information on the effect of myrrh extracts as well as its bioactive compounds on the functions of white blood cells and inflammatory mediators. Relevant information about the impact of Myrrh on the functions of white blood cells and inflammatory mediators was collected from established scientific databases such as NCBI, Web of Science, and Google Scholar. A few books were also referred to as obtaining important information. Myrrh and its bioactive molecules have been shown to have potential effects on the functions of white blood cells and immunomodulatory activities. However, few studies have reported these effects. In-depth studies are necessary to determine the effect of Myrrh and its bioactive molecules on immune cells and inflammatory mediators.

Keywords: Myrrh; white blood cells; inflammatory mediators.

1. Introduction

Natural herbal medicines have been used for therapeutic purposes throughout the ancient world. The genus Commiphora comprises between 150 and 200 species, and the majority are native to different dry regions such as Africa, Arabia, and India. The word Commiphora is derived from the word commis in Latin and kommi in Greek (meaning 'gum') and phoros (meaning 'bearing') [1]. Myrrh is a yellow fragrant oleo-gum resin exuded from the bark of trees belonging to the Commiphora species. Commiphora resin has long been used as a traditional medicine in various societies to treat different diseases such as tumors, fever, and stomach complaints [2-4]. It contains many active ingredients, which have the potential for the treatment of various diseases. Previous investigations have revealed that Myrrh contains about 3% –8% of essential oil, 25% –40% alcohol-soluble resin, and 30% –60% water-soluble gum [5]. The essential oil of Myrrh contains different chemical constituents, including monoterpenes, sesquiterpenes, and aromatic compounds. In addition, other chemical compounds present in myrrh resins include triterpenoids, diterpenoids, steroids, and lignans. These chemical constituents were reviewed in more detail by Cao et al. (2019). Myrrh resin has been shown to have antimicrobial, anticancer, and anti-inflammatory effects [6-11]. These effects might be directly or indirectly associated with immune cells and inflammatory mediators. White blood cells (WBCs) play an important role in innate and adaptive immunity, wound healing, and tumor surveillance. The response of WBCs to immune stimuli activates

functions such as proliferation, activation, recruitment, and secretion of mediators, which contribute to both the onset and resolution of inflammation. Inflammatory mediators such as cytokines and chemokines coordinate the immune response by targeting cells of the innate and adaptive immune system [12]. Few studies have shed light on the effects of Myrrh on immune responses. This paper reviews the effect of Myrrh and its bioactive molecules on the functions of white blood cells and inflammatory mediators.

2. Myrrh and Neutrophils

Polymorphonuclear neutrophils are part of the innate immune system that is produced in the bone marrow and are the predominant leukocytes in peripheral blood. Their lifespan in circulation is about 4-10 h, and their half-life in the tissue is 1-2 days [13]. In response to immune stimuli, the production of neutrophils increases from the bone marrow into the peripheral blood. In addition, they are activated to eliminate the invading microorganisms or cellular debris. Their functions include margination, adhesion cascade, phagocytosis, and generation of reactive oxygen species. Different studies have examined the effect of Myrrh on leukocyte function. It has been reported that Myrrh exerts healing benefits during injuries by enhancing neutrophil proliferation and differentiation. Wistar albino male rat models with skin injuries and gastric ulcers treated with Myrrh showed an increase in the neutrophil proliferation and maturation process during healing, compared to untreated animals [14]. In addition, the effect of Myrrh on neutrophil infiltration into the other tissues was investigated. In an experimental model, inducing septic shock by cecal ligation and puncture (CLP), followed by administration of Myrrh, decreased the CLP-induced mortality and levels of inflammatory mediators. Furthermore, mice treated with Myrrh showed decreased infiltration of neutrophils in the peritoneal cavity and liver tissue [15]. Neutrophil gelatinase-associated lipocalin (NGAL) is a biomarker protein that is produced from the epithelial cells and activated neutrophils, as an indicator of tubular injury in the kidney. A recent study investigated the effect of Myrrh on NGAL levels in rats treated with cadmium chloride to induce renal failure. It was found that the development of chronic renal failure in experimental rats led to an elevation in serum NAGL in the group treated with cadmium chloride compared to that in the control group. Interestingly, it has been shown that the treatment of chronic renal failure in rats with Myrrh significantly reduced NAGL levels in their serum compared to that in the control group [16]. The anti-inflammatory effects of guggulsterone (GS), which is a chemical constituent found at high levels in Commiphora myrrha, were assessed. GS has been shown to attenuate the development of cerulein-induced acute pancreatitis in mice, by inhibiting the infiltration of neutrophils in the pancreas and reducing the levels of inflammatory mediators such as tumor necrosis factor α (TNF-α) and interleukin-1β (IL-1β) [17]. The commercial extract of Myrrh is sold as Mirazid® in Egyptian pharmacies. It has been reported that Mirazid® led to a significant increase in the neutrophil count in treated mice compared to that in the control groups [18, 19].

