Heme oxygenase-1: potential therapeutic targets for periodontitis

Weiwei Lv[1,2,*], Shichen Hu[1,2,*], Fei Yang[1,2], Dong Lin[1,2], Haodong Zou[1,2], Wanyan Zhang[1,2], Qin Yang[3], Lihua Li[1,2], Xiaowen Chen[4] and Yan Wu[1,2]

[1] Department of Stomatology, Affiliated Hospital of North Sichuan Medical College, Nanchong, Sichuan, China
[2] Department of Stomatology, North Sichuan Medical College, Nanchong, Sichuan, China
[3] School of Pharmacy, North Sichuan Medical College, Nanchong, Sichuan, China
[4] School of Medical Imaging, North Sichuan Medical College, Nanchong, Sichuan, China
* These authors contributed equally to this work.

ABSTRACT

Periodontitis is one of the most prevalent inflammatory disease worldwide, which affects 11% of the global population and is a major cause of tooth loss. Recently, oxidative stress (OS) has been found to be the pivital pathophysiological mechanism of periodontitis, and overactivated OS will lead to inflammation, apoptosis, pyroptosis and alveolar bone resorption. Interestingly, heme oxygenase-1 (HO-1), a rate-limiting enzyme in heme degradation, can exert antioxidant activites through its products—carbon monoxide (CO), Fe^{2+}, biliverdin and bilirubin in the inflammatory microenvironment, thus exhibiting anti-inflammatory, anti-apoptotic, anti-pyroptosis and bone homeostasis-regulating properties. In this review, particular focus is given to the role of HO-1 in periodontitis, including the spatial-temporal expression in periodental tissues and pathophysiological mechanisms of HO-1 in periodontitis, as well as the current therapeutic applications of HO-1 targeted drugs for periodontitis. This review aims to elucidate the potential applications of various HO-1 targeted drug therapy in the management of periodontitis, investigate the influence of diverse functional groups on HO-1 and periodontitis, and pave the way for the development of a new generation of therapeutics that will benefit patients suffering from periodontitis.

Subjects Cell Biology, Molecular Biology, Dentistry
Keywords HO-1, Periodontitis, Oxidative stress, Heme, Drug therapy

INTRODUCTION

Periodontitis is recognized as one of the most prevalent chronic inflammatory diseases affecting the oral cavity in humans and is the primary cause of tooth loss among adults. Severe periodontitis exerts a significant socio-economic impact on a global scale. Recent estimates suggest that the economic burden of severe periodontitis amounts to approximately $54 billion annually. Moreover, as the population ages, both the incidence of periodontitis and its associated burden are projected to increase each year (*Tonetti et al., 2017*).

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Corresponding author
Yan Wu, yanwu@nsmc.edu.cn

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Nevertheless, owing to the intricate nature of the pathogenesis of periodontitis, current therapeutic interventions remain insufficient to achieve complete resolution in the majority of cases. When exploring the various factors involved in the pathogenesis of periodontitis, it was found that although plaque biofilm is the initiator of periodontitis, other factors (*e.g.*, genetics, obesity, systemic systemic diseases, smoking, *etc.*) also have an impact on the inflammatory response of periodontal tissues (*Genco & Borgnakke, 2013*). Epigenetics can regulate gene expression without altering the DNA sequence, thereby affecting the inflammatory process by suppressing or overstimulating genes. For example, LncRNAZFY-AS1 can inhibit periodontitis and reduce oxidative stress by regulating microRNA-129-5p to promote DEAD-Box helicase 3 X-Link (*Cheng et al., 2022*). Interestingly, the Third National Health and Nutrition Examination Survey in the United States reported a significant association between obesity and the incidence of periodontitis in young people (*Al-Zahrani, Bissada & Borawskit, 2003*), and previous studies found that exercises could reduce systemic reactive oxygen species (ROS) and effectively inhibit gingival oxidative stress caused by obesity (*Azuma et al., 2011*). On the other hand, chronic periodontitis is the sixth complication of diabetes mellitus, and local and systemic oxidative damage exacerbated the severity of periodontitis in diabetes in a rat mode (*Li et al., 2018*). A comprehensive analysis of data from the 2016–2018 National Health and Nutrition Examination Survey in South Korea revealed that smokers exhibited a significantly higher risk of periodontitis compared to nonsmokers (*Sim et al., 2023*). Research indicated that smoking led to heightened total oxidative stress and reduced antioxidant capacity within periodontal tissue (*Lütfioğlu et al., 2021*).

Consequently, numerous factors indicate that oxidative stress, particularly ROS, plays a pivotal role in the pathogenesis of periodontitis (*Nazir, 2017*; *Xie et al., 2023*). Upon stimulation by bacterial lipopolysaccharide (LPS), various inflammatory cells aggregate into the periodontal tissues, of which neutrophils produce ROS to eliminate pathogens. However, prolonged stimulation by dental plaque biofilm leads to excessive ROS production, causing toxic effects on cellular macromolecules and mitochondrial damage. Then, mitochondrial damage further disrupts cellular energy metabolism, ultimately leading to cell death. On the other hand, excess ROS as well as insufficient antioxidant capacity of the body contribute to the disruption of the balance between oxidation and antioxidation in periodontal tissues. Cell membranes contain large amounts of polyunsaturated fatty acids esterified on phospholipids and free cholesterol, and these lipids are the main targets of ROS attack (*Kumar et al., 2017*). Additionally, it has been found that oxidative stress may indirectly affect oral bone tissue by generating oxidized fatty acids, which activate adipogenesis and inhibit osteoblastogenesis while directly impact osteoclasts. Detaily, ROS upregulates the expression of receptor activator of nuclear factor κB ligand (RANKL) and tumor necrosis factor-α (TNF-α), which are considered as important driving factors for osteoclast formation and bone resorption activity (*Żukowski, Maciejczyk & Waszkiel, 2018*).

Oxidative stress is characterized by an imbalance between oxidative and antioxidative processes within the body. The assessment indices encompass superoxide dismutase (SOD), catalase (CAT), malondialdehyde (MDA), glutathione (GSH), 8-hydroxylated

deoxyguanosine (8-OHdG) and ROS, among others, which collectively reflect the extent of oxidative stress and associated bodily damage. Randomized controlled trials investigating antioxidant capacity have revealed elevated levels of oxidative stress markers and diminished antioxidant status in the saliva or blood of periodontitis patients, in comparison to a control group (*Baltacıoğlu et al., 2014*). Data from the Third National Health and Nutrition Examination Survey in the United States demonstrated a negative correlation between indicators of serum antioxidant status—including serum vitamin C, bilirubin and total antioxidant capacity (TAOC)—and the prevalence of periodontitis (*Chapple, Milward & Dietrich, 2007*). Antioxidant enzymes, such as SOD, CAT and glutathione peroxidase (GPx), exhibited diminished activity levels in individuals diagnosed with periodontitis (*Huang et al., 2014*). MDA, a byproduct of membrane lipid peroxidation, was found to be significantly elevated in the saliva of patients suffering from periodontitis (*Cherian et al., 2019*). GSH, a critical antioxidant engaged in scavenging free radicals and participating in various antioxidative reactions, was observed to be significantly reduced in the serum levels of patients diagnosed with periodontitis (*Biju et al., 2014*). 8-OHdG, a significant indicator of oxidative DNA damage, demonstrated a substantial positive correlation with the severity of periodontitis (*Varghese et al., 2020*). Furthermore, Gustafsson reported that peripheral blood neutrophils exhibited elevated production of ROS in patients with chronic or aggressive periodontitis, indicating heightened neutrophil reactivity among these patients (*Gustafsson & Asman, 1996*). Collectively, these findings suggest that the inhibition of ROS levels may exert a beneficial effect on mitigating periodontal tissue destruction and suppressing alveolar bone resorption.

Current studies have revealed that over-activated oxidative stress would induce several cytokines and signal pathways to protect the body against ROS damage, including transcription factors (TFs), activator protein-1 (AP-1), NF-κB, mitogen-activated protein kinase (MAPK) and nuclear factor erythrocyte 2-related factor 2 (Nrf2). Interestingly, most of these cytokines and signal pathways could activate the heme oxygenase (HO) system to play an important antioxidant role to protect periodontal cells (*Huang et al., 2021a*; *Zhou et al., 2018*). The HO system was first identified in 1968 and recognized as a coupled NADPH-dependent microsomal oxygenase system (*Tenhunen, Marver & Schmid, 1968*). The HO system consist of three isozymes, including HO-1, HO-2 and HO-3 (*McCoubrey, Huang & Maines, 1997*). Of these, HO-2 is constitutively expressed at high levels in brain, testis, or endothelial cells, whereas HO-3 was only rarely observed in rat astrocytes (*Fernández-Fierro et al., 2020*). However, both HO-2 and HO-3 are constitutively expressed, undergo intense expression independent of external stimuli, and function primarily in normal heme capture and metabolism (*Naito et al., 2011*; *Donnelly & Barnes, 2001*). In addition, HO-1, a heat shock protein 32 (HSP32), is a stress-inducible isoform encoded by the human HMOX1 gene, and widely expressed in various tissues (*Leal & Carvalho, 2022*). Genetic defects in HO-1 can cause endothelial cell damage, anemia, and aberrant tissue iron accumulation stimulated by oxidative stress (*Yachie et al., 1999*). Moreover, HO-1 was found to have antioxidant effects through increasing the activities of antioxidant enzymes such as GPx, SOD and CAT, while decreasing the

expression of MDA, a marker of oxidative stress (*Rizzardini et al., 1994*; *Rawlinson et al., 1998*; *Ding et al., 2016*; *Wei et al., 2015*). Consequently, HO-1 has been recognized as an anti-inflammatory mediator involved in several inflammatory diseases such as hepatitis, neuritis and nephritis (*Ma et al., 2024a*; *Tao et al., 2024*; *Berköz, Yiğit & Krośniak, 2023*). We hypothesized that regulating the expression and activity of HO-1 may provide new ideas for the treatment of periodontitis. This review will discuss the current research progress on HO-1 and focus on its mechanism of action in different periodontitis phenotypes, as well as its upstream and downstream related targets and potential targeted therapeutic agents. Ultimately, we will use these interventions to target HO-1 in the treatment of periodontitis.

SURVEY METHODOLOGY

We conducted a comprehensive literature review on HO-1 in the context of periodontitis through searches on various platforms, including the Web, Google Scholar, and PubMed. The search terms employed included "HO-1", "oxidative stress", "periodontitis" and "ROS". This was achieved by intersecting these descriptors utilizing Boolean operators, specifically "OR" and "AND". Primarily, we included pertinent articles published from 2010 until July 2024 or earlier. Articles pertaining to cancer, non-oxidative stress-related diseases, viral infections, and those unrelated to periodontitis and HO-1 were systematically excluded. In summarizing the degradation products of HO-1, we incorporated key search terms such as "heme", "carbon monoxide", "Fe^{2+}", "biliverdin" and "bilirubin". To elucidate the molecular mechanisms of periodontitis associated with HO-1, we also integrated terms such as "PI3K/Akt", "Nrf2", "HMGB1", "MAPK" and "NF-κB". In organizing the literature concerning the biological behaviors associated with periodontitis, we further included keywords such as "inflammation", "bone resorption", "apoptosis" and "pyroptosis". Additionally, we incorporated terms such as "polyphenols", "terpenoids", "isothiocyanates", "saponins" and "alkaloids" as significant search keywords for HO-1-targeted therapies related to the treatment of periodontitis. In summary, this review identified a total of 215 pertinent research articles that examined the influence of HO-1 on the biological behaviors associated with periodontitis, as well as the roles of various functional groups in this context.

HO-1 metabolite

Basically, HO-1 exerts its effects through the degradation of heme. Heme (iron protoporphyrin IX), an iron porphyrin compound, is a cofactor of hemoglobin, myoglobin, cytochromes, peroxidases and catalase (*Wagener et al., 2001*). Heme is involved in a variety of biological processes, such as oxygen transport, signal transduction, peroxide metabolism and energy production (*Chiabrando et al., 2014*). The metabolism of periodontal cells cannot be achieved without the help of heme, but excessive free heme may activate Toll-like receptor 4 (TLR4) to produce deleterious effects by catalyzing the production of ROS, leading to oxidative stress and inducing cellular damage (*Ryter & Tyrrell, 2000*; *Janciauskiene, Vijayan & Immenschuh, 2020*). Furthermore, *Porphyromonas gingivalis*, the primary causative agent of periodontitis, is unable to proliferate without the

presence of heme (*Gao et al., 2018*). Consequently, high expression of HO-1 under the sustained effect of periodontal inflammation can degrade free heme to avoid cellular damage and act as an antimicrobial agent to a certain extent. Simultaneously, in response to periodontal inflammation, HO-1 forms a complex with heme and NADPH-cytochrome P450 reductase (*Yoshida & Kikuchi, 1978*). NADPH serves as an electron donor, while molecular oxygen binds to the complex, resulting in the production of CO, Fe^{2+} and biliverdin (*Yoshida, Noguchi & Kikuchi, 1980*). Subsequently, biliverdin is enzymatically converted to bilirubin by biliverdin reductase (*Wang & de Montellano, 2003*). HO-1 exerts its antioxidant effects *via* the degradation of these byproducts, thereby providing protective benefits to periodontal cells.

Carbon monoxide

Carbon monoxide (CO), a small molecule gas, contributes at least 86% of the endogenous carbon monoxide (*Ryter, Alam & Choi, 2006*). Low concentrations of CO have protective, anti-inflammatory, antioxidant and antibacterial properties (*Di Pietro et al., 2020*). MAPK are important targets of CO, regulating various important physiological and pathological processes such as cell growth, differentiation, environmental adaptation and inflammatory responses. In rheumatoid arthritis studies, CO was found to exert antioxidant properties by reducing ROS activity through inhibition of NF-κB expression rather than the MAPK pathway (*Ryter, Ma & Choi, 2018*). However, in the study on gingival fibroblasts, it was found that CO only activated P38 MAPK and had no effect on JNK and ERK expression (*Song et al., 2011*). Further research is needed to confirm whether CO affects the expression of MAPKs in other periodontal-related cells. Additionally, the anti-inflammatory effects of CO are related to the regulation of TLR4. CO can inhibit the expression of inflammatory factors such as IL-1β, PGE_2 and inducible nitric oxide synthase(iNOS) in periodontitis (*Song et al., 2017*; *Choi et al., 2021*). It was found that in diabetic periodontitis, CO could mediate the RAGE/NF-κB pathway to suppress periodontal tissue inflammation (*Tian et al., 2024*). Reports indicate that CO inhibits osteoclast formation while simultaneously promoting osteogenic differentiation in the context of periodontitis (*Song et al., 2017*). The Nrf2/HO-1 pathway is another target of CO, which exerts antioxidant effects by activating antioxidant enzymes such as SOD, CAT and GPx (*Di Pietro et al., 2020*). Moreover, transcription activation factor-3 (STAT-3), phosphatidylinositol 3-kinase/Akt (PI3K/Akt) and HIF-1, are also the targets of CO, which are involved in the regulation of cell protection (*Ryter, Ma & Choi, 2018*).

Fe^{2+}

Free ferrous iron exhibits elevated expression levels during the pathological progression of periodontitis and plays a crucial role in essential physiological activities, including DNA synthesis, ATP synthesis, and oxygen transport (*Chen et al., 2022a*; *Frey & Reed, 2012*). However, when excessive storage of ferrous ions occurs, resulting in iron overload, it may initiate the Fenton reaction, catalyzing the generation of ROS and leading to lipid peroxidation and subsequent oxidative damage to tissues (*Rehncrona et al., 1982*).

HO-1 plays an important role in cytoprotection, effectively helping cells to resist damage. However, concurrently, Fe^{2+}, another metabolite of HO-1, has the potential to contribute to the generation of free radicals. This apparent contradiction has long perplexed researchers and has stimulated related studies to explore this phenomenon more deeply. It has been proposed that this may be closely linked to the observation that Fe^{2+} produced by HO-1 activity is associated with elevated levels of ferritin and transferrin (*Lanceta et al., 2013*; *Paiva et al., 2012*). These proteins are integral to the pathology of periodontitis, particularly in the regulation of iron metabolism and the mitigation of oxidative stress. The ferroxidase center located within the ferritin heavy chain may further facilitate the oxidation of Fe^{2+} to the relatively less reactive ferric iron (Fe^{3+}) (*Bou-Abdallah, 2010*; *Lawson et al., 1989*). It has been proposed that HO-1 deficiency may result in disruptions in iron metabolism, consequently leading to reduced transferrin levels (*Kartikasari et al., 2009*). However, following 3 months of non-periodontal surgical treatment, serum transferrin levels increased significantly, indicating that these proteins are crucial in the management of periodontitis (*Shirmohamadi et al., 2016*). Furthermore, transferrin receptor 2 has been reported to effectively modulate the inflammatory response in periodontitis, thereby attenuating alveolar bone loss (*Lösser et al., 2024*). Thus, HO-1 not only safeguards cells from damage but may also mitigate alveolar bone loss induced by periodontitis by regulating the expression of transferrin and the ferritin heavy chain. Therefore, the regulatory relationship between Fe^{2+} produced by HO-1 activity and transferrin as well as the ferritin heavy chain may be of significant importance in the treatment and prevention of periodontitis, warranting careful consideration.