3. Myrrh and Eosinophils

Polymorphonuclear eosinophils usually have a bilobed nucleus and are larger than neutrophils. The half-life of eosinophils is approximately 24 h in circulation and 8-12 days in the tissues. These cells can synthesize and secrete different growth factors and cytokines and regulate innate and adaptive immune responses. Eosinophils play an important role in fighting

infections and allergic reactions and have antiparasitic properties [20]. A study was designed to investigate the efficacy of drugs extracted from Myrrh in patients with fascioliasis. In this study, investigators concluded that the extracted drug improved the general condition of patients and ameliorated all symptoms and signs. In addition, the high eosinophilic counts returned to normal levels in all patients [21]. It has been demonstrated that treatment with Myrrh resulted in elevated leukocyte levels throughout the period of an actual injury to a host and even in the absence of injury [14]. Similar findings were found in a study of toxic effects of ether and ethanol extracts of Myrrh in Wistar rats [22]. The effect of the commercial extract of Myrrh, Mirazid®, on eosinophils has also been investigated. It was reported that the treatment of fascioliasis with Mirazid® did not show any visible effect on eosinophilia [23]. In another study, it was reported that Mirazid® reduces eosinophilia in patients with fascioliasis [24][25]. In addition, Alkazzaz *et al.* (2018) reported that mice infected with *Schistosoma mansoni* had elevated eosinophil counts. In these infected mice, Mirazid® caused a significant reduction in eosinophils.

4. Myrrh and Basophils

Polymorphonuclear basophils are granulocytes that are characterized by a bilobed nucleus and have the ability to survive in the circulation for many days. Basophils are the least common blood granulocytes, and their functions are not fully understood. Basophils are thought to be the secretors of cytokines, serotonin, histamine, interleukin-4 (IL-4), and interleukin-3 (IL-13) to protect against helminth infections and pathogens. In addition, these cells are involved in allergy and chronic inflammation [20]. In a study by Haffor (2010), animal models with a skin injury and gastric ulcer showed a significant increase in the basophil counts when treated with Myrrh. Conversely, basophil counts of mice infected with *Schistosoma mansoni* showed no significant changes, and the effect of Myrrh was not observed in these cells [18].

5. Myrrh and Monocytes

Monocytes are mononuclear phagocytic cells that play an essential role in the innate immune system. Monocytes are the largest white blood cells and contain a partially lobulated nucleus. Monocytes remain in circulation for a relatively long time with the lifespan being 3 days, while the cells recruited to tissues survive for a longer period and can further differentiate into different types of tissue macrophages and dendritic cells [26]. Monocytes mediate host antimicrobial defense and secrete many cytokines such as interleukin-1 (IL-1), interleukin-6 (IL-6), and interleukin-12 (IL-12) to stimulate the inflammatory response [20]. It has been found that treatment with Myrrh increases the level of monocytes [14]. The influence of Myrrh on gene expression and protein release in activated human macrophages has also been investigated. Researchers indicated that the extract of Myrrh inhibits the production of CXCL13 and TNFα by suppressing chemokine gene expression in activated human macrophages [27]. T-cadinol is a chemical compound found in myrrh [28]. It is a potential regulator of dendritic cell differentiation [29].

6. Myrrh and Lymphocytes

Lymphocytes are the smallest white blood cells, and their lifespan varies. They are divided into B cells, T cells, and natural killer (NK) cells, and each type has a unique function.

Despite their different functions, all B, T, and natural killer cells develop from the same lymphoid progenitor stem cells, which produce all lymphocytes. T and B cells play essential roles in adaptive immunity, and their names are related to the organs in which they develop. The maturation T cell precursors occur in the thymus, and B cells develop in the bone marrow. Effector helper T cells secrete a variety of cytokine mediators. T cells are divided into cytotoxic T cells that kill the infected cells, and helper T cells, which activate macrophages, B cells, and cytotoxic T cells. Effector B cells secrete antibodies, and their mature form is known as plasma cells. Natural killer cells are responsible for innate responses against virus-infected and tumor cells [20][30]. A recent study aimed to determine the toxicity developed by feeding experimental male Wistar albino rats with different concentrations of myrrh extracts and to evaluate the hematological changes. Their results showed a significant reduction in the lymphocytes in animals that were fed ether and ethanol extracts of myrrh [22]. This finding is in agreement with other studies, which demonstrated that myrrh treatment significantly increased all white blood cells, including lymphocytes [14]. A study investigated the effect of frankincense and myrrh extract on the subsets of lymphocytes $CD8^{+}$T cells and NK cells in mice with hepatocellular carcinoma, which is a type of inflammation-related cancer. The depletion of CD8+ T cells abrogated the antitumor effect of frankincense and Myrrh. The authors concluded that CD8+ T cells, but not NK cells, mediate the antitumor activity of frankincense and Myrrh [31]. In addition, Myrrh enhanced the cellular immune response through stimulation of lymphocyte transformation and might increase the proliferation of both B and T cells [32]. It has been reported that administration of **7,** 12-Dimethylbenz(A)Anthracene induced carcinogenesis showed a reduction in the total number of lymphocytes in mammary glands of rats. This reduction was corrected after the administration of Myrrh for 15 consecutive days, which resulted in a significant increase in the percentage of lymphocytes [33].