Biliverdin and bilirubin

Biliverdin is produced by HO-1-catalyzed degradation of heme. It can be converted to bilirubin by biliverdin reductase and nicotinamide adenine dinucleotide phosphate (NADPH) (*Zhu et al., 2011*). Previously, bilirubin was thought to be a hazardous waste product that could lead to liver disease or neonatal jaundice. However, a research in 1954 showed that bilirubin exhibited antioxidant properties that protected vitamin A and unsaturated fatty acids from oxidation (*Osiak et al., 2020*). Further studies have found that the antioxidant activity of bilirubin increased in the conditions of change from atmospheric oxygen concentration (20%) to tissue oxygen concentration (2%). Moreover, bilirubin could effectively scavenge single-linear oxygen molecules, disrupt free radical chain reactions, and act as a potent antioxidant, surpassing even the antioxidant alpha-tocopherol (*Stocker et al., 1987*). Low levels of hyperbilirubinemia may reduce the incidence of oxidative stress-related diseases such as cardiovascular disease, diabetes, obesity and metabolic syndrome. For example, it has been shown that topical application of bilirubin promoted healing of diabetic skin wounds by upregulating antioxidant status, promoting angiogenesis and collagen deposition (*Zhao et al., 2024*). In addition, bilirubin has shown some anti-inflammatory effects, and it was found that bilirubin treatment significantly reduced the expression levels of iNOS, cyclooxygenase-2 (COX-2) and IL-6, which in turn alleviated gastrointestinal inflammation (*Nakao et al., 2004*). Also, bilirubin treatment could reduce the levels of pro-apoptotic genes and improve the function and

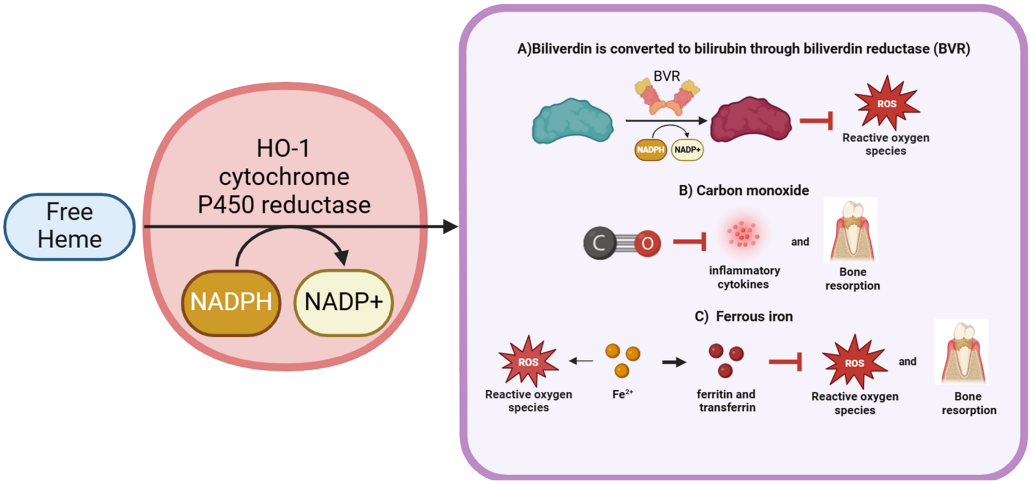

Figure 1 The activity and final product generation of HO-1. HO-1 is an enzyme that effectively degrades free heme, resulting in the production of biliverdin along with the release of carbon monoxide and Fe^{2+}. During the metabolism of biliverdin, it can be enzymatically converted to bilirubin by the action of biliverdin reductase. Notably, both biliverdin and bilirubin possess significant antioxidant properties, demonstrating the ability to effectively scavenge and neutralize ROS. Furthermore, carbon monoxide, a gaseous byproduct, inhibits the synthesis of inflammatory cytokines and partially attenuates alveolar bone resorption. Although Fe^{2+} acts as a pro-oxidant, contributing to elevated ROS levels, HO-1, recognized as a potent antioxidant, facilitates the release of Fe^{2+}, which enhances the expression of ferritin and transferrin, thereby exerting antioxidant effects and regulating bone homeostasis. Thus, HO-1 plays a pivotal role in cytoprotection, with its mechanism of action primarily manifested through the regulation of inflammatory responses, enhancement of antioxidant capacity, and maintenance of bone homeostasis. HMGB1 is a potential downstream target of HO-1, which regulates periodontal inflammation by inhibiting HMGB1. Figure drawing was supported by Biorender (https://app.biorender.com/).
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survival of allografts. Importantly, in treatments targeting periodontitis, researchers have found a negative correlation between bilirubin serum concentrations and the severity of periodontitis (*Chapple, Milward & Dietrich, 2007*). Bilirubin, derived from the reduction of biliverdin, is a potent antioxidant that effectively scavenges ROS, thereby preventing both protein and lipid peroxidation (*Zhou et al., 2021*) (Fig. 1).

Expression levels of HO-1 in periodontal tissues

Many studies have shown that HO-1 was expressed at low levels in normal periodontal tissues, and only small amounts were secreted to maintain the balance between oxidative and antioxidant status within the cell (*Kim et al., 2009*; *Pi et al., 2010*; *Cho & Kim, 2013*). *Chen et al. (2021a)*, detected the expression of HO-1 in normal periodontal tissues of young and aged mice, and found that the expression of HO-1 was significantly higher in aged mice compared to young mice, which suggested that the expression of HO-1 may be related to the aging. Additionally, HO-1 can also be induced in the periodontal tissues by various stimuli, including oxidative stress, inflammation, high oxygen, hypoxia and tissue injury (*Hanselmann, Mauch & Werner, 2001*). Infected periodontal tissues may secrete HO-1, which participates in the protection of periodontal cells due to its anti-inflammatory, antioxidative and anti-apoptotic effects (*Park et al., 2011b*; *Liu et al., 2017*; *Zhao et al., 2021*). It has been reported that nicotine/LPS stimulation induced HO-1

expression in human gingival fibroblasts (*Chang et al., 2005*; *Qi et al., 2018*). Nicotine, LPS, IL-1β and TNF-α can also promote the secretion of HO-1 in periodontal ligament cells (*Kim et al., 2009*; *Pi et al., 2010*). Macrophages, derived from monocytes migrating to tissues and differentiating into mature cells, play important roles as immune accessory cells in both normal physiological processes and pathological processes. In inflamed periodontal sites, macrophages account for approximately 5–30% of infiltrating cells. LPS from *Porphyromonas gingivalis* or *Prevotella intermedia* can induce the secretion of HO-1 in RAW264. 7 macrophages (*Cho & Kim, 2013*; *Park et al., 2011b*). Furthermore, human periodontal ligament stem cells (HPDLSCs) are another important cellular component in periodontal ligaments. They possess self-renewal and multidirectional differentiation potential, maintain periodontal homeostasis and participate in periodontal regeneration. H_2O_2 stimulated HO-1 expression in HPDLSCs (*Liu et al., 2017*). LPS promoted HO-1 expression in human oral gingival epithelial keratinocytes (*Hagiu et al., 2020*). Substance P, as a pro-inflammatory peptide involved in inflammation and immune response, increased HO-1 expression in periodontal ligament cells (*Lee et al., 2007*). Milk can promote the expression of inflammatory factors and matrix metalloproteinases (MMPs), while also inducing HO-1 secretion in human periodontal ligament cells (*Choi et al., 2015c*). In an *in vivo* experiment using a mouse periodontitis model, HO-1 expression was upregulated (*Kataoka et al., 2016*). However, it is still unknown which tissue is the main source of HO-1 production in periodontal tissues. Interestingly, not all studies have demonstrated high expression of HO-1 in inflamed periodontal tissues. In human gingival fibroblasts, one report indicated that LPS reduces HO-1 expression (*Huang et al., 2022*). In a simulated diabetic periodontal cell model, the expression of HO-1 in HPDLSCs was decreased (*Mohamed Abdelgawad et al., 2021*). The differential expression of HO-1 in various cell types and species may be attributed to polymorphic segments within the HO-1 promoter gene (*Taha et al., 2010*). It has been shown that longer polymorphic fragment sequences are associated with reduced HO-1 expression and reduced resistance to oxidative stress (*Loboda et al., 2008*). Furthermore, no researchers have yet examined the changes in HO-1 expression between normal and inflamed periodontal tissues in humans, which needs to be further investigated.

HO-1 and periodontitis

Pathophysiological mechanism

The development of periodontitis involves several factors, including inflammation, oxidative stress, apoptosis, pyroptosis and alveolar bone resorption.

Inflammation

When the host is infected with periodontal pathogens, the body activates the immune system to generate a defense response. Periodontal tissues recruit large numbers of neutrophilic polymorphonuclear leukocytes that produce the release of proinflammatory factors such as iNOS, IL-1β, IL-6 and IL-18 to destroy periodontal pathogens (*Sculley & Langley-Evans, 2002*; *Zhang et al., 2021*; *Huang et al., 2020*). On the one hand, NO is usually produced through the metabolism of the L-arginine catalyzed by nitric oxide

synthase (NOS) enzymes. To date, two isoforms of constitutive expression (nNOS and eNOS) have been identified, whereas the iNOS isoform is induced only in response to infection, inflammation, or trauma (*Nathan & Xie, 1994*). The HO-1 inhibitor tin protoporphyrin IX (SnPP) reduces the expression of ROS, which in turn inhibits the expression of iNOS in periodontitis (*Choi et al., 2013*). Studies have reported a shift in iNOS from NO production to ROS production, and iNOS is regulated by ROS (*Sun, Druhan & Zweier, 2010*).

Oxidative stress and apoptosis

ROS is a general term for oxygen radicals and peroxides, which have important roles in intracellular signaling and antimicrobial activity. Excess ROS can exert cytotoxicity and induce lipid peroxidation. MDA is used as a reliable indicator of oxidative damage in periodontitis. The results of the study showed that lipid peroxidation levels were higher in periodontitis patients than in periodontally healthy individuals, and MDA levels were closely associated with periodontal tissue inflammation and supporting tissue destruction (*Mohideen et al., 2023*). The construction of a mouse model of periodontitis found that high expression of HO-1 reduced the expression of ROS and oxidative stress damage marker MDA (*Zhao et al., 2021*). In addition, excessive ROS can induce oxidative DNA damage. For example, patients with chronic periodontitis have significantly elevated levels of 8-OHdG, a marker of oxidative DNA damage (*Chen et al., 2019a*). This oxidative DNA damage can interfere with cell cycle progression, ultimately leading to apoptosis of periodontal cells (*Chang et al., 2013*; *Yu et al., 2012*). *Jiang et al. (2022)* found that activation of the Nrf2/HO-1 pathway inhibited the expression of apoptosis markers Caspase3/9, which, in turn, produced a protective effect on periodontal cells.

Pyroptosis

On the other hand, NLRP3 seems to be associated with the production and maturation of pro-inflammatory cytokines (*e.g.*, IL-1β and IL-18) as well as the onset of pyroptosis, leading to chronic inflammation. However, the conversion of IL-1β and IL-18 to an active state as well as the promotion of highly inflammatory forms of programmed cell death (i.e., pyroptosis) are not possible without the help of caspase-1 (*Huang et al., 2020*). Thus, there is evidence that ROS may promote periodontal tissue inflammation by inducing NLRP3-caspase-1-IL-1β (*Yoon et al., 2018*). Recent studies have found that HO-1 has a regulatory effect on cellular pyroptosis. Unlike apoptosis, pyroptosis is a mechanism of programmed cell death of inflammatory cells mediated by caspase-1/-4/-5/-11, which is characterized by cell lysis and release of proinflammatory factors. HO-1 inhibits NLRP3 inflammasome and subsequently suppresses Caspase-1 activity, thereby preventing pyroptosis in gingival fibroblasts (*Huang et al., 2020*).

Alveolar bone resorption

Kim et al. (2005) demonstrated that osteoclast differentiation could not be achieved without the help of nuclear factor of activated T-cell c1 (NFATc1). RANKL-mediated ROS activation of NFATc1 promotes osteoclast differentiation (*AlQranei et al., 2020*). *Liu et al. (2019a)* further confirmed that activation of HO-1 reduces ROS to inhibit NFATc1, which

in turn inhibited bone destruction in a variety of diseases including periodontitis. Other studies have confirmed that both diabetes and periodontitis can undergo varying degrees of oxidative stress damage, and that promoting HO-1 expression results in decreased ROS levels, reduced bone resorption, wound healing, and amelioration of diabetic damage to periodontal tissues (*Liu et al., 2021*).

Molecular mechanism

Studies have shown that pathological processes such as inflammation, oxidative stress, apoptosis, pyroptosis and alveolar bone resorption in the treatment of periodontitis are closely related to the regulation of HO-1. Therefore, HO-1 has gradually become an important hub in the treatment of periodontitis, attracting great attention from scholars. It has been shown that inducers can regulate HO-1 expression through multiple signaling pathways, which include NF-κB, PI3K-Akt, p38 MAPK and Nrf2, *etc.*, (*Park et al., 2011a*; *Jin et al., 2012*; *Du et al., 2022*).

The NF-κB signaling pathway is activated by ROS, culminating in the upregulation of pro-inflammatory cytokines and chemokines, which ultimately leads to the destruction of periodontal tissues (*Özcan et al., 2017*). Moreover, numerous studies have demonstrated that CO, a catabolic byproduct of HO-1, can alleviate periodontal inflammation by inhibiting the NF-κB signaling pathway (*Song et al., 2017*; *Choi et al., 2021*, *2022*). Additionally, the PI3K/Akt pathway is pivotal in the progression of periodontitis, influencing cell proliferation, apoptosis, cytokine secretion and osteoblast differentiation (*Liu et al., 2019b*). Notably, researchers have revealed that the activation of the PI3K/AKT/HO-1 signaling cascade inhibits periodontal inflammation and imparts significant anti-oxidative stress properties (*Park et al., 2011a*). On the other hand, the family of MAPKs (including ERK1/2, JNK, and p38) mediates fundamental biological processes and cellular responses in response to hormones, growth factors, cytokines, bacterial antigens and environmental stresses (*Souza et al., 2012*). JNK has been shown to exert anti-apoptotic effects in response to bacterial invasion, with its activation stimulating the expression of genes associated with resistance to oxidative stress and apoptosis (*Wang et al., 2015*). Furthermore, several studies have indicated that the activation of specific signaling cascades, such as ERK/HO-1 and JNK/HO-1, can induce an anti-oxidative stress response, thereby effectively suppressing periodontal inflammation (*Park et al., 2011a*; *Jeong et al., 2010*).

Nrf2 serves as the principal activator of HO-1. In its resting state, Nrf2 associates with kelch-like ECH-associated protein 1 (Keap1), which is sequestered in the cytoplasm and subjected to degradation *via* ubiquitination. Under oxidative stress conditions, Keap1 dissociates from Nrf2, resulting in the translocation of Nrf2 to the nucleus, the dissociation of BTB and CNC homology 1 (Bach1) from the HO-1 promoter, and subsequently, the activation of HMOX1 gene expression (which encodes HO-1) (*Zhou et al., 2021*). For instance, metformin induces the dissociation of Keap1 from Nrf2, thereby enhancing HO-1 expression and exerting a therapeutic effect on diabetic periodontitis (*Mohamed Abdelgawad et al., 2021*). Furthermore, research has demonstrated that inhibition of the DNA-binding activity of Bach1, coupled with the promotion of its degradation, can lead to

the upregulation of HO-1 expression, thereby facilitating periodontal tissue regeneration (*Yuan et al., 2024*). Beyond the Nrf2/HO-1 signaling mechanism, various other factors influencing HO-1 expression have been extensively investigated. For example, ginsenosides promote HO-1 expression *via* epidermal growth factor receptor (EGFR), and knockdown of EGFR leads to decreased HO-1 expression, which in turn reverses the anti-inflammatory and osteogenic effects of periodontal tissues (*Kim et al., 2021*). Additionally, microRNAs are implicated in the regulation of HMOX1 and its upstream genes (*e.g.*, Nrf2, Keap1, Bach1, *etc.*), offering new avenues for research into the regulation of HO-1.

HO-1 may also play a role in regulating the expression of high mobility group box 1 (HMGB1), a highly conserved nuclear protein implicated in the development of various inflammatory diseases, including periodontitis. The release of HMGB1 may be induced under conditions of oxidative stress. However, the activation of HO-1 contributes to the suppression of HMGB1 expression (*Yao et al., 2022*). In a murine model of neuropathic pain, activation of HO-1 was found to inhibit HMGB1 expression, consequently reducing the levels of pro-inflammatory factors (*Chen et al., 2019b*). *Ha et al. (2012)* demonstrated that the HO-1 inhibitor zinc protoporphyrin (ZnPP) exacerbates brain injury by inducing the expression of HMGB1. Additionally, elevated levels of HMGB1 were detected in the gingival sulcus fluid of patients with periodontitis, where HMGB1 induced the expression of pro-inflammatory factors in periodontal cells *via* activation of the NF-κB pathway (*Kim et al., 2010*; *Luo et al., 2011*). Consequently, HMGB1 may serve as a promising downstream target of HO-1 in the context of periodontitis.

In summary, the potential mechanisms underlying the role of HO-1 in periodontitis necessitate further in-depth investigation. By modulating HO-1 and its associated signaling pathways, novel strategies may emerge for the effective treatment of periodontitis. Currently, while gingival sulcus fluid and saliva are readily accessible in clinical settings, there are limited relevant clinical markers available for detecting the onset and progression of periodontitis. HMGB1, as a potential downstream target of HO-1, is anticipated to serve as a significant biomarker for the diagnosis and treatment of periodontitis. However, the majority of studies on periodontitis and biomarkers have been limited to cross-sectional investigations, primarily reporting correlations between biomarkers and periodontitis, while longitudinal studies examining these biomarkers throughout the progression of periodontitis are notably lacking. This limitation represents a significant challenge currently confronting periodontists. For example, it has been demonstrated that HMGB1 is highly expressed in the gingival sulcus fluid of individuals with periodontitis; however, the dynamics of HMGB1 during the progression of periodontitis and in response to HO-1-targeted therapy remain to be fully explored, which will be the focus of our future research. Further investigation into the potential mechanisms of action of HO-1 in periodontitis will pave the way for future personalized treatment strategies utilizing saliva and gingival sulcus fluid. Future studies should concentrate on effectively activating HO-1, mitigating its double-edged sword effect, and elucidating the specific roles of HO-1-related factors, such as HMGB1, in periodontitis. Furthermore, investigating the relationships between additional biomarkers and the

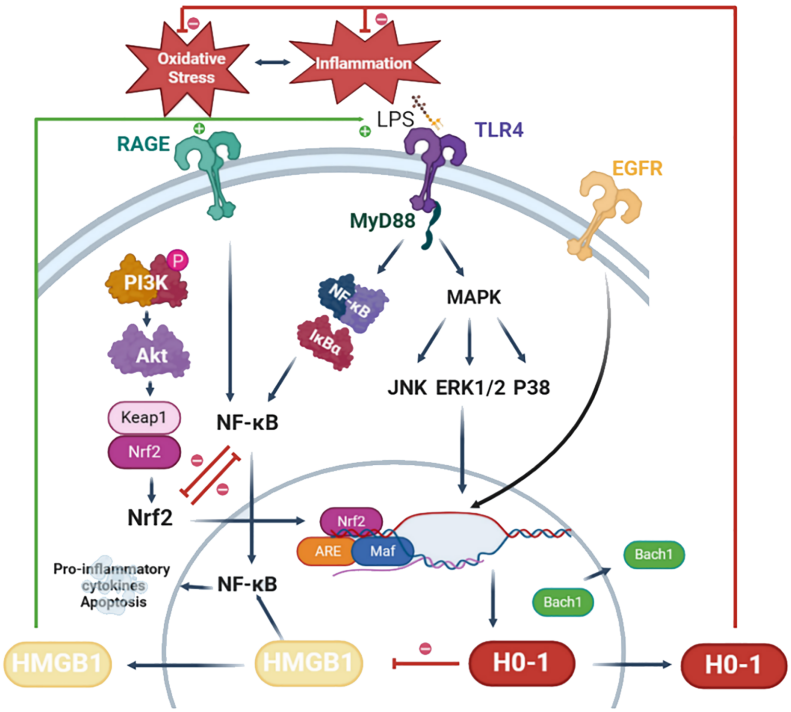

Figure 2 Potential mechanisms of HO-1 in periodontitis. LPS activates TLR4 signaling and initiates myeloid differentiation primary response protein 88-dependent (MyD88-dependent) pathway. MyD88 triggers the expression of NF-κB and MAPK leading to cell apoptosis and the production of pro-inflammatory cytokines. In particular, the MAPK pathway is involved in the regulation of HO-1. Phosphorylated expression of PI3K is increased in response to stimulation by anti-inflammatory drugs. Akt serves as a downstream target of PI3K. Akt stimulates the dissociation of Nrf2 and Keap1, translocating them into the nucleus. Bach1 bind to antioxidant response element (ARE) in the promoter region of the HO-1 gene, suppressing HO-1 expression. Nrf2 translocates into the nucleus, reducing Bach1's DNA-binding activity, inducing Bach1 nuclear export, and proteasome-dependent degradation. Nrf2 forms a complex with small Maf proteins (sMaf) and ARE. This complex facilitates the transcription of HO-1 and inhibits oxidative stress feedback. HMGB1 translocates from the nucleus to the cytoplasm, often undergoing post-translational modifications such as acetylation or phosphorylation. Through exocytosis, cells secrete HMGB1. Extracellularly, HMGB1 can activate and bind to its receptors, receptor for advanced glycation end products (RAGE), and TLR4, leading to NF-κB activation. This leads to the production and release of inflammatory cytokines and chemokines, triggering periodontal inflammation. Figure drawing was supported by Biorender (https://app.biorender.com/).

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development of periodontitis aims to facilitate the development of more effective diagnostic methods and targeted therapies for the prevention and clinical management of periodontitis (Fig. 2).

HO-1 targeted drug therapy for periodontitis

The present study demonstrated a robust correlation between oxidative stress and periodontitis, as evidenced by elevated levels of the oxidative damage marker MDA and reduced antioxidant capacity identified in the gingival sulcus fluid (*Lutfioğlu et al., 2017*). Subsequent to systematic scaling and root planing interventions, reduced levels of reactive oxygen species and enhanced antioxidant capacity were observed (*Bansal et al., 2017*; *Marconcini et al., 2021*). Combined antibiotic therapy suppresses oxidative stress as well as

improves clinical parameters in periodontitis (*Boia et al., 2019*). Recent studies have revealed that antibiotic treatments like josamycin and tetracycline effectively inhibit periodontitis *via* the HO-1 pathway (*Choi et al., 2018*; *Murakami et al., 2020*). Due to the emergence of antibiotic resistance, there has been a transition towards exploring the utilization of antioxidants for clinical therapy. For instance, the amalgamation of scaling and root planing with antioxidants such as green coffee bean extract oral supplements, lycopene, or green tea extract has demonstrated efficacy in the management of periodontitis (*Saha et al., 2024*; *Tripathi et al., 2019*). For example, a randomized controlled trial of 110 subjects by scholars found that patients with periodontitis had increased clinical attachment levels and reduced gingival inflammation, periodontal pocket depth and oxidative damage after 3 months of topical lycopene application (*Chandra et al., 2012*). Numerous studies have reported significant reductions in probing depth and bleeding index, along with an eight-fold increase in the antioxidant capacity of gingival sulcus fluid following supragingival cleaning and root planing combined with green tea-assisted treatment (*Taleghani et al., 2018*; *Chopra et al., 2016*). In the future, HO-1-targeted antioxidant therapy may represent a significant direction for research, and we will further investigate HO-1-targeted drug development in periodontitis utilizing natural extracts, clinical drugs and novel HO-1 inducers.

Natural extracts

In recent years, the anti-inflammatory and antioxidant effects of bioactive substances of plant origin as well as herbal medicines have been extensively studied (*Chen et al., 2022b*; *Gu, Hao & Xiao, 2022*). Many natural extracts have been found to exert protective effects on animal models of periodontitis by activating HO-1. HO-1 inducers, such as magnolol, schisandra chinensis α-iso-cubebenol, 6-Shogaol, hesperetin, resveratrol and quercetin, have been investigated for the treatment of periodontitis (*Cho & Kim, 2013*; *Zhao et al., 2021*; *Liu et al., 2019a*, *2021*; *Park et al., 2011a*; *Nonaka et al., 2019*; *Bhattarai et al., 2016*).

Polyphenol compound

Polyphenols are primarily categorized into tannins, flavonoids and lignin-carbohydrate complexes, and are well-known for their antimicrobial, antioxidant and anti-inflammatory properties. In studies pertaining to periodontitis, polyphenols promote collagen synthesis through the activation of fibroblasts, upregulation of collagen gene expression, inhibition of MMPs and antioxidant effects. Furthermore, polyphenols exert anti-inflammatory and antimicrobial effects, as well as inhibit alveolar bone resorption (*Bunte, Hensel & Beikler, 2019*). These mechanisms contribute to the repair, regeneration and maintenance of periodontal tissues, rendering polyphenols valuable therapeutic agents for the treatment of periodontal diseases. Currently, natural extracts of polyphenols, including magnolol, resveratrol, chlorogenic acid, quercetin, hesperetin, isorhamnetin and cardamonin, mediate the inhibition of periodontal inflammation through HO-1 pathways (*Cho & Kim, 2013*; *Huang et al., 2022*; *Liu et al., 2019a*, *2021*; *Ma et al., 2024b*; *Jin et al., 2013*; *Okamoto et al., 2024a*). For example, magnolol is a polyphenolic compound extracted from the deciduous tree *Magnolia officinalis*, which belongs to the Magnoliaceae family. Magnolol

exhibits several pharmacological effects, such as anti-inflammatory, antibacterial, anti-ulcer, antioxidant, anticancer and platelet aggregation inhibition. It is mainly used in the treatment of acute enteritis, bacterial or amoebic dysentery, and chronic gastritis. The earliest research on the use of magnolol in periodontal treatment was conducted by *Chang et al. (1998)* who studied the minimum inhibitory concentration (MIC) of magnolol on its antibacterial effect *in vitro*. They found that magnolol had significant antibacterial effects against *Porphyromonas gingivalis*, Actinomyces and *Prevotella intermedia* when the MIC dose was 25 μg/mL (*Chang et al., 1998*; *Cicalău et al., 2021*). Moreover, magnolol could prevent alveolar bone resorption in ligature-induced rat periodontitis by activating the Nrf2/HO-1 pathway, thereby preventing oxidative stress and inflammation (*Lu, Huang & Chou, 2013*; *Lu et al., 2015*). Interestingly, *Liu et al. (2021)* further discovered that magnolol could treat diabetic periodontitis by activating the Nrf2/HO-1 pathway. However, due to the fact that some compounds can regulate different signaling pathways and lack selectivity towards HO-1, many phytochemicals have low bioavailability and may produce certain side effects (*Zhou et al., 2021*). Additionally, resveratrol, a polyphenol found in a variety of foods, has been recognized as a potentially therapeutic drug for the prevention and treatment of inflammatory diseases by targeting and modulating the Nrf2/HO-1 pathway. A clinical study showed that treatment utilizing resveratrol reduced inflammatory markers in the serum and gingival sulcus fluid of patients with periodontitis compared to placebo. However, poor water solubility, rapid decomposition, short serum half-life as well as poor solubility and rapid hepatic and intestinal metabolism result in the low bioavailability of resveratrol (*Zhang et al., 2022*). To solve this problem, researchers grafted resveratrol into mesoporous silica nanoparticles, which improved its bioavailability and allowed for longer drug duration (*Tan et al., 2022*). In addition, there are researchers who have developed a resveratrol delivery system in the form of cyclodextrin and xanthan gum-based oral tablets, which increased the solubility of resveratrol and eliminated bypass enterohepatic metabolism (*Paczkowska-Walendowska et al., 2021*). Moreover, quercetin, a flavonoid compound found in foods such as apples, potatoes, tomatoes and onions, has received much attention for its mediation of the HO-1 pathway and its potent antioxidant and anti-inflammatory properties (*Wei et al., 2021*). However, its functionality is limited due to its water solubility and bioavailability. It was found that combining quercetin with a nanoemulsion increased its absorption rate and eliminated the variability of absorption. The resulting nanoemulsion gel could release 92.4% of quercetin within 6 h (*Aithal et al., 2018*).

Terpenoid

Terpenoids are categorized into sesquiterpenes, monoterpenes and diterpenes based on the number of isoprene units they contain. Terpenoids exhibit antimicrobial and anti-inflammatory activities that disrupt microbial biofilms and modulate host immune responses, rendering them valuable in periodontal therapy (*Masyita et al., 2022*). Schisandra is rich in a variety of terpenoids that have been utilized to treat numerous types of inflammation, demonstrating antioxidant, anti-inflammatory, antimicrobial and neuroprotective effects. *Schisandra chinensis* α-iso-cubebenol, extracted from *Schisandra*

chinensis, belongs to the sesquiterpenoid group and mediates the PI3K/AKT and ERK pathways to induce HO-1 expression in periodontitis. This process alters the permeability of the outer membrane of periodontally pathogenic bacteria, resulting in microbial destruction while exerting antimicrobial and anti-inflammatory effects (*Park et al., 2011a*).

Isothiocyanate compounds

Isothiocyanates represent a class of compounds characterized by the -N=C=S chemical group, formed by substituting sulfur for oxygen in the isocyanate group. Isothiocyanates are known for their antimicrobial, anti-inflammatory, anticancer and antioxidant properties. Among the various isothiocyanates, benzyl isothiocyanate (BITC) is commonly found in cruciferous vegetables such as broccoli, cabbage and bean sprouts (*Rask et al., 2000*). The unique properties of BITC enable it to penetrate the bacterial outer membrane and interfere with the bacterial redox system. Studies have demonstrated its inhibitory activity against certain Gram-negative periodontal pathogens, including Actinomyces and *Porphyromonas gingivalis* (*Sofrata et al., 2011*). Furthermore, several studies have indicated that isothiocyanates, such as sulforaphane, can activate the Nrf2/HO-1 signaling pathway (*Chen et al., 2024*; *Hosokawa et al., 2024*; *Chen et al., 2021b*). Iberin, an isothiocyanate present in green and yellow vegetables, is a specific member of this compound family that exhibits low cytotoxicity to normal cells (*El Badawy et al., 2021*). Research has shown that Iberin can upregulate HO-1 expression and significantly reduce the production of inflammatory mediators in periodontal tissues, including IL-6, CXCL10, VCAM-1, iNOS and COX-2 (*Hosokawa et al., 2022*). Additionally, bertereroin is a bioactive compound classified as an isothiocyanate, primarily found in cruciferous vegetables such as cabbage, arugula and salad greens. Bertereroin has been shown to reduce the production of ROS in periodontal lesions by enhancing the expression of HO-1 (*Hosokawa et al., 2024*).

Saponin compounds

The amphiphilic structure of saponins comprises a hydrophilic glycosidic portion and a hydrophobic glycosidic element (saponin backbone), which facilitates the efficient embedding of saponins in the cell membranes of microorganisms. Simultaneously, saponins can interfere with the production of the extracellular matrix necessary for bacterial surface adhesion and biofilm formation (*Khan et al., 2022*). By penetrating the biofilm matrix, saponins induce the death of microbial cells within the structure, thereby disrupting the established biofilm (*Adnan et al., 2023*). Furthermore, saponins derived from various plants exhibit significant antimicrobial, anti-inflammatory and immunomodulatory properties, highlighting their considerable potential for the treatment of periodontal disease. For instance, ginseng is extensively utilized in traditional Chinese medicine to alleviate various diseases, including diabetes, hypertension, gastric ulcers, inflammatory diseases and cancer. Ginseng is characterized by its anticancer, anti-inflammatory, antioxidant and immunomodulatory properties (*Carota et al., 2019*). Research indicates that ginsenosides, the primary pharmacologically active components of ginseng, are closely associated with the regulation of the EGFR/HO-1 pathway. Their

effects on periodontal tissues encompass various aspects, including the regulation of osteoblast and osteoclast functions, inhibition of connective tissue degradation, and exertion of anti-inflammatory, antimicrobial and antioxidant effects (*Kim et al., 2021*).

In summary, plant-derived bioactive compounds and herbs demonstrate significant therapeutic potential in the treatment of periodontitis. Specifically, compounds such as polyphenols, terpenoids, isothiocyanates and saponins significantly influence various aspects of periodontitis, and this effect is closely related to the regulation of HO-1. Moving forward, alongside in-depth studies on the application of these classes of compounds in periodontitis treatment, alkaloids, polysaccharides and quinones are anticipated to function as HO-1 inducers, thereby playing an active role in the prevention and treatment of periodontitis. For example, research has demonstrated that the effectiveness of berberine as an alkaloid, lycium barbarum polysaccharide (LBP) as a polysaccharide and tanshinone IIA as a quinone in various inflammatory diseases is contingent upon the modulatory effect of HO-1 (*Sun et al., 2024*; *Yang et al., 2023*; *Wang et al., 2022a*). Additionally, evidence supports that berberine, LBP and tanshinone IIA may play significant roles in the treatment of periodontitis (*Liu et al., 2019c*; *Qin et al., 2024*; *Wang et al., 2023*; *Mohammadian Haftcheshmeh & Momtazi-Borojeni, 2021*; *Lai et al., 2023*). Consequently, further exploration into whether these alkaloids, polysaccharides and quinones exert their effects *via* the HO-1 pathway will be essential for future studies on the combination and precise medication of multiple compounds. At the same time, future studies should also concentrate on factors such as the route of drug administration, dosage and bioavailability to ensure that these therapeutic approaches are both safer and more effective in clinical applications (Table 1).

Clinical drugs

Currently, several clinical drugs have been found to activate HO-1 and exhibit potential value in the treatment of periodontitis. For example, nifedipine, a calcium channel blocker widely used in cardiovascular disease treatment, has been reported to possess anti-inflammatory and antioxidant effects. Nifedipine can alleviate osteoarthritis by activating the Nrf2/HO-1 signaling pathway to counteract oxidative stress caused by free radicals (*Yao et al., 2020*). In a mouse macrophage environment stimulated by *Porphyromonas gingivalis* lipopolysaccharide (a periodontal pathogen), nifedipine upregulated HO-1 expression and inhibited the release of inflammatory substances such as NO (*Choe et al., 2021*). Strontium ranelate is an anti-osteoporosis drug with dual effects of promoting bone formation and inhibiting bone resorption (*Yu et al., 2022*). *Souza et al. (2018)* found promotion of HO-1 signaling and inhibition of alveolar bone resorption after ligating the maxillary molars of rats treated with strontium ranelate (100 mg/kg) for 7 days. Dimethyl fumarate (DMF), a drug used for psoriasis and other immune-mediated diseases, weakens intracellular ROS induced by RANKL by enhancing HO-1 expression while inhibiting osteoclastogenesis (*Yamaguchi et al., 2018*; *Matteo et al., 2022*). It is speculated that DMF may be a potential inhibitor of bone destruction in periodontitis. However, the specific efficacy of DMF in periodontitis treatment requires further experimental validation.

Table 1 Advances *in vitro* therapy with natural extracts.