7. Myrrh and Inflammatory Mediators

Extracellular mediators and regulators such as cytokines, growth factors, and eicosanoids are inflammatory mediators that control inflammation. In most published studies, Myrrh showed anti-inflammatory properties by inhibiting pro-inflammatory mediators and enhancing anti-inflammatory mediators [34] [35]. The anti-inflammatory properties of Myrrh are used in the treatment of oral inflammations such as periodontal diseases, gingivitis [36, 37], and for reducing the regrowth of plaques [38]. In vitro studies have reported that prolonged exposure to Myrrh decreases the production of IL-1β - stimulated IL-6 and interleukin-8 (IL-8). Exposure to Myrrh reduced the inflammatory state in gingival fibroblasts, indirectly preventing osteoclast breakdown or bone resorption by IL-6 and IL-8. A similar decrease in the inflammatory state following myrrh exposure was not observed in oral epithelial cells [39]. Myrrh suppressed IL-1β stimulated IL-6 expression in fibroblasts by inhibition of prostaglandin E_2 (PGE_2) [40]. In vitro, Myrrh exerts a barrier-stabilizing effect and a protective effect against TNFα-induced barrier breakdown in human intestinal epithelial cell models, by inhibiting PI3 kinase and signal transducer and activator of transcription 6 (STAT6) signaling pathways [41]. A previous study evaluated the effect of Myrrh against Trichinella spiralis compared to albendazole in mice. Myrrh was found to be highly effective against Trichinella spiralis and showed the highest expression of inducible nitric oxide synthase (iNOS) compared to albendazole [42]. In addition, in parasitic infections, Myrrh increased the level of IL-10 in

mice infected with S. Mansoni compared to the control group [43]. More studies showing the effect of Myrrh on inflammatory mediators are summarized in Table 1.

Table 1. The effect myrrh on inflammatory mediators.

Myrrh or a compound extracted from Myrrh	Effect of Myrrh on an experimental model	Effect myrrh on inflammatory mediators	Ref.
Myrrh	Myrrh inhibited LPS-induced productions of inflammatory mediators in septic mice	↓NO ↓PGE2 ↓IL-1β, ↓IL-6, ↓TNF-α	[15]
Myrrh	Myrrh attenuates ammonia-induced inflammation in hyperammonemic rats	↓ TNF-α	[44]
Myrrh	Myrrh inhibits paw edema in mice induced by formalin	↓ PGE_2	[45]
Myrrh	Myrrh down-regulates of inflammatory mediators in acute hepatic injury in Albino male Wistar rats	↓TNF-α mRNA expression ↓IL-6 mRNA expression ↓ IL-10 mRNA expression ↓ iNOS-2 mRNA expression ↓ HO-1	[46]
Myrrh	Myrrh attenuates the upregulation of inflammatory biomarkers in an ulcerative colitis rat model	↓ TNF-α ↓ IL-1β ↓ IL-6 ↓ PGE_2 ↑ NO ↑ IL-10	[47]
Myrrh	Myrrh decrease circulating markers of inflammation in a hepatocarcinogenesis rat model	↓ IL-6	[48]
Mirazid®+Doxycycline	Combination therapy of doxycycline and Myrrh have potential prophylactic therapy in patients with spontaneous bacterial peritonitis	↓ IL-6 ↓ CRP	[49]
Frankincense +Myrrh	Frankincense and Myrrh modulate antitumor immune responses in hepatocellular carcinoma models	↓TNF-α ↓IL-6	[31]
Guggulsterone	Guggulsterone attenuates acute pancreatitis in mice.	↓ TNF-α ↓ IL-1β ↓ IL-6	[17]

Tumor necrosis factor alpha (TNF-α), nitric oxide (NO), prostaglandin E2 (PGE2), interleukin 1 beta (IL-1β), interleukin 6 (IL-6), interleukin 10 (IL-10), inducible nitric oxide synthase-2 (iNOS-2), heme oxygenase-1 (HO-1), and C-reactive protein (CRP).

8. Conclusion

This review discussed the impact of Myrrh on the functions of white blood cells and its anti-inflammatory properties. Few studies have reported the potential effect of Myrrh on cellular functions of white blood cells. In addition, the exact mechanisms by which Myrrh or its bioactive compounds have a direct or indirect effect on leukocyte function has not been clearly elucidated. It is necessary to conduct more in-depth investigations to establish the anti-inflammatory properties of Myrrh. In addition, there are still research gaps to be filled to understand the role of bioactive constituents of myrrh activity in inflammation.

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Conflicts of Interest

The authors declare no conflict of interest.

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