Specific drugs or chemicals	Cell type	Effects on cells	Mechanism	Literatures
Chlorogenic acid	HGF	Prevention of LPS-induced inflammatory response	Activation of the Nrf2/HO-1 **anti-inflammatory pathway**	*Huang et al. (2022)*
Ginsenosides	HPDL	Promote osteogenic differentiation and inhibit bone resorption, prevent LPS-induced inflammatory response	Promotion of HO-1 **antioxidant and anti-inflammatory pathways** through activation of EGFR	*Kim et al. (2021)*
Magnolol	HGF	Prevention of AGEs-induced inflammatory response and apoptosis	Activation of Nrf2/HO-1 **antioxidant and anti-inflammatory pathways**	*Liu et al. (2021)*
Panax ginseng fruit	HPDL	Promote osteogenic differentiation and inhibit bone resorption, prevent LPS-induced inflammatory response	Activated HO-1 **antioxidant pathway**	*Kim et al. (2020b)*
Resveratrol	HGF	Prevention of LPS-induced inflammatory response	Activation of the Nrf2/HO-1 **antioxidant pathway**	*Bhattarai et al. (2016)*
	PDLSC	Prevention of LPS-induced inflammatory response	Promotion of Nrf2/HO-1 **antioxidant and anti-inflammatory** pathways and inhibition of NF-κB signaling	*Ma et al. (2024b)*
Isorhamnetin	HGF	Prevention of LPS-induced inflammatory response	Promotion of Nrf2/HO-1 **antioxidant and anti-inflammatory** pathways and inhibition of NF-κB signaling	*Qi et al. (2018)*
	RAW264. 7	Prevention of LPS-induced inflammatory response	Promotion of HO-1 **anti-inflammatory pathway** and inhibition of NF-κB signaling	*Jin et al. (2013)*
Quercetin	RAW264. 7	Prevention of LPS-induced inflammatory response	Promotion of HO-1 **anti-inflammatory pathway** and inhibition of STAT1 signaling	*Cho & Kim (2013)*
Hesperetin	RAW264. 7	Inhibition of osteoclast differentiation and activity	Promotion of Nrf2/HO-1 **antioxidant pathway**	*Liu et al. (2019a)*
Schisandra chinensis α-iso-cubebenol	THP-1	Prevention of LPS-induced inflammatory response	Promotion of Akt(ERK)/Nrf2/HO-1 **anti-inflammatory pathway**, inhibition of NF-κB signaling	*Park et al. (2011a)*
6-Shogaol	HGF	Prevention of AGEs-induced inflammatory response and apoptosis	Promotion of HO-1 **antioxidant and anti-inflammatory pathways**, inhibition of MAPK and NF-κB signaling	*Nonaka et al. (2019)*
Green tea	HGEK	Prevention of LPS-induced inflammatory response	Promotion of Nrf2/HO-1 **antioxidant and anti-inflammatory pathways**	*Hagiu et al. (2020)*
Ecklonia cava	RAW264. 7	Prevention of LPS-induced inflammatory response	Promotion of Nrf2/HO-1 **anti-inflammatory pathway** and inhibition of NF-κB signaling	*Kim et al. (2019)*
Ginkgo biloba	RAW264. 7	Prevention of LPS-induced inflammatory response	Promoting the Nrf2/HO-1 **anti-inflammatory pathway**	*Ryu et al. (2012)*
Sappanchalcone	HPDL	Prevention of LPS-induced inflammatory response	Promoting the JNK/HO-1 **anti-inflammatory pathway**	*Jeong et al., 2010*)
Kaempferol	RAW264. 7	Prevention of LPS-induced inflammatory response	Promoting HO-1 **antioxidant and anti-inflammatory pathways**	*Choi et al. (2013)*
Cardamonin	HPDL	Prevention of IL-1β-induced inflammatory response	Promoting HO-1 **anti-inflammatory pathway**, inhibiting NF-κB and STAT3 signalling	*Okamoto et al. (2024b)*
Xanthones	PDLSC	Prevention of H_2O_2-induced inflammation, promotion of osteogenic differentiation	Promoting the Nrf2/HO-1 **antioxidant pathway**	*Ruangsawasdi et al. (2023)*
Notopterol	HGF	Prevention of LPS-induced inflammatory response	Inhibition of NF-κB and promotion of the PI3K/AKT/HO-1 signalling pathway	*Zhou et al. (2023)*

(Continued)

Table 1 (continued)

Specific drugs or chemicals	Cell type	Effects on cells	Mechanism	Literatures
Berteroin	HPDL	Prevention of IL-1 β or TNF-α induced inflammatory response	Promoting HO-1 **anti-inflammatory pathway**, inhibiting NF-κB and STAT3 signalling	*Hosokawa et al. (2024)*
curcumin	H400 oral epithelial cell	Prevention of Fusobacterium nucleatum-induced inflammatory response	Promoting the HO-1/CO **anti-inflammatory pathway**	*Grant et al. (2023)*
Iberin	TR146 cells	Prevention of TNF-α-induced inflammatory response	Promoting HO-1 **anti-inflammatory pathway**, inhibiting NF-κB, STAT 3 and S6 signalling	*Hosokawa et al. (2022)*

Note:
HGFs, human gingival fibroblasts; HPDL, human periodontal ligament cells; THP-1, human monocytes; HGEK, human gingival epithelial keratin-forming cells; PDLSC, periodontal stem cells; TR146, a human oral epithelial cell; AGEs, advanced glycosylation end products; LPS, lipopolysaccharides; EGFR, epidermal growth factor receptor.

Additionally, commonly used hypoglycemic agents for diabetes, a prevalent oxidative stress disorder, include biguanides (*e.g.*, metformin) and GLP-1 (glucagon-like peptide-1) receptor agonists. Metformin is regarded as the first-line choice for treating type 2 diabetes, effectively reducing intracellular free radical levels, enhancing insulin sensitivity, and exerting a cytoprotective effect through the upregulation of HO-1 expression (*Wang et al., 2022b*). Conversely, GLP-1 receptor agonists (*e.g.*, liraglutide) represent an emerging class of antidiabetic drugs that stimulate insulin secretion primarily by mimicking the biological effects of GLP-1. Research has demonstrated that GLP-1 receptor agonists induce HO-1 expression, promote endothelial cell protection and angiogenesis, contribute to diabetic wound healing, and reduce the risk of diabetes-related complications, thereby enhancing the overall prognosis of diabetic patients (*Huang et al., 2021c*). The pathogenesis of periodontitis, an oxidative stress disorder closely associated with diabetes, involves the interplay between oxidative stress and inflammatory responses. Numerous studies have demonstrated that both biguanides and GLP-1 receptor agonists effectively inhibit the development and progression of periodontitis (*Pang et al., 2019*; *Sawada et al., 2020*; *Zhang et al., 2020*; *Neves et al., 2023*). Consequently, an in-depth investigation into the specific role of HO-1 in the pathogenesis of periodontitis concerning biguanides and GLP-1 receptor agonists is essential for future treatment and management strategies.

Furthermore, atherosclerosis is an oxidative stress disorder primarily characterized by lipid accumulation within the vessel wall. Research indicates that statins effectively reduce oxidative stress and enhance endothelial function by increasing HO-1 expression levels and inhibiting NADPH oxidase activity, thereby minimizing vascular damage and preserving vascular structural integrity (*Piechota-Polanczyk & Jozkowicz, 2017*). In a randomized controlled trial concerning periodontitis, scaling and root planing combined with adjunctive statin treatment significantly improved clinical attachment levels and reduced periodontal pocket depth, while effectively decreasing the incidence of bleeding on probing (*Alkakhan et al., 2023*). Recent studies further suggest that statins possess significant potential for periodontal regeneration, osteoclast modulation and antimicrobial effects in periodontitis (*de Carvalho et al., 2021*; *Parolina de Carvalho et al., 2024*). An in-depth study of the mechanism of action of statins in periodontitis, especially the way

Table 2 Advances in clinical drug therapy *in vitro*.

Specific drugs or chemicals	Cell type	Effects on cells	Mechanism	Literatures
Nifedipine	RAW264.7 Cell	Prevention of LPS-induced inflammatory response	Promotes HO-1 **anti-inflammatory pathway**, inhibits NF-κB and STAT 1/3 signaling, and promotes M2 macrophage polarization	*Yao et al. (2020)*
Josamycin	RAW264.7 Cell	Prevention of LPS-induced inflammatory response	Promotion of HO-1 **anti-inflammatory pathway** and inhibition of NF-κB signaling	*Choi et al. (2018)*
Telmisartan	RAW264.7 Cell	Prevention of LPS-induced inflammatory response	Promotes HO-1 **anti-inflammatory pathway**, inhibits NF-κB and STAT 1/3 signaling, and promotes M2 macrophage polarization	*Choe et al. (2019)*
Dimethyl fumarate	RAW264.7 Cell	Inhibits osteoclast formation and activity	**Inhibition of oxidative stress** *via* the Nrf2/HO-1 pathway	*Yamaguchi et al. (2018)*
Tetracycline	RAW264.7 Cell	Prevention of LPS-induced inflammatory response	Promoting HO-1 **antioxidant and anti-inflammatory pathways**	*Murakami et al. (2020)*

they exert their effects through the HO-1 pathway, will bring important insights and guidance for the future treatment and management of periodontitis.

In summary, the management of oxidative stress disorders is closely linked to the function of HO-1. Consequently, a thorough investigation into the specific applications of these HO-1-targeted drugs in periodontitis will be vital for future research endeavors. This approach will not only facilitate the enhancement of combination drug strategies for patients with concomitant systemic oxidative stress disorders, thereby avoiding unnecessary duplication of therapy, but is also expected to achieve optimal efficacy and a favorable prognosis. From the perspective of drug regulatory approvals and safety studies, the available clinical drugs that act as HO-1 inducers demonstrate the potential to become effective options for the treatment of periodontitis (Table 2).

Novel HO-1 inducers

In addition to the use of plants, herbs and clinical drugs for HO-1 induction, there has been a recent interest in other modes of obtaining HO-1 inducers for the treatment of periodontitis. Carbon monoxide has been shown to play a significant role in various cellular biological processes, including cell apoptosis and immune-inflammatory responses. Carbon monoxide-releasing molecules (CORMs), as a novel type of compound, can release carbon monoxide in a controlled manner under physiological conditions, thereby increasing the expression of HO-1 in various animal models and cell types (*Lv et al., 2020*). *Choi et al. (2021*, *2022*, *2015a)* demonstrated that lipophilic CORM-2 and water-soluble CORM-3, CORM-401 had inhibitory effects on the inflammatory response induced by *Porphyromonas gingivalis* lipopolysaccharide through NF-κB inhibition. Additionally, it has been reported that CORM-3 can suppress the expression of the osteoclast factor RANKL and upregulate the expression of osteoprotegerin (OPG), which may have potential therapeutic value in inhibiting bone resorption in periodontitis (*Lv et al., 2020*). Moreover, vitamin D has been found to have regulatory effects in various inflammatory diseases. ED-71, as an analog of vitamin D, can activate the Nrf2/HO-1 pathway and inhibit the expression of NLRP3, Caspase-1 and IL-1β in gingival fibroblasts

under inflammatory conditions, thereby suppressing pyroptosis (*Huang et al., 2020*). Interestingly, coffee is a common dietary ingredient in everyday life, and opinions differ as to whether it is beneficial or harmful to health. A survey of 16, 730 adults in Korea found that increased coffee intake may further predispose to periodontitis (*Han, Hwang & Park, 2016*). However, a Japanese cross-sectional study found that coffee consumption during periodontal maintenance treatment was associated with a reduction in the prevalence of severe periodontitis (*Machida et al., 2014*). As coffee is a complex mixture, different types of coffee have different compositions and different biological effects. This is perhaps why the results of current coffee research are inconsistent (*Song et al., 2022*). The main components of coffee are caffeine and chlorogenic acid, which are absorbed by the body. Caffeine and chlorogenic acid have been reported to promote the expression of Nrf2 translocation and HO-1, showing antioxidant effect (*Huang et al., 2022*; *Khan et al., 2019*). In contrast, a recent study showed that caffeine and chlorogenic acid preparation of artificial coffee promoted AMP-activated protein kinase phosphorylation and reduced the NF-κB pathway to exert anti-inflammatory effects on periodontal cells (*Song et al., 2022*). However, based on the uncertainty that still exists regarding the toxicity of these synthetic as well as dietary-acquired substances, and what constitutes a safe and effective dosage. Further studies need to be conducted before the substances are ultimately converted into clinical drugs (Tables 3 and 4).

In summary, natural extracts exhibit a reduced incidence of side effects and a lower propensity for resistance compared to their chemical counterparts. Nevertheless, they are confronted with challenges related to extraction purity, potency, and dosage. Polyphenols, terpenoids, isothiocyanates and saponins have been shown to significantly influence various facets of periodontitis *via* the modulation of HO-1 activity. These compounds have been extensively investigated within the domain of periodontitis. Future research should prioritize the exploration of additional polyphenols, terpenoids, isothiocyanates and saponins, as well as the translation of experimental findings into clinical applications. Furthermore, alkaloids, polysaccharides and quinones exhibit a strong correlation with HO-1, oxidative stress disorders and chronic inflammatory diseases. Nonetheless, there exists a paucity of studies addressing the principal pathways of these compound classes in periodontitis, including HO-1, warranting our sustained long-term research efforts. The adverse effects associated with marketed clinical drugs are more explicitly delineated, and their safety and efficacy are thoroughly documented through clinical trials. The HO-1-targeted clinical drugs employed in the treatment of oxidative stress-related diseases represent promising candidates for the management of periodontitis. Researchers have initiated investigations into novel HO-1 inducers, including synthetic CORM, periostin and compounds derived from dietary vitamins and coffee. However, these innovative HO-1 inducers presently lack adequate clinical evidence to substantiate their efficacy. Consequently, a significant focus of future research will involve the application of acquired clinical data to the development of clinical therapeutics for periodontal disease. Furthermore, it is crucial to persist in investigating the role of HO-1 in periodontitis management as mediated by natural extracts and clinical drugs. This ongoing research will facilitate the development of diverse structures and functional groups to enhance HO-1

Table 3 Advances *in vitro* therapy with novel HO-1 inducers.

Specific drugs or chemicals	Cell type	Effects on cells	Mechanism	Literatures
CORM-2	RAW264. 7	Prevention of LPS-induced inflammatory response	Promotion of HO-1/CO **anti-inflammatory pathway**, inhibition of NF-κB and STAT 1/3 signaling	*Choi et al. (2021)*
CORM-3	HPDL	Prevention of nicotine/LPS-induced inflammatory responses and inhibition of osteoclast formation and activity	Promoting HO-1/CO pathway **antioxidant and anti-inflammatory** pathway	*Song et al. (2017)*
CORM-401	RAW264. 7	Prevention of LPS-induced inflammatory response	Promotion of HO-1/CO **anti-inflammatory pathway**, inhibition of NF-κB pathway	*Choi et al. (2022)*
Caffeine	Oral keratinocytes	Prevention of LPS-induced inflammatory response	Promotion of Nrf2/HO-1 **antioxidant and anti-inflammatory pathways**	*Song et al. (2022)*
DHA	RAW264. 7	Prevention of LPS-induced inflammatory response	Promotion of HO-1 **anti-inflammatory pathway**, inhibition of NF-κB and JNK1/2 pathways	*Choi et al. (2014)*
Caffeic acid phenethyl ester	THP-1	Prevention of saliva-induced inflammatory response in patients with periodontitis	Promotion of HO-1 **anti-inflammatory pathway**, inhibition of NF-κB pathway	*Huang et al. (2021b)*
	RAW264. 7	Prevention of LPS-induced inflammatory response	Promotion of HO-1 **anti-inflammatory pathway**, inhibition of SOCS1, inhibition of NF-κB and STAT 1/3 signaling	*Choi et al. (2015b)*
Periostin	PDLF	Prevention of LPS-induced inflammatory response and apoptosis	Promotion of Nrf2/HO-1 **antioxidant and anti-inflammatory pathways**	*Jiang et al. (2022)*
Surfactin	HGFs, THP-1	Prevention of PM-induced inflammatory response	Promotion of Nrf2/HO-1 **antioxidant and anti-inflammatory pathway**, inhibition of VCAM-1-dependent pathway	*Vo et al. (2022)*
ED-71	HGFs	Prevention of LPS-induced cellular pyroptosis	Promotion of Nrf2/HO-1 **antioxidant pathway**, inhibition of NLRP3 inflammatory vesicles	*Huang et al. (2020)*
Melatonin-derived carbon dots	RAW264. 7	Prevention of H_2O_2-induced inflammatory response	Promoting Nrf2/HO-1 **antioxidant** and **anti-inflammatory pathways**	*Xin et al. (2024)*
BML-111	PDLF	Prevention of H_2O_2-induced cellular pyroptosis and osteogenic dysfunction	Promoting Nrf2/HO-1 **antioxidant and anti-inflammatory pathways**	*Xu et al. (2024)*
Nitro-conjugated linoleic acid	Raw 264. 7	Prevention of LPS-induced inflammatory response	Promoting HO-1 **anti-inflammatory pathway**, inhibiting NF-κB and STAT 1/3 signalling, and promoting M2 macrophage polarisation	*Lee et al. (2024)*
Glutathione Peroxidase-Mimicking Nanozyme	PDLSC	Prevention of H_2O_2-induced inflammation, promotion of osteogenic differentiation	Promotion of Nrf2/HO-1 **antioxidant pathway**, promotion of PI3K/Akt signalling	*Zhu et al. (2024)*
vitamin D	HGF	Prevention of AGEs-induced inflammatory response	Promoting Nrf2/HO-1 **antioxidant and anti-inflammatory pathways**	*Lu et al. (2023)*
Cl-amidine	HGF	Prevention of LPS-induced inflammatory response	Promoting Nrf2/HO-1 **antioxidant and anti-inflammatory pathway**, inhibiting NF-κB and JNK/MAPK signaling	*Du et al. (2022)*

Note:
CORM, carbon dioxide releasing molecule; ED-71, vitamin D analog; PDLF, periodontal fibroblasts; PM, particulate matter; SOCS1, suppressor of cytokine signaling; VCAM-1, vascular cell adhesion molecule-1.

Table 4 Advances *in vivo* pharmacotherapy of HO-1-induced periodontitis.

Types of HO-1 inducers	Specific drugs or chemicals	Mouse type/ human	Effects on mice	Literatures
Natural extracts	Chlorogenic acid	Male C57BL/6 mice	Chlorogenic acid-loaded nanomicelles lead to reduced inflammation and inhibited bone resorption in a simulated experimental periodontitis model	*Li et al. (2022)*
	Magnolol	Male Sprague Dawley rats	Reduction of inflammation and inhibition of bone resorption in a simulated experimental periodontitis model	*Lu, Huang & Chou (2013)*
	Quercetin	Male C57BL/6 mice	Elevated Nrf2 expression in a simulated experimental periodontitis model leads to reduced oxidative damage, reduced inflammation, and inhibition of bone resorption	*Wei et al. (2021)*
		Male wistar rats	Reduction of inflammation and inhibition of bone resorption in a simulated experimental periodontitis model	*Taskan & Gevrek (2020)*
	6-Shogaol	Male C57BL/6 mice	Reduction of inflammation and inhibition of bone resorption in a simulated experimental periodontitis model	*Kim et al. (2020a)*
	Green tea	Male C57BL/6 mice	Reduction of inflammation and inhibition of bone resorption in a simulated experimental periodontitis model	*Kaboosaya et al. (2020)*
	Ginkgo biloba	Male Wistar rats	Inhibition of bone resorption in a simulated experimental periodontitis model	*Sezer et al. (2013)*
	Kaempferol	Wistar rats	Reduction of alveolar bone resorption, attachment loss, and MMP-1 and 8 production in experimental periodontitis.	*Balli et al. (2016)*
	Mono-carbonyl analogues of curcumin (MCACs)	Male Sprague Dawley rats	Reduction of inflammation and inhibition of bone resorption in a simulated experimental periodontitis model	*Zhao et al. (2021)*
	Panax ginseng fruit	Sprague Dawley rats	Reduced inflammation in a simulated experimental periodontitis model	*Kim et al. (2020b)*
	Resveratrol	Male Sprague Dawley rats	Reduction of inflammation and inhibition of bone resorption in a simulated experimental periodontitis model	*Bhattarai et al. (2016)*
	Ecklonia cava	Male Sprague Dawley rats	Reduction of inflammation and inhibition of bone resorption in a simulated experimental periodontitis model	*Kim et al. (2019)*
	Epigallocatechin-3-gallate	Sprague Dawley rats	Reduced inflammation, antioxidants, and inhibition of bone resorption in a simulated experimental periodontitis model	*Fan et al. (2023)*
Clinical drugs	Nifedipine	male BALB/c mice	Inhibition of bone resorption in a simulated experimental periodontitis model	*Lee et al. (2023b)*
	Strontium ranelate	Male Wistar rats	Inhibition of bone resorption in a simulated experimental periodontitis model	*Souza et al. (2018)*
	Dimethyl fumarate	male BALB/c mice	Inhibition of bone resorption in a simulated experimental periodontitis model	*Yamaguchi et al. (2018)*
	Tetracycline	Human	Reduction of periodontal pocket depth and clinical attachment levels in patients with periodontitis	*Sinha et al. (2014)*

Table 4 (continued)

Types of HO-1 inducers	Specific drugs or chemicals	Mouse type/ human	Effects on mice	Literatures
Novel HO-1 inducers	CORM-2	Wistar rats	Reduced inflammation in a simulated experimental periodontitis model	*Hou et al. (2014)*
	caffeine	Male Wistar rats	Antimicrobial action, promotion of alveolar bone repair in a simulated experimental periodontitis model	*Sari et al. (2023)*
	caffeic acid phenethyl ester	Male Wistar rats	Reduced inflammation, antioxidants, and inhibition of bone resorption in a simulated experimental periodontitis model	*Yiğit et al. (2021)*
	Melatonin-derived carbon dots	Male C57BL/6 mice	Reduced inflammation, antioxidants, and inhibition of bone resorption in a simulated experimental periodontitis model	*Xin et al. (2024)*
	Ixeris dentata and *Lactobacillus gasseri* media	Male C57BL/6 mice	Reduced inflammation, antioxidants, and inhibition of bone resorption in a simulated experimental periodontitis model	*Lee et al. (2023a)*

expression and the treatment of periodontitis, ultimately leading to the innovation of novel compounds aimed at achieving a comprehensive cure for this condition.

CONCLUSION

In recent years, researchers have made significant strides in elucidating the pathogenesis of periodontitis through a comprehensive analysis of the underlying mechanisms of oxidative stress involved in this condition. This review delineates the multifaceted functions of HO-1, encompassing its roles in antioxidant activity, anti-apoptosis, anti-pyroptosis, anti-inflammatory responses and regulation of bone homeostasis, positing HO-1 as a promising novel target for the development of therapies for periodontitis. Numerous studies have demonstrated that natural extracts, clinical drugs and novel HO-1 inducers have investigated the potential of targeting periodontitis through the augmentation of HO-1 expression. Nevertheless, despite notable progress, the therapeutic potential of HO-1 has yet to be fully realized within a clinical context.

Firstly, existing investigations on periodontitis predominantly remain at the cellular and animal experiment stages, necessitating further validation through clinical trials. Secondly, the dualistic role of HO-1 in the treatment of periodontitis warrants attention. Sustained overexpression of HO-1 may result in the accumulation of heme degradation products, which not only proves detrimental to the treatment of periodontitis but may also enhance cytotoxicity. Therefore, optimizing therapeutic efficacy while ensuring the safety of HO-1-targeted therapies represents a crucial avenue for future research. Thirdly, to thoroughly investigate the role of polyphenols, terpenoids, isothiocyanates, saponins, alkaloids, polysaccharides and quinones in the HO-1-related pathway associated with periodontitis, it is crucial to examine the interrelationships between various functional groups, HO-1 and periodontitis. This study aims to elucidate the potential of these compounds in the treatment of periodontitis, thereby offering innovative insights and opportunities for the future development of novel HO-1 compounds. Furthermore, investigating the effects of HO-1 targeted drugs related to oxidative stress diseases on the development and

progression of periodontitis may mitigate the risk of medication duplication in patients suffering from systemic oxidative stress diseases concomitant with periodontitis, thereby facilitating more precise therapeutic interventions for optimal efficacy and prognosis. Currently, the antioxidant and anti-inflammatory regulatory mechanisms associated with the HO-1 signaling pathway remain to be fully elucidated. Future investigations should delve into the involvement of HO-1 in the inter-regulation of critical pathways, including MAPK, NF-κB and PI3K/Akt, as well as the potential of HMGB1 as a significant target for the regulation of periodontitis treatment by HO-1. Identifying drugs that target HO-1-related microRNAs or downstream target genes associated with HO-1 may offer novel insights for the treatment of periodontitis.

In conclusion, HO-1 serves as a potentially crucial anti-inflammatory, antioxidant, immunomodulator and bone modulator in the context of periodontitis, necessitating comprehensive exploration to ascertain the bioavailability and safety of HO-1-targeted therapeutic agents. Moving forward, it is essential to elucidate the regulatory mechanisms of HO-1 as a potent antioxidant, address the limitations of HO-1-targeted therapies for periodontitis treatment, and ultimately achieve the clinical application of these drugs as innovative therapeutic agents for periodontitis.

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Competing Interests

The authors declare that they have no competing interests.

Author Contributions

- Weiwei Lv conceived and designed the experiments, performed the experiments, analyzed the data, prepared figures and/or tables, and approved the final draft.
- Shichen Hu conceived and designed the experiments, performed the experiments, analyzed the data, prepared figures and/or tables, and approved the final draft.
- Fei Yang performed the experiments, prepared figures and/or tables, and approved the final draft.
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- Lihua Li analyzed the data, authored or reviewed drafts of the article, and approved the final draft.
- Xiaowen Chen analyzed the data, authored or reviewed drafts of the article, and approved the final draft.
- Yan Wu conceived and designed the experiments, analyzed the data, authored or reviewed drafts of the article, and approved the final draft.

Data Availability

The following information was supplied regarding data availability:

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REFERENCES

Adnan M, Siddiqui AJ, Ashraf SA, Ashraf MS, Alomrani SO, Alreshidi M, Tepe B, Sachidanandan M, Danciu C, Patel M. 2023. Saponin-derived silver nanoparticles from phoenix dactylifera (Ajwa Dates) exhibit broad-spectrum bioactivities combating bacterial infections. *Antibiotics* **12(9)**:1415 DOI 10.3390/antibiotics12091415.

Aithal GC, Nayak UY, Mehta C, Narayan R, Gopalkrishna P, Pandiyan S, Garg S. 2018. Localized in situ nanoemulgel drug delivery system of quercetin for periodontitis: development and computational simulations. *Molecules* **23(6)**:23–26 DOI 10.3390/molecules23061363.

Al-Zahrani MS, Bissada NF, Borawskit EA. 2003. Obesity and periodontal disease in young, middle-aged, and older adults. *Journal of Periodontology* **74(5)**:610–615 DOI 10.1902/jop.2003.74.5.610.

Alkakhan W, Farrar N, Sikora V, Emecen-Huja P, Huja SS, Yilmaz Ö, Pandruvada SN. 2023. Statins modulate microenvironmental cues driving macrophage polarization in simulated periodontal inflammation. *Cells* **12(15)**:1961 DOI 10.3390/cells12151961.

AlQranei MS, Aljohani H, Majumdar S, Senbanjo LT, Chellaiah MA. 2020. C-phycocyanin attenuates RANKL-induced osteoclastogenesis and bone resorption in vitro through inhibiting ROS levels, NFATc1 and NF-κB activation. *Scientific Reports* **10**:2513 DOI 10.1038/s41598-020-59363-y.

Azuma T, Tomofuji T, Endo Y, Tamaki N, Ekuni D, Irie K, Kasuyama K, Kato T, Morita M. 2011. Effects of exercise training on gingival oxidative stress in obese rats. *Archives of Oral Biology* **56(8)**:768–774 DOI 10.1016/j.archoralbio.2011.01.008.

Balli U, Cetinkaya BO, Keles GC, Keles ZP, Guler S, Sogut MU, Erisgin Z. 2016. Assessment of MMP-1, MMP-8 and TIMP-2 in experimental periodontitis treated with kaempferol. *Journal of Periodontal & Implant Science* **46(2)**:84–95 DOI 10.5051/jpis.2016.46.2.84.

Baltacıoğlu E, Yuva P, Aydın G, Alver A, Kahraman C, Karabulut E, Akalın FA. 2014. Lipid peroxidation levels and total oxidant/antioxidant status in serum and saliva from patients with chronic and aggressive periodontitis. Oxidative stress index: a new biomarker for periodontal disease. *Journal of Periodontology* **85(10)**:1432–1441 DOI 10.1902/jop.2014.130654.

Bansal N, Gupta ND, Bey A, Sharma VK, Gupta N, Trivedi H. 2017. Impact of nonsurgical periodontal therapy on total antioxidant capacity in chronic periodontitis patients. *Journal of Indian Society of Periodontology* **21(4)**:291–295 DOI 10.4103/jisp.jisp_281_15.

Berköz M, Yiğit A, Krośniak M. 2023. Protective role of myricetin and fisetin against nephrotoxicity caused by lead acetate exposure through Up-regulation of Nrf2/HO-1 signalling pathway. *Biological Trace Element Research* **202**:1–15 DOI 10.1007/s12011-023-03977-6.

Bhattarai G, Poudel SB, Kook SH, Lee JC. 2016. Resveratrol prevents alveolar bone loss in an experimental rat model of periodontitis. *Acta Biomaterialia* **29(40)**:398–408 DOI 10.1016/j.actbio.2015.10.031.

Biju T, Shabeer MM, Amitha R, Rajendra BP, Suchetha K. 2014. Comparative evaluation of serum superoxide dismutase and glutathione levels in periodontally diseased patients: an interventional study. *Indian Journal of Dental Research* **25(5)**:613–616 DOI 10.4103/0970-9290.147105.

Boia S, Boariu M, Baderca F, Rusu D, Muntean D, Horhat F, Boia ER, Borza C, Anghel A, Stratul ŞI. 2019. Clinical, microbiological and oxidative stress evaluation of periodontitis patients treated with two regimens of systemic antibiotics, adjunctive to non-surgical therapy: a placebo-controlled randomized clinical trial. *Experimental and Therapeutic Medicine* **18(6)**:5001–5015 DOI 10.3892/etm.2019.7856.

Bou-Abdallah F. 2010. The iron redox and hydrolysis chemistry of the ferritins. *Biochimica et biophysica acta* **1800(8)**:719–731 DOI 10.1016/j.bbagen.2010.03.021.

Bunte K, Hensel A, Beikler T. 2019. Polyphenols in the prevention and treatment of periodontal disease: a systematic review of in vivo, ex vivo and in vitro studies. *Fitoterapia* **132(4)**:30–39 DOI 10.1016/j.fitote.2018.11.012.

Carota G, Raffaele M, Sorrenti V, Salerno L, Pittalà V, Intagliata S. 2019. Ginseng and heme oxygenase-1: the link between an old herb and a new protective system. *Fitoterapia* **139**:104370 DOI 10.1016/j.fitote.2019.104370.

Chandra RV, Sandhya YP, Nagarajan S, Reddy BH, Naveen A, Murthy KR. 2012. Efficacy of lycopene as a locally delivered gel in the treatment of chronic periodontitis: smokers vs nonsmokers. *Quintessence International* **43**:401–411.

Chang YC, Lai CC, Lin LF, Ni WF, Tsai CH. 2005. The up-regulation of heme oxygenase-1 expression in human gingival fibroblasts stimulated with nicotine. *Journal of Periodontal Research* **40(3)**:252–257 DOI 10.1111/j.1600-0765.2005.00804.x.

Chang B, Lee Y, Ku Y, Bae K, Chung C. 1998. Antimicrobial activity of magnolol and honokiol against periodontopathic microorganisms. *Planta Medica* **64(4)**:367–369 DOI 10.1055/s-2006-957453.

Chang MC, Tsai YL, Chen YW, Chan CP, Huang CF, Lan WC, Lin CC, Lan WH, Jeng JH. 2013. Butyrate induces reactive oxygen species production and affects cell cycle progression in human gingival fibroblasts. *Journal of Periodontal Research* **48(1)**:66–73 DOI 10.1111/j.1600-0765.2012.01504.x.

Chapple IL, Milward MR, Dietrich T. 2007. The prevalence of inflammatory periodontitis is negatively associated with serum antioxidant concentrations. *The Journal of Nutrition* **137(3)**:657–664 DOI 10.1093/jn/137.3.657.

Chen M, Cai W, Zhao S, Shi L, Chen Y, Li X, Sun X, Mao Y, He B, Hou Y, Zhou Y, Zhou Q, Ma J, Huang S. 2019a. Oxidative stress-related biomarkers in saliva and gingival crevicular fluid associated with chronic periodontitis: a systematic review and meta-analysis. *Journal of Clinical Periodontology* **46(6)**:608–622 DOI 10.1111/jcpe.13112.

Chen K, Ma S, Deng J, Jiang X, Ma F, Li Z. 2022a. Ferroptosis: a new development trend in periodontitis. *Cells* **11(21)**:3349 DOI 10.3390/cells11213349.

Chen X, Pan S, Li F, Xu X, Xing H. 2022b. Plant-derived bioactive compounds and potential health benefits: involvement of the gut microbiota and its metabolic activity. *Biomolecules* **12(12)**:1817 DOI 10.3390/biom12121871.

Chen G, Shen L, Hu H, Feng Y, Wen D, Liu Y, Zhai H, Sun W, Wang M, Lei X, Li P, Xiong Q, Wu C. 2024. Sulforaphane inhibits oxidative stress and may exert anti-pyroptotic effects by modulating NRF2/NLRP3 signaling pathway in mycobacterium tuberculosis-infected macrophages. *Microorganisms* **12(6)**:1191 DOI 10.3390/microorganisms12061191.

Chen H, Xie K, Chen Y, Wang Y, Wang Y, Lian N, Zhang K, Yu Y. 2019b. Nrf2/HO-1 signaling pathway participated in the protection of hydrogen sulfide on neuropathic pain in rats. *International Immunopharmacology* **75(4)**:105746 DOI 10.1016/j.intimp.2019.105746.

Chen J, Zhang Y, Gao J, Li T, Gan X, Yu H. 2021a. Sirtuin 3 deficiency exacerbates age-related periodontal disease. *Journal of Periodontal Research* **56(6)**:1163–1173 DOI 10.1111/jre.12930.

Chen L, Zhang WL, Xie DQ, Jia W. 2021b. Sulforaphane alleviates hepatic ischemia-reperfusion injury through promoting the activation of Nrf-2/HO-1 signaling. *Transplant Immunology* **68(5)**:101439 DOI 10.1016/j.trim.2021.101439.

Cheng L, Fan Y, Cheng J, Wang J, Liu Q, Feng Z. 2022. Long non-coding RNA ZFY-AS1 represses periodontitis tissue inflammation and oxidative damage via modulating microRNA-129-5p/DEAD-Box helicase 3 X-linked axis. *Bioengineered* **13(5)**:12691–12705 DOI 10.1080/21655979.2021.2019876.

Cherian DA, Peter T, Narayanan A, Madhavan SS, Achammada S, Vynat GP. 2019. Malondialdehyde as a marker of oxidative stress in periodontitis patients. *Journal of Pharmacy and Bioallied Sciences* **11(6)**:S297–S300 DOI 10.4103/JPBS.JPBS_17_19.

Chiabrando D, Vinchi F, Fiorito V, Mercurio S, Tolosano E. 2014. Heme in pathophysiology: a matter of scavenging, metabolism and trafficking across cell membranes. *Frontiers in Pharmacology* **5(77)**:61 DOI 10.3389/fphar.2014.00061.

Cho YJ, Kim SJ. 2013. Effect of quercetin on the production of nitric oxide in murine macrophages stimulated with lipopolysaccharide from Prevotella intermedia. *Journal of Periodontal & Implant Science* **43(4)**:191–197 DOI 10.5051/jpis.2013.43.4.191.

Choe SH, Choi EY, Hyeon JY, Keum BR, Choi IS, Kim SJ. 2019. Telmisartan, an angiotensin II receptor blocker, attenuates Prevotella intermedia lipopolysaccharide-induced production of nitric oxide and interleukin-1β in murine macrophages. *International Immunopharmacology* **75**:105750 DOI 10.1016/j.intimp.2019.105750.

Choe SH, Choi EY, Hyeon JY, Keum BR, Choi IS, Kim SJ. 2021. Effect of nifedipine, a calcium channel blocker, on the generation of nitric oxide and interleukin-1β by murine macrophages activated by lipopolysaccharide from Prevotella intermedia. *Naunyn-Schmiedeberg's Archives of Pharmacology* **394(1)**:59–71 DOI 10.1007/s00210-020-01958-3.

Choi EY, Choe SH, Hyeon JY, Choi JI, Choi IS, Kim SJ. 2015a. Carbon monoxide-releasing molecule-3 suppresses Prevotella intermedia lipopolysaccharide-induced production of nitric oxide and interleukin-1β in murine macrophages. *European Journal of Pharmacology* **764**:22–29 DOI 10.1016/j.ejphar.2015.06.039.

Choi EY, Choe SH, Hyeon JY, Choi JI, Choi IS, Kim SJ. 2015b. Effect of caffeic acid phenethyl ester on Prevotella intermedia lipopolysaccharide-induced production of proinflammatory mediators in murine macrophages. *Journal of Periodontal Research* **50(6)**:737–747 DOI 10.1111/jre.12260.

Choi EY, Choe SH, Hyeon JY, Park HR, Choi IS, Kim SJ. 2018. Josamycin suppresses Prevotella intermedia lipopolysaccharide-induced production of nitric oxide and interleukin-1β in murine macrophages. *Biomedicine & Pharmacotherapy* **105**:498–505 DOI 10.1016/j.biopha.2018.05.139.

Choi IS, Choi EY, Jin JY, Park HR, Choi JI, Kim SJ. 2013. Kaempferol inhibits P. intermedia lipopolysaccharide-induced production of nitric oxide through translational regulation in murine macrophages: critical role of heme oxygenase-1-mediated ROS reduction. *Journal of Periodontology* **84(4)**:545–555 DOI 10.1902/jop.2012.120180.

Choi EY, Jin JY, Choi JI, Choi IS, Kim SJ. 2014. DHA suppresses Prevotella intermedia lipopolysaccharide-induced production of proinflammatory mediators in murine macrophages. *British Journal of Nutrition* **111(7)**:1221–1230 DOI 10.1017/S0007114513003681.

Choi EY, Keum BR, Choe SH, Hyeon JY, Choi IS, Kim SJ. 2021. Tricarbonyldichlororuthenium (II) dimer, the lipid-soluble carbon monoxide-releasing molecule, attenuates Prevotella intermedia lipopolysaccharide-induced production of nitric oxide and interleukin-1β in murine macrophages. *International Immunopharmacology* **90(8)**:107190 DOI 10.1016/j.intimp.2020.107190.

Choi EY, Lee JE, Lee AR, Choi IS, Kim SJ. 2022. Carbon monoxide-releasing molecule-401, a water-soluble manganese-based metal carbonyl, suppresses Prevotella intermedia lipopolysaccharide-induced production of nitric oxide in murine macrophages. *Immunopharmacology and Immunotoxicology* **45**:1–8 DOI 10.1080/08923973.2022.2119998.

Choi SC, Seo YH, Bae WJ, Lee HS, Choi YC, Kim EC. 2015c. Milk activates the expression of cytokines via Nrf2/HO-1 pathway in human periodontal ligament cells. *Dental Traumatology* **31(6)**:457–464 DOI 10.1111/edt.12188.

Chopra A, Thomas BS, Sivaraman K, Prasad HK, Kamath SU. 2016. Green tea intake as an adjunct to mechanical periodontal therapy for the management of mild to moderate chronic periodontitis: a randomized controlled clinical trial. *Oral Health & Preventive Dentistry* **14**:293–303 DOI 10.3290/j.ohpd.a36100.

Cicalău G, Babes PA, Calniceanu H, Popa A, Ciavoi G, Iova GM, Ganea M, Scrobotă L. 2021. Anti-inflammatory and antioxidant properties of carvacrol and magnolol, in periodontal disease and diabetes mellitus. *Molecules* **26(22)**:6899 DOI 10.3390/molecules26226899.

de Carvalho R, Casarin R, de Lima PO, Cogo-Müller K. 2021. Statins with potential to control periodontitis: from biological mechanisms to clinical studies. *Journal of Oral Biosciences* **63(3)**:232–244 DOI 10.1016/j.job.2021.06.002.

Di Pietro C, Öz HH, Murray TS, Bruscia EM. 2020. Targeting the heme oxygenase 1/Carbon monoxide pathway to resolve lung hyper-inflammation and restore a regulated immune response in cystic fibrosis. *Frontiers in Pharmacology* **11**:1059 DOI 10.3389/fphar.2020.01059.

Ding Y, Hou X, Chen L, Zhou H, Gong Y, Dai L, Zheng Y. 2016. Heme oxygenase-1 dependant pathway contributes to protection by tetramethylpyrazine against chronic hypoxic injury on medulla oblongata in rats. *Journal of the Neurological Sciences* **361(2)**:101–111 DOI 10.1016/j.jns.2015.12.026.

Donnelly LE, Barnes PJ. 2001. Expression of heme oxygenase in human airway epithelial cells. *American Journal of Respiratory Cell and Molecular Biology* **24(3)**:295–303 DOI 10.1165/ajrcmb.24.3.4001.

Du J, Wang N, Sun H, Zheng L, Qi X. 2022. Cl-amidine attenuates lipopolysaccharide-induced inflammation in human gingival fibroblasts via the JNK/MAPK, NF-κB, and Nrf2 signalling pathways. *Human Cell* **36(1)**:223–233 DOI 10.1007/s13577-022-00822-1.

El Badawy SA, Ogaly HA, Abd-Elsalam RM, Azouz AA. 2021. Benzyl isothiocyanates modulate inflammation, oxidative stress, and apoptosis via Nrf2/HO-1 and NF-κB signaling pathways on indomethacin-induced gastric injury in rats. *Food & Function* **12(13)**:6001–6013 DOI 10.1039/D1FO00645B.

Fan Q, Zhou XH, Wang TF, Zeng FJ, Liu X, Gu Y, Chen B, Yang J, Pang ZY, Liu JG, Bai GH. 2023. Effects of epigallocatechin-3-gallate on oxidative stress, inflammation, and bone loss in a rat periodontitis model. *Journal of Dental Sciences* **18(4)**:1567–1575 DOI 10.1016/j.jds.2023.02.019.

Fernández-Fierro A, Funes SC, Rios M, Covián C, González J, Kalergis AM. 2020. Immune modulation by inhibitors of the HO system. *International Journal of Molecular Sciences* **22(1)**:294 DOI 10.3390/ijms22010294.

Frey PA, Reed GH. 2012. The ubiquity of iron. *ACS Chemical Biology* **7(9)**:1477–1481 DOI 10.1021/cb300323q.

Gao JL, Kwan AH, Yammine A, Zhou X, Trewhella J, Hugrass BM, Collins DAT, Horne J, Ye P, Harty D, Nguyen KA, Gell DA, Hunter N. 2018. Structural properties of a haemophore facilitate targeted elimination of the pathogen Porphyromonas gingivalis. *Nature Communications* **9(1)**:4097 DOI 10.1038/s41467-018-06470-0.

Genco RJ, Borgnakke WS. 2013. Risk factors for periodontal disease. *Periodontology 2000* **62(1)**:59–94 DOI 10.1111/j.1600-0757.2012.00457.x.

Grant MM, Scott AE, Matthews JB, Griffiths HR, Chapple I. 2023. Pre-conditioning of gingival epithelial cells with sub-apoptotic concentrations of curcumin prevents pro-inflammatory cytokine release. *Journal of Periodontal Research* **58(3)**:634–645 DOI 10.1111/jre.13114.

Gu X, Hao D, Xiao P. 2022. Research progress of Chinese herbal medicine compounds and their bioactivities: fruitful 2020. *Chinese Herbal Medicines* **14(2)**:171–186 DOI 10.1016/j.chmed.2022.03.004.

Gustafsson A, Asman B. 1996. Increased release of free oxygen radicals from peripheral neutrophils in adult periodontitis after Fc delta-receptor stimulation. *Journal of Clinical Periodontology* **23(1)**:38–44 DOI 10.1111/j.1600-051X.1996.tb00502.x.

Ha YM, Kim MY, Park MK, Lee YS, Kim YM, Kim HJ, Lee JH, Chang KC. 2012. Higenamine reduces HMGB1 during hypoxia-induced brain injury by induction of heme oxygenase-1 through PI3K/Akt/Nrf-2 signal pathways. *Apoptosis* **17(5)**:463–474 DOI 10.1007/s10495-011-0688-8.

Hagiu A, Attin T, Schmidlin PR, Ramenzoni LL. 2020. Dose-dependent green tea effect on decrease of inflammation in human oral gingival epithelial keratinocytes: in vitro study. *Clinical Oral Investigations* **24(7)**:2375–2383 DOI 10.1007/s00784-019-03096-4.

Han K, Hwang E, Park JB. 2016. Association between consumption of coffee and the prevalence of periodontitis: the 2008–2010 Korea national health and nutrition examination survey. *PLOS ONE* **11(7)**:e0158845 DOI 10.1371/journal.pone.015884.

Hanselmann C, Mauch C, Werner S. 2001. Haem oxygenase-1: a novel player in cutaneous wound repair and psoriasis. *Biochemical Journal* **353(Pt 3)**:459–466 DOI 10.1042/bj3530459.

Hosokawa Y, Hosokawa I, Shimoyama M, Fujii A, Sato J, Kadena K, Ozaki K, Hosaka K. 2022. The anti-inflammatory effects of iberin on TNF-α-stimulated human oral epithelial cells: in vitro research. *Biomedicines* **10(12)**:3155 DOI 10.3390/biomedicines10123155.

Hosokawa Y, Hosokawa I, Shimoyama M, Okamoto R, Ozaki K, Hosaka K. 2024. The effects of berteroin on inflammatory mediators and antioxidant enzymes expression in human periodontal ligament cells. *Naunyn-Schmiedeberg's Archives of Pharmacology* **397(4)**:2233–2240 DOI 10.1007/s00210-023-02761-6.

Hou M, Wang P, Zhao L, Li Y, Zhao HQ, Song H. 2014. Effect of CORM-2 on atherosclerosis in experimental periodontitis of rats. *Shanghai Kou Qiang Yi Xue* **23(5)**:531–538.

Huang YP, Chen DR, Lin WJ, Lin YH, Chen JY, Kuo YH, Chung JG, Hsia TC, Hsieh WT. 2021a. Ergosta-7, 9(11), 22-trien-3β-ol attenuates inflammatory responses via inhibiting MAPK/AP-1 induced IL-6/JAK/STAT pathways and activating Nrf2/HO-1 signaling in LPS-stimulated macrophage-like cells. *Antioxidants* **10(9)**:1430 DOI 10.3390/antiox10091430.

Huang X, Liu Y, Shen H, Fu T, Guo Y, Qiu S. 2022. Chlorogenic acid attenuates inflammation in LPS-induced Human gingival fibroblasts via CysLT1R/Nrf2/NLRP3 signaling. *International Immunopharmacology* **107(7)**:108706 DOI 10.1016/j.intimp.2022.108706.

Huang YK, Tseng KF, Tsai PH, Wang JS, Lee CY, Shen MY. 2021b. IL-8 as a potential therapeutic target for periodontitis and its inhibition by caffeic acid phenethyl ester in vitro. *International Journal of Molecular Sciences* **22(7)**:3641 DOI 10.3390/ijms22073641.

Huang H, Wang L, Qian F, Chen X, Zhu H, Yang M, Zhang C, Chu M, Wang X, Huang X. 2021c. Liraglutide via activation of AMP-activated protein kinase-hypoxia inducible factor-1α-heme oxygenase-1 signaling promotes wound healing by preventing endothelial dysfunction in diabetic mice. *Frontiers in Physiology* **12**:660263 DOI 10.3389/fphys.2021.660263.

Huang C, Zhang C, Yang P, Chao R, Yue Z, Li C, Guo J, Li M. 2020. Eldecalcitol inhibits LPS-induced NLRP3 inflammasome-dependent pyroptosis in human gingival fibroblasts by activating the Nrf2/HO-1 signaling pathway. *Drug Design, Development and Therapy* **14**:4901–4913 DOI 10.2147/DDDT.S269223.

Huang Y, Zhu M, Li Z, Sa R, Chu Q, Zhang Q, Zhang H, Tang W, Zhang M, Yin H. 2014. Mass spectrometry-based metabolomic profiling identifies alterations in salivary redox status and fatty acid metabolism in response to inflammation and oxidative stress in periodontal disease. *Free Radical Biology and Medicine* **70**:223–232 DOI 10.1016/j.freeradbiomed.2014.02.024.

Janciauskiene S, Vijayan V, Immenschuh S. 2020. TLR4 signaling by heme and the role of heme-binding blood proteins. *Frontiers in Immunology* **11**:1964 DOI 10.3389/fimmu.2020.01964.

Jeong GS, Lee DS, Li B, Lee HJ, Kim EC, Kim YC. 2010. Effects of sappanchalcone on the cytoprotection and anti-inflammation via heme oxygenase-1 in human pulp and periodontal ligament cells. *European Journal of Pharmacology* **644(1–3)**:230–237 DOI 10.1016/j.ejphar.2010.06.059.

Jiang Y, Yang P, Li C, Lu Y, Kou Y, Liu H, Guo J, Li M. 2022. Periostin regulates LPS-induced apoptosis via Nrf2/HO-1 pathway in periodontal ligament fibroblasts. *Oral Diseases* **29(5)**:2188–2204 DOI 10.1111/odi.14189.

Jin JY, Choi EY, Park HR, Choi JI, Choi IS, Kim SJ. 2013. Isorhamnetin inhibits Prevotella intermedia lipopolysaccharide-induced production of interleukin-6 in murine macrophages via anti-inflammatory heme oxygenase-1 induction and inhibition of nuclear factor-κB and signal transducer and activator of transcription 1 activation. *Journal of Periodontal Research* **48(6)**:687–695 DOI 10.1111/jre.12054.

Jin GH, Park SY, Kim E, Ryu EY, Kim YH, Park G, Lee SJ. 2012. Anti-inflammatory activity of Bambusae Caulis in Taeniam through heme oxygenase-1 expression via Nrf-2 and p38 MAPK signaling in macrophages. *Environmental Toxicology and Pharmacology* **34(2)**:315–323 DOI 10.1016/j.etap.2012.05.001.

Kaboosaya B, Wulansari LK, Trang Nguyen VN, Kasugai S. 2020. Drinking green tea alleviates alveolar bone resorption in ligature-induced periodontitis in mice. *Journal of Oral Biosciences* **62(2)**:162–168 DOI 10.1016/j.job.2020.04.002.

Kartikasari AE, Wagener FA, Yachie A, Wiegerinck ET, Kemna EH, Swinkels DW. 2009. Hepcidin suppression and defective iron recycling account for dysregulation of iron homeostasis in heme oxygenase-1 deficiency. *Journal of Cellular and Molecular Medicine* **13(9b)**:3091–3102 DOI 10.1111/j.1582-4934.2008.00494.x.

Kataoka K, Ekuni D, Tomofuji T, Irie K, Kunitomo M, Uchida Y, Fukuhara D, Morita M. 2016. Visualization of oxidative stress induced by experimental periodontitis in keap1-dependent oxidative stress detector-luciferase mice. *International Journal of Molecular Sciences* **17(11)**:1907 DOI 10.3390/ijms17111907.

Khan A, Ikram M, Muhammad T, Park J, Kim MO. 2019. Caffeine modulates cadmium-induced oxidative stress, neuroinflammation, and cognitive impairments by regulating Nrf-2/HO-1 in vivo and in vitro. *Journal of Clinical Medicine* **8(5)**:680 DOI 10.3390/jcm8050680.

Khan MI, Karima G, Khan MZ, Shin JH, Kim JD. 2022. Therapeutic effects of saponins for the prevention and treatment of cancer by ameliorating inflammation and angiogenesis and inducing antioxidant and apoptotic effects in human cells. *International Journal of Molecular Sciences* **23(18)**:10665 DOI 10.3390/ijms231810665.

Kim S, Choi SI, Kim GH, Imm JY. 2019. Anti-inflammatory effect of ecklonia cava extract on porphyromonas gingivalis lipopolysaccharide-stimulated macrophages and a periodontitis rat model. *Nutrients* **11(5)**:1143 DOI 10.3390/nu11051143.

Kim EN, Kaygusuz O, Lee HS, Jeong GS. 2021. Simultaneous quantitative analysis of ginsenosides isolated from the fruit of Panax ginseng C. A. Meyer and regulation of HO-1 expression through EGFR signaling has anti-inflammatory and osteogenic induction effects in HPDL cells. *Molecules* **26**:2092 DOI 10.3390/molecules26072092.

Kim YG, Kim MO, Kim SH, Kim HJ, Pokhrel NK, Lee JH, Lee HJ, Kim JY, Lee Y. 2020a. 6-Shogaol, an active ingredient of ginger, inhibits osteoclastogenesis and alveolar bone resorption in ligature-induced periodontitis in mice. *Journal of Periodontology* **91(6)**:809–818 DOI 10.1002/JPER.19-0228.

Kim K, Kim JH, Lee J, Jin H-M, Lee S-H, Fisher DE, Kook H, Kim KK, Choi Y, Kim N. 2005. Nuclear factor of activated T cells c1 induces osteoclast-associated receptor gene expression

during tumor necrosis factor-related activation-induced cytokine-mediated osteoclastogenesis. *Journal of Biological Chemistry* **280(42)**:35209–35216 DOI 10.1074/jbc.M505815200.

Kim EN, Kim TY, Park EK, Kim JY, Jeong GS. 2020b. Panax ginseng Fruit Has Anti-inflammatory effect and induces osteogenic differentiation by regulating Nrf2/HO-1 signaling pathway in in vitro and in vivo models of periodontitis. *Antioxidants* **9(12)**:1221 DOI 10.3390/antiox9121221.

Kim YS, Lee YM, Park JS, Lee SK, Kim EC. 2010. SIRT1 modulates high-mobility group box 1-induced osteoclastogenic cytokines in human periodontal ligament cells. *Journal of Cellular Biochemistry* **111(5)**:1310–1320 DOI 10.1002/jcb.22858.

Kim YS, Pi SH, Lee YM, Lee SI, Kim EC. 2009. The anti-inflammatory role of heme oxygenase-1 in lipopolysaccharide and cytokine-stimulated inducible nitric oxide synthase and nitric oxide production in human periodontal ligament cells. *Journal of Periodontology* **80(12)**:2045–2055 DOI 10.1902/jop.2009.090145.

Kumar J, Teoh SL, Das S, Mahakknaukrauh P. 2017. Oxidative stress in oral diseases: understanding its relation with other systemic diseases. *Frontiers in Physiology* **8**:693 DOI 10.3389/fphys.2017.00693.

Lai S, Liu C, Liu C, Fan L, Li X, Yang Y, Zhu Y, Deng L, Xiao L, Mu Y. 2023. Lycium barbarum polysaccharide-glycoprotein promotes osteogenesis in hPDLSCs via ERK activation. *Oral Diseases* **29(8)**:3503–3513 DOI 10.1111/odi.14409.

Lanceta L, Li C, Choi AM, Eaton JW. 2013. Haem oxygenase-1 overexpression alters intracellular iron distribution. *Biochemical Journal* **449(1)**:189–194 DOI 10.1042/BJ20120936.

Lawson DM, Treffry A, Artymiuk PJ, Harrison PM, Yewdall SJ, Luzzago A, Cesareni G, Levi S, Arosio P. 1989. Identification of the ferroxidase centre in ferritin. *FEBS Letters* **254(1–2)**:207–210 DOI 10.1016/0014-5793(89)81040-3.

Leal EC, Carvalho E. 2022. Heme oxygenase-1 as therapeutic target for diabetic foot ulcers. *International Journal of Molecular Sciences* **23(19)**:12043 DOI 10.3390/ijms231912043.

Lee JE, Lee AR, Choi EY, Choi IS, Kim SJ. 2024. Effect of nitro-conjugated linoleic acid on the inflammatory response of murine macrophages activated with lipopolysaccharide derived from Prevotella intermedia. *Inflammopharmacology* **32(1)**:561–573 DOI 10.1007/s10787-023-01340-8.

Lee HY, Lee GH, Kim JH, Cheng J, Cho JH, Suh JW, Chae HJ. 2023a. Ixeris dentata and Lactobacillus gasseri media protect against periodontitis through Nrf2-HO-1 signalling pathway. *Scientific Reports* **13(1)**:12861 DOI 10.1038/s41598-023-39853-5.

Lee Y, Lee JE, Lee AR, Choi EY, Choi IS, Kim SJ. 2023b. Nifedipine attenuates alveolar bone destruction and improves trabecular microarchitectures in mice with experimental periodontitis. *Naunyn-Schmiedeberg's Archives of Pharmacology* **396(12)**:3627–3633 DOI 10.1007/s00210-023-02557-8.

Lee SK, Pi SH, Kim SH, Min KS, Lee HJ, Chang HS, Kang KH, Kim HR, Shin HI, Lee SK, Kim EC. 2007. Substance P regulates macrophage inflammatory protein 3alpha/chemokine C-C ligand 20 (CCL20) with heme oxygenase-1 in human periodontal ligament cells. *Clinical and Experimental Immunology* **150(3)**:567–575 DOI 10.1111/j.1365-2249.2007.03514.x.

Li X, Sun X, Zhang X, Mao Y, Ji Y, Shi L, Cai W, Wang P, Wu G, Gan X, Huang S, Kouretas D. 2018. Enhanced oxidative damage and Nrf2 downregulation contribute to the aggravation of periodontitis by diabetes mellitus. *Oxidative Medicine and Cellular Longevity* **2018(1)**:9421019 DOI 10.1155/2018/9421019.

Li H, Xu J, Hu JF, Hu QY, Fang X, Sun ZJ, Xu Z, Zhang L. 2022. Sustained release of chlorogenic acid-loaded nanomicelles alleviates bone loss in mouse periodontitis. *Biomaterials Science* **10(19)**:5583–5595 DOI 10.1039/D2BM01099B.

Liu CM, Chen SH, Liao YW, Yu CH, Yu CC, Hsieh PL. 2021. Magnolol ameliorates the accumulation of reactive oxidative stress and inflammation in diabetic periodontitis. *Journal of the Formosan Medical Association* **120(7)**:1452–1458 DOI 10.1016/j.jfma.2021.01.010.

Liu H, Dong Y, Gao Y, Zhao L, Cai C, Qi D, Zhu M, Zhao L, Liu C, Guo F, Xiao J, Huang H. 2019a. Hesperetin suppresses RANKL-induced osteoclastogenesis and ameliorates lipopolysaccharide-induced bone loss. *Journal of Cellular Physiology* **234(7)**:11009–11022 DOI 10.1002/jcp.27924.

Liu F, Huang X, He JJ, Song C, Peng L, Chen T, Wu BL. 2019b. Plantamajoside attenuates inflammatory response in LPS-stimulated human gingival fibroblasts by inhibiting PI3K/AKT signaling pathway. *Microbial Pathogenesis* **127(Suppl 4S)**:208–211 DOI 10.1016/j.micpath.2018.11.034.

Liu X, Niu Y, Xie W, Wei D, Du Q. 2019c. Tanshinone IIA promotes osteogenic differentiation of human periodontal ligament stem cells via ERK1/2-dependent Runx2 induction. *American Journal of Translational Research* **11**:340–350.

Liu Y, Yang H, Wen Y, Li B, Zhao Y, Xing J, Zhang M, Chen Y. 2017. Nrf2 inhibits periodontal ligament stem cell apoptosis under excessive oxidative stress. *International Journal of Molecular Sciences* **18(5)**:1076 DOI 10.3390/ijms18051076.

Loboda A, Jazwa A, Grochot-Przeczek A, Rutkowski AJ, Cisowski J, Agarwal A, Jozkowicz A, Dulak J. 2008. Heme oxygenase-1 and the vascular bed: from molecular mechanisms to therapeutic opportunities. *Antioxidants & Redox Signaling* **10(10)**:1767–1812 DOI 10.1089/ars.2008.2043.

Lösser L, Ledesma-Colunga MG, Andrés Sastre E, Scholtysek C, Hofbauer LC, Noack B, Baschant U, Rauner M. 2024. Transferrin receptor 2 mitigates periodontitis-driven alveolar bone loss. *Journal of Cellular Physiology* **239**:e31172 DOI 10.1002/jcp.31172.

Lu SH, Hsu WL, Chen TH, Chou TC. 2015. Activation of Nrf2/HO-1signaling pathway involves the anti-inflammatory activity of magnolol in Porphyromonas gingivalis lipopolysaccharide-stimulated mouse RAW 264. 7 macrophages. *International Immunopharmacology* **29(2)**:770–778 DOI 10.1016/j.intimp.2015.08.042.

Lu SH, Huang RY, Chou TC. 2013. Magnolol ameliorates ligature-induced periodontitis in rats and osteoclastogenesis: in vivo and in vitro study. *Evidence-Based Complementary and Alternative Medicine* **2013**:634095 DOI 10.1155/2013/634095.

Lu HC, Lin T, Ng MY, Hsieh CW, Liao YW, Chen CC, Yu CC, Chen CJ. 2023. Anti-inflammaging effects of vitamin D in human gingival fibroblasts with advanced glycation end product stimulation. *Journal of Dental Sciences* **18(2)**:666–673 DOI 10.1016/j.jds.2022.10.003.

Luo L, Xie P, Gong P, Tang XH, Ding Y, Deng LX. 2011. Expression of HMGB1 and HMGN2 in gingival tissues, GCF and PICF of periodontitis patients and peri-implantitis. *Archives of Oral Biology* **56(10)**:1106–1111 DOI 10.1016/j.archoralbio.2011.03.020.

Lutfioğlu M, Aydoğdu A, Atabay VE, Sakallioğlu EE, Avci B. 2017. Gingival crevicular fluid oxidative stress level in patients with periodontal disease and hyperlipidemia. *Brazilian Oral Research* **31**:e110 DOI 10.1590/1807-3107bor-2017.vol31.0110.

Lütfioğlu M, Sakallıoğlu U, Sakallıoğlu EE, Özden FO, Ürkmez SS, Bilgici B. 2021. Effects of smoking on the gingival crevicular fluid levels of interleukin-17A, interleukin-17E, and oxidative stress following periodontal treatment process. *Journal of Periodontal Research* **56(2)**:388–396 DOI 10.1111/jre.12831.

Lv J, Liu Y, Jia S, Zhang Y, Tian H, Li J, Song H. 2020. Carbon monoxide-releasing molecule-3 suppresses tumor necrosis Factor-α- and interleukin-1β-induced expression of junctional molecules on human gingival fibroblasts via the heme oxygenase-1 pathway. *Mediators of Inflammation* **2020**:6302391 DOI 10.1155/2020/6302391.

Ma W, Liu K, He Y, Deng S, Liu Y, Wang D. 2024a. Sodium humate ameliorates LPS-induced liver injury in mice by inhibiting TLR4/NF-κB and activating NRF2/HO-1 signaling pathways. *Molecular Biology Reports* **51(1)**:204 DOI 10.1007/s11033-023-09083-z.

Ma Y, Qian Y, Chen Y, Ruan X, Peng X, Sun Y, Zhang J, Luo J, Zhou S, Deng C. 2024b. Resveratrol modulates the inflammatory response in hPDLSCs via the NRF2/HO-1 and NF-κB pathways and promotes osteogenic differentiation. *Journal of Periodontal Research* **59(1)**:162–173 DOI 10.1111/jre.13200.

Machida T, Tomofuji T, Ekuni D, Azuma T, Takeuchi N, Maruyama T, Mizutani S, Kataoka K, Kawabata Y, Morita M. 2014. Severe periodontitis is inversely associated with coffee consumption in the maintenance phase of periodontal treatment. *Nutrients* **6(10)**:4476–4490 DOI 10.3390/nu6104476.

Marconcini S, Giammarinaro E, Cosola S, Oldoini G, Genovesi A, Covani U. 2021. Effects of non-surgical periodontal treatment on reactive oxygen metabolites and glycemic control in diabetic patients with chronic periodontitis. *Antioxidants* **10(7)**:1056 DOI 10.3390/antiox10071056.

Masyita A, Mustika Sari R, Dwi Astuti A, Yasir B, Rahma Rumata N, Emran TB, Nainu F, Simal-Gandara J. 2022. Terpenes and terpenoids as main bioactive compounds of essential oils, their roles in human health and potential application as natural food preservatives. *Food Chemistry: X* **13**:100217 DOI 10.1016/j.fochx.2022.100217.

Matteo P, Federico D, Emanuela M, Giulia R, Tommaso B, Alfredo G, Anna C, Annamaria O. 2022. New and old horizons for an ancient drug: pharmacokinetics, pharmacodynamics, and clinical perspectives of dimethyl fumarate. *Pharmaceutics* **14(12)**:2732 DOI 10.3390/pharmaceutics14122732.

McCoubrey WK Jr, Huang TJ, Maines MD. 1997. Isolation and characterization of a cDNA from the rat brain that encodes hemoprotein heme oxygenase-3. *European Journal of Biochemistry* **247(2)**:725–732 DOI 10.1111/j.1432-1033.1997.00725.x.

Mohamed Abdelgawad L, Abd El-Hamed MM, Sabry D, Abdelgwad M. 2021. Efficacy of Photobiomodulation and metformin on diabetic cell line of human periodontal ligament stem cells through Keap1/Nrf2/Ho-1 Pathway. *Reports of Biochemistry and Molecular Biology* **10(1)**:30–40 DOI 10.52547/rbmb.10.1.30.

Mohammadian Haftcheshmeh S, Momtazi-Borojeni AA. 2021. Berberine as a promising natural compound for the treatment of periodontal disease: a focus on anti-inflammatory properties. *Journal of Cellular and Molecular Medicine* **25(24)**:11333–11337 DOI 10.1111/jcmm.17019.

Mohideen K, Chandrasekar K, Ramsridhar S, Rajkumar C, Ghosh S, Dhungel S. 2023. Assessment of oxidative stress by the estimation of lipid peroxidation marker malondialdehyde (MDA) in patients with chronic periodontitis: a systematic review and meta-analysis. *International Journal of Dentistry* **2023(2)**:6014706 DOI 10.1155/2023/6014706.

Murakami Y, Kawata A, Suzuki S, Fujisawa S. 2020. Radical-scavenging and Pro-/anti-inflammatory activity of tetracycline and related phenolic compounds with or without visible light irradiation. *In Vivo* **34(1)**:81–94 DOI 10.21873/invivo.11748.

Naito Y, Takagi T, Uchiyama K, Yoshikawa T. 2011. Heme oxygenase-1: a novel therapeutic target for gastrointestinal diseases. *Journal of Clinical Biochemistry and Nutrition* **48(2)**:126–133 DOI 10.3164/jcbn.10-61.

Nakao A, Otterbein LE, Overhaus M, Sarady JK, Tsung A, Kimizuka K, Nalesnik MA, Kaizu T, Uchiyama T, Liu F, Murase N, Bauer AJ, Bach FH. 2004. Biliverdin protects the functional integrity of a transplanted syngeneic small bowel. *Gastroenterology* **127(2)**:595–606 DOI 10.1053/j.gastro.2004.05.059.

Nathan C, Xie QW. 1994. Nitric oxide synthases: roles, tolls, and controls. *Cell* **78(6)**:915–918 DOI 10.1016/0092-8674(94)90266-6.

Nazir MA. 2017. Prevalence of periodontal disease, its association with systemic diseases and prevention. *International Journal of Health Sciences* **11(2)**:72–80.

Neves VCM, Satie Okajima L, Elbahtety E, Joseph S, Daly J, Menon A, Fan D, Volkyte A, Mainas G, Fung K, Dhami P, Pelegrine AA, Sharpe P, Nibali L, Ide M. 2023. Repurposing Metformin for periodontal disease management as a form of oral-systemic preventive medicine. *Journal of Translational Medicine* **21(1)**:655 DOI 10.1186/s12967-023-04456-1.

Nonaka K, Bando M, Sakamoto E, Inagaki Y, Naruishi K, Yumoto H, Kido J-I. 2019. 6-Shogaol inhibits advanced glycation end-products-induced IL-6 and ICAM-1 expression by regulating oxidative responses in human gingival fibroblasts. *Molecules* **24(20)**:3705 DOI 10.3390/molecules24203705.

Okamoto R, Hosokawa Y, Hosokawa I, Ozaki K, Hosaka K. 2024a. Cardamonin inhibits the expression of inflammatory mediators in TNF-α-stimulated human periodontal ligament cells. *Immunopharmacology and Immunotoxicology* **46(4)**:521–528 DOI 10.1080/08923973.2024.2373217.

Okamoto R, Hosokawa Y, Hosokawa I, Ozaki K, Hosaka K. 2024b. Cardamonin decreases inflammatory mediator expression in IL-1β-stimulated human periodontal ligament cells. *Molecular Biology Reports* **51(1)**:222 DOI 10.1007/s11033-023-09204-8.

Osiak W, Wątroba S, Kapka-Skrzypczak L, Kurzepa J. 2020. Two faces of heme catabolic pathway in newborns: a potential role of bilirubin and carbon monoxide in neonatal inflammatory diseases. *Oxidative Medicine and Cellular Longevity* **2020(3)**:7140496 DOI 10.1155/2020/7140496.

Özcan E, Saygun NI, Ilıkçı R, Karslıoğlu Y, Muşabak U, Yeşillik S. 2017. Increased visfatin expression is associated with nuclear factor-kappa B and phosphatidylinositol 3-kinase in periodontal inflammation. *Clinical Oral Investigations* **21(4)**:1113–1121 DOI 10.1007/s00784-016-1871-7.

Paczkowska-Walendowska M, Dvořák J, Rosiak N, Tykarska E, Szymańska E, Winnicka K, Ruchała MA, Cielecka-Piontek J. 2021. Buccal resveratrol delivery system as a potential new concept for the periodontitis treatment. *Pharmaceutics* **13(3)**:417 DOI 10.3390/pharmaceutics13030417.

Paiva CN, Feijó DF, Dutra FF, Carneiro VC, Freitas GB, Alves LS, Mesquita J, Fortes GB, Figueiredo RT, Souza HSP, Fantappié MR, Lannes-Vieira J, Bozza MT. 2012. Oxidative stress fuels Trypanosoma cruzi infection in mice. *Journal of Clinical Investigation* **122(7)**:2531–2542 DOI 10.1172/JCI58525.

Pang Y, Yuan X, Guo J, Wang X, Yang M, Zhu J, Wang J. 2019. The effect of liraglutide on the proliferation, migration, and osteogenic differentiation of human periodontal ligament cells. *Journal of Periodontal Research* **54(2)**:106–114 DOI 10.1111/jre.12607.

Park SY, Park DJ, Kim YH, Kim Y, Choi YW, Lee SJ. 2011a. Schisandra chinensis α-iso-cubebenol induces heme oxygenase-1 expression through PI3K/Akt and Nrf2 signaling and has anti-inflammatory activity in Porphyromonas gingivalis lipopolysaccharide-stimulated macrophages. *International Immunopharmacology* **11(11)**:1907–1915 DOI 10.1016/j.intimp.2011.07.023.

Park SY, Park DJ, Kim YH, Kim YH, Kim SG, Shon KJ, Choi YW, Lee SJ. 2011b. Upregulation of heme oxygenase-1 via PI3K/Akt and Nrf-2 signaling pathways mediates the anti-inflammatory activity of Schisandrin in Porphyromonas gingivalis LPS-stimulated macrophages. *Immunology Letters* **139(1–2)**:93–101 DOI 10.1016/j.imlet.2011.05.007.

Parolina de Carvalho RD, de Andrade Moreno J, Roque SM, Chan D, Torrez WB, Stipp RN, Bueno-Silva B, de Lima PO, Cogo-Müller K. 2024. Statins and oral biofilm: simvastatin as a promising drug to control periodontal dysbiosis. *Oral Dis* **30(2)**:669–680 DOI 10.1111/odi.14446.

Pi SH, Jeong GS, Oh HW, Kim YS, Pae HO, Chung HT, Lee SK, Kim EC. 2010. Heme oxygenase-1 mediates nicotine- and lipopolysaccharide-induced expression of cyclooxygenase-2 and inducible nitric oxide synthase in human periodontal ligament cells. *Journal of Periodontal Research* **45(2)**:177–183 DOI 10.1111/j.1600-0765.2009.01215.x.

Piechota-Polanczyk A, Jozkowicz A. 2017. The role of statins in the activation of heme oxygenase-1 in cardiovascular diseases. *Current Drug Targets* **18(6)**:674–686 DOI 10.2174/1389450117666160401123600.

Qi F, Sun JH, Yan JQ, Li CM, Lv XC. 2018. Anti-inflammatory effects of isorhamnetin on LPS-stimulated human gingival fibroblasts by activating Nrf2 signaling pathway. *Microbial Pathogenesis* **120**:37–41 DOI 10.1016/j.micpath.2018.04.049.

Qin Z, Han Y, Du Y, Zhang Y, Bian Y, Wang R, Wang H, Guo F, Yuan H, Pan Y, Jin J, Zhou Q, Wang Y, Han F, Xu Y, Jiang J. 2024. Bioactive materials from berberine-treated human bone marrow mesenchymal stem cells promote alveolar bone regeneration by regulating macrophage polarization. *Science China Life Sciences* **67(5)**:1010–1026 DOI 10.1007/s11427-023-2454-9.

Rask L, Andréasson E, Ekbom B, Eriksson S, Pontoppidan B, Meijer J. 2000. Myrosinase: gene family evolution and herbivore defense in Brassicaceae. *Plant Molecular Biology* **42**:93–113 DOI 10.1023/A:1006380021658.

Rawlinson SC, Zaman G, Mosley JR, Pitsillides AA, Lanyon LE. 1998. Heme oxygenase isozymes in bone: induction of HO-1 mRNA following physiological levels of mechanical loading in vivo. *Bone* **23(5)**:433–436 DOI 10.1016/s8756-3282(98)00125-2.

Rehncrona S, Westerberg E, Akesson B, Siesjö BK. 1982. Brain cortical fatty acids and phospholipids during and following complete and severe incomplete ischemia. *Journal of Neurochemistry* **38(1)**:84–93 DOI 10.1111/j.1471-4159.1982.tb10857.x.

Rizzardini M, Carelli M, Cabello Porras MR, Cantoni L. 1994. Mechanisms of endotoxin-induced haem oxygenase mRNA accumulation in mouse liver: synergism by glutathione depletion and protection by N-acetylcysteine. *Biochemical Journal* **304(Pt 2)**:477–483 DOI 10.1042/bj3040477.

Ruangsawasdi N, Boonnak N, Pruksaniyom C, Rodanant P. 2023. Xanthones isolated from Cratoxylum cochinchinensis reduced oxidative stress in periodontal ligament stem cells. *International Journal of Molecular Sciences* **24(19)**:14675 DOI 10.3390/ijms241914675.

Ryter SW, Alam J, Choi AM. 2006. Heme oxygenase-1/carbon monoxide: from basic science to therapeutic applications. *Physiological Reviews* **86(2)**:583–650 DOI 10.1152/physrev.00011.2005.

Ryter SW, Ma KC, Choi A. 2018. Carbon monoxide in lung cell physiology and disease. *American Journal of Physiology-Cell Physiology* **314(2)**:C211–C227 DOI 10.1152/ajpcell.00022.2017.

Ryter SW, Tyrrell RM. 2000. The heme synthesis and degradation pathways: role in oxidant sensitivity. Heme oxygenase has both pro- and antioxidant properties. *Free Radical Biology and Medicine* **28(2)**:289–309 DOI 10.1016/S0891-5849(99)00223-3.

Ryu EY, Park AJ, Park SY, Park SH, Eom HW, Kim YH, Park G, Lee SJ. 2012. Inhibitory effects of Ginkgo biloba extract on inflammatory mediator production by Porphyromonas gingivalis

lipopolysaccharide in murine macrophages via Nrf-2 mediated heme oxygenase-1 signaling pathways. *Inflammation* **35(4)**:1477–1486 DOI 10.1007/s10753-012-9461-6.

Saha S, Mahilkar S, Abraham DV, S S, Bhat N, Srivastava DS. 2024. A comparative analysis of three antioxidants in addition to scaling and root planing in stage three grade B periodontitis. *Cureus* **16(1)**:e51916 DOI 10.7759/cureus.51916.

Sari DS, Pujiastuti P, Fatmawati D, Mardiyana MA, Wulandari AT, Arina Y. 2023. Inhibiting the growth of periopathogenic bacteria and accelerating bone repair processes by using robusta coffee bean extract. *The Saudi Dental Journal* **35(4)**:322–329 DOI 10.1016/j.sdentj.2023.03.007.

Sawada N, Adachi K, Nakamura N, Miyabe M, Ito M, Kobayashi S, Miyajima SI, Suzuki Y, Kikuchi T, Mizutani M, Toriumi T, Honda M, Mitani A, Matsubara T, Naruse K, Saisho Y. 2020. Glucagon-like peptide-1 receptor agonist liraglutide ameliorates the development of periodontitis. *Journal of Diabetes Research* **2020**:8843310 DOI 10.1155/2020/8843310.

Sculley DV, Langley-Evans SC. 2002. Salivary antioxidants and periodontal disease status. *Proceedings of the Nutrition Society* **61(1)**:137–143 DOI 10.1079/PNS2001141.

Sezer U, Kara Mİ, Ercıyas K, Özdemir H, Üstün K, Özer H, Göze F. 2013. Protective effects of Ginkgo biloba extract on ligature-induced periodontitis in rats. *Acta Odontologica Scandinavica* **71(1)**:38–44 DOI 10.3109/00016357.2011.650195.

Shirmohamadi A, Chitsazi MT, Faramarzi M, Salari A, Naser Alavi F, Pashazadeh N. 2016. Effect of non-surgical periodontal treatment on transferrin serum levels in patients with chronic periodontitis. *Journal of Dental Research, Dental Clinics, Dental Prospects* **10(3)**:169–175 DOI 10.15171/joddd.2016.027.

Sim KY, Jang YS, Jang YS, Nerobkova N, Park EC. 2023. Association between smoking and periodontal disease in South Korean adults. *International Journal of Environmental Research and Public Health* **20(5)**:4423 DOI 10.3390/ijerph20054423.

Sinha S, Kumar S, Dagli N, Dagli RJ. 2014. Effect of tetracycline HCl in the treatment of chronic periodontitis—a clinical study. *Journal of International Society of Preventive and Community Dentistry* **4(3)**:149–153 DOI 10.4103/2231-0762.142011.

Sofrata A, Santangelo EM, Azeem M, Borg-Karlson AK, Gustafsson A, Pütsep K. 2011. Benzyl isothiocyanate, a major component from the roots of Salvadora persica is highly active against Gram-negative bacteria. *PLOS ONE* **6**:e23045 DOI 10.1371/journal.pone.0023045.

Song J, Kim B, Kim O, Yang Y, Liu D, Fu W, Ma G, Kim Y, Kim O. 2022. Effect of coffee on lipopolysaccharide-induced immortalized human oral keratinocytes. *Foods* **11(15)**:2199 DOI 10.3390/foods11152199.

Song L, Li J, Yuan X, Liu W, Chen Z, Guo D, Yang F, Guo Q, Song H. 2017. Carbon monoxide-releasing molecule suppresses inflammatory and osteoclastogenic cytokines in nicotine- and lipopolysaccharide-stimulated human periodontal ligament cells via the heme oxygenase-1 pathway. *International Journal of Molecular Medicine* **40(5)**:1591–1601 DOI 10.3892/ijmm.2017.3129.

Song H, Zhao H, Qu Y, Sun Q, Zhang F, Du Z, Liang W, Qi Y, Yang P. 2011. Carbon monoxide releasing molecule-3 inhibits concurrent tumor necrosis factor-α- and interleukin-1β-induced expression of adhesion molecules on human gingival fibroblasts. *Journal of Periodontal Research* **46(1)**:48–57 DOI 10.1111/j.1600-0765.2010.01307.x.

Souza RB, Gomes FIF, Pereira KMA, Dutra PGP, da Cunha RMS, Chaves HV, Bezerra MM. 2018. Strontium ranelate elevates expression of heme oxygenase-1 and decreases alveolar bone loss in rats. *Journal of Oral and Maxillofacial Research* **9(4)**:e4 DOI 10.5037/jomr.2018.9404.

Souza JA, Rossa C Jr, Garlet GP, Nogueira AV, Cirelli JA. 2012. Modulation of host cell signaling pathways as a therapeutic approach in periodontal disease. *Journal of Applied Oral Science* **20(2)**:128–138 DOI 10.1590/S1678-77572012000200002.

Stocker R, Yamamoto Y, McDonagh AF, Glazer AN, Ames BN. 1987. Bilirubin is an antioxidant of possible physiological importance. *Science* **235(4792)**:1043–1046 DOI 10.1126/science.3029864.

Sun J, Druhan LJ, Zweier JL. 2010. Reactive oxygen and nitrogen species regulate inducible nitric oxide synthase function shifting the balance of nitric oxide and superoxide production. *Archives of Biochemistry and Biophysics* **494(2)**:130–137 DOI 10.1016/j.abb.2009.11.019.

Sun A, Yang H, Li T, Luo J, Zhou L, Chen R, Han L, Lin Y. 2024. Molecular mechanisms, targets and clinical potential of berberine in regulating metabolism: a review focussing on databases and molecular docking studies. *Frontiers in Pharmacology* **15**:1368950 DOI 10.3389/fphar.2024.1368950.

Taha H, Skrzypek K, Guevara I, Nigisch A, Mustafa S, Grochot-Przeczek A, Ferdek P, Was H, Kotlinowski J, Kozakowska M, Balcerczyk A, Muchova L, Vitek L, Weigel G, Dulak J, Jozkowicz A. 2010. Role of heme oxygenase-1 in human endothelial cells: lesson from the promoter allelic variants. *Arteriosclerosis, Thrombosis, and Vascular Biology* **30(8)**:1634–1641 DOI 10.1161/ATVBAHA.110.207316.

Taleghani F, Rezvani G, Birjandi M, Valizadeh M. 2018. Impact of green tea intake on clinical improvement in chronic periodontitis: a randomized clinical trial. *Journal of Stomatology, Oral and Maxillofacial Surgery* **119(5)**:365–368 DOI 10.1016/j.jormas.2018.04.010.

Tan Y, Feng J, Xiao Y, Bao C. 2022. Grafting resveratrol onto mesoporous silica nanoparticles towards efficient sustainable immunoregulation and insulin resistance alleviation for diabetic periodontitis therapy. *Journal of Materials Chemistry B* **10(25)**:4840–4855 DOI 10.1039/D2TB00484D.

Tao L, Yu W, Liu Z, Zhao D, Lin S, Szalóki D, Kicsák M, Kurtán T, Zhang H. 2024. JE-133 Suppresses LPS-induced neuroinflammation associated with the regulation of JAK/STAT and Nrf2 signaling pathways. *ACS Chemical Neuroscience* **15(2)**:258–267 DOI 10.1021/acschemneuro.3c00454.

Taskan MM, Gevrek F. 2020. Quercetin decreased alveolar bone loss and apoptosis in experimentally induced periodontitis model in wistar rats. *Anti-Inflammatory & Anti-Allergy Agents in Medicinal Chemistry* **19(4)**:436–448 DOI 10.2174/1871523019666200124114503.

Tenhunen R, Marver HS, Schmid R. 1968. The enzymatic conversion of heme to bilirubin by microsomal heme oxygenase. *Proceedings of the National Academy of Sciences* **61(2)**:748–755 DOI 10.1073/pnas.61.2.748.

Tian H, Chen H, Yin X, Lv M, Wei L, Zhang Y, Jia S, Li J, Song H. 2024. CORM-3 inhibits the inflammatory response of human periodontal ligament fibroblasts stimulated by LPS and high glucose. *Journal of Inflammation Research* **17**:4845–4863 DOI 10.2147/JIR.S460954.

Tonetti MS, Jepsen S, Jin L, Otomo-Corgel J. 2017. Impact of the global burden of periodontal diseases on health, nutrition and wellbeing of mankind: a call for global action. *Journal of Clinical Periodontology* **44(5)**:456–462 DOI 10.1111/jcpe.12732.

Tripathi P, Blaggana V, Upadhyay P, Jindal M, Gupta S, Nishat S. 2019. Antioxidant therapy (lycopene and green tea extract) in periodontal disease: a promising paradigm. *Journal of Indian Society of Periodontology* **23(1)**:25–30 DOI 10.4103/jisp.jisp_277_18.

Varghese J, Bhat V, Chianeh YR, Kamath V, Al-Haj Husain N, Özcan M. 2020. Salivary 8-hydroxyguanosine levels in smokers and non-smokers with chronic periodontitis. *Odontology* **108(4)**:569–577 DOI 10.1007/s10266-020-00496-x.

Vo TTT, Huang HW, Wee Y, Feng SW, Cheng HC, Tuan VP, Lee IT. 2022. Surfactin reduces particulate matter-induced VCAM-1-dependent monocyte adhesion in human gingival fibroblasts by increasing Nrf2-dependent HO-1 expression. *Journal of Periodontal Research* **57(1)**:115–130 DOI 10.1111/jre.12944.

Wagener F, Eggert A, Boerman OC, Oyen WJG, Verhofstad A, Abraham NG, Adema G, van Kooyk Y, de Witte T, Figdor CG. 2001. Heme is a potent inducer of inflammation in mice and is counteracted by heme oxygenase. *Blood* **98(6)**:1802–1811 DOI 10.1182/blood.V98.6.1802.

Wang J, de Montellano PR. 2003. The binding sites on human heme oxygenase-1 for cytochrome p450 reductase and biliverdin reductase. *Journal of Biological Chemistry* **278(22)**:20069–20076 DOI 10.1074/jbc.M300989200.

Wang C, Liu C, Liang C, Qu X, Zou X, Du S, Zhang Q, Wang L. 2023. Role of berberine thermosensitive hydrogel in periodontitis via PI3K/AKT pathway in vitro. *International Journal of Molecular Sciences* **24(7)**:6364 DOI 10.3390/ijms24076364.

Wang Q, Sztukowska M, Ojo A, Scott DA, Wang H, Lamont RJ. 2015. FOXO responses to Porphyromonas gingivalis in epithelial cells. *Cellular Microbiology* **17(11)**:1605–1617 DOI 10.1111/cmi.12459.

Wang X, Wang WM, Han H, Zhang Y, Liu JL, Yu JY, Liu HM, Liu XT, Shan H, Wu SC. 2022a. Tanshinone IIA protected against lipopolysaccharide-induced brain injury through the protective effect of the blood-brain barrier and the suppression of oxidant stress and inflammatory response. *Food & Function* **13(15)**:8304–8312 DOI 10.1039/D2FO00710J.

Wang G, Wang Y, Yang Q, Xu C, Zheng Y, Wang L, Wu J, Zeng M, Luo M. 2022b. Metformin prevents methylglyoxal-induced apoptosis by suppressing oxidative stress in vitro and in vivo. *Cell Death & Disease* **13(1)**:29 DOI 10.1038/s41419-021-04478-x.

Wei J, Fan G, Zhao H, Li J. 2015. Heme oxygenase-1 attenuates inflammation and oxidative damage in a rat model of smoke-induced emphysema. *International Journal of Molecular Medicine* **36(5)**:1384–1392 DOI 10.3892/ijmm.2015.2353.

Wei Y, Fu J, Wu W, Ma P, Ren L, Yi Z, Wu J. 2021. Quercetin prevents oxidative stress-induced injury of periodontal ligament cells and alveolar bone loss in periodontitis. *Drug Design, Development and Therapy* **15**:3509–3522 DOI 10.2147/DDDT.S315249.

Xie Y, Xiao S, Huang L, Guo J, Bai M, Gao Y, Zhou H, Qiu L, Cheng C, Han X. 2023. Cascade and ultrafast artificial antioxidases alleviate inflammation and bone resorption in periodontitis. *ACS Nano* **17(15)**:15097–15112 DOI 10.1021/acsnano.3c04328.

Xin X, Liu J, Liu X, Xin Y, Hou Y, Xiang X, Deng Y, Yang B, Yu W. 2024. Melatonin-derived carbon dots with free radical scavenging property for effective periodontitis treatment via the Nrf2/HO-1 pathway. *ACS Nano* **18(11)**:8307–8324 DOI 10.1021/acsnano.3c12580.

Xu Y, Chu Y, Yang W, Chu K, Li S, Guo L. 2024. BML-111 inhibit H(2)O(2)-induced pyroptosis and osteogenic dysfunction of human periodontal ligament fibroblasts by activating the Nrf2/HO-1 pathway. *BMC Oral Health* **24(1)**:40 DOI 10.1186/s12903-023-03827-w.

Yachie A, Niida Y, Wada T, Igarashi N, Kaneda H, Toma T, Ohta K, Kasahara Y, Koizumi S. 1999. Oxidative stress causes enhanced endothelial cell injury in human heme oxygenase-1 deficiency. *Journal of Clinical Investigation* **103(1)**:129–135 DOI 10.1172/JCI4165.

Yamaguchi Y, Kanzaki H, Katsumata Y, Itohiya K, Fukaya S, Miyamoto Y, Narimiya T, Wada S, Nakamura Y. 2018. Dimethyl fumarate inhibits osteoclasts via attenuation of reactive oxygen species signalling by augmented antioxidation. *Journal of Cellular and Molecular Medicine* **22(2)**:1138–1147 DOI 10.1111/jcmm.13367.

Yang Y, Yu L, Zhu T, Xu S, He J, Mao N, Liu Z, Wang D. 2023. Neuroprotective effects of Lycium barbarum polysaccharide on light-induced oxidative stress and mitochondrial damage via the

Nrf2/HO-1 pathway in mouse hippocampal neurons. *International Journal of Biological Macromolecules* **251**:126315 DOI 10.1016/j.ijbiomac.2023.126315.

Yao J, Long H, Zhao J, Zhong G, Li J. 2020. Nifedipine inhibits oxidative stress and ameliorates osteoarthritis by activating the nuclear factor erythroid-2-related factor 2 pathway. *Life Sciences* **253(3)**:117292 DOI 10.1016/j.lfs.2020.117292.

Yao J, Miao Y, Zhang Y, Zhu L, Chen H, Wu X, Yang Y, Dai X, Hu Q, Wan M, Tang W. 2022. Dao-chi powder ameliorates pancreatitis-induced intestinal and cardiac injuries via regulating the Nrf2-HO-1-HMGB1 signaling pathway in rats. *Frontiers in Pharmacology* **13**:922130 DOI 10.3389/fphar.2022.922130.

Yiğit U, Kırzıoğlu FY, Özmen Ö, Uğuz AC. 2021. Protective effects of caffeic acid phenethyl ester on the heart in experimental periodontitis against oxidative stress in rats. *Dental and Medical Problems* **58(3)**:335–341 DOI 10.17219/dmp/132388.

Yoon Y, Kim TJ, Lee JM, Kim DY. 2018. SOD2 is upregulated in periodontitis to reduce further inflammation progression. *Oral Diseases* **24(8)**:1572–1580 DOI 10.1111/odi.12933.

Yoshida T, Kikuchi G. 1978. Features of the reaction of heme degradation catalyzed by the reconstituted microsomal heme oxygenase system. *Journal of Biological Chemistry* **1978(253)**:4230–4236 DOI 10.1016/S0021-9258(17)34708-7.

Yoshida T, Noguchi M, Kikuchi G. 1980. Oxygenated form of heme . heme oxygenase complex and requirement for second electron to initiate heme degradation from the oxygenated complex. *Journal of Biological Chemistry* **255(10)**:4418–4420 DOI 10.1016/S0021-9258(19)85506-0.

Yu JY, Lee SY, Son YO, Shi X, Park SS, Lee JC. 2012. Continuous presence of H_2O_2 induces mitochondrial-mediated, MAPK- and caspase-independent growth inhibition and cytotoxicity in human gingival fibroblasts. *Toxicology in Vitro* **26(4)**:561–570 DOI 10.1016/j.tiv.2012.01.022.

Yu H, Liu Y, Yang X, He J, Zhong Q, Guo X. 2022. The anti-inflammation effect of strontium ranelate on rat chondrocytes with or without IL-1β in vitro. *Experimental and Therapeutic Medicine* **23(3)**:208 DOI 10.3892/etm.2022.11131.

Yuan Z, Li J, Xiao F, Wu Y, Zhang Z, Shi J, Qian J, Wu X, Yan F. 2024. Sinensetin protects against periodontitis through binding to Bach1 enhancing its ubiquitination degradation and improving oxidative stress. *International Journal of Oral Science* **16(1)**:38 DOI 10.1038/s41368-024-00305-z.

Zhang Q, Xu S, Xu W, Zhou Y, Luan H, Wang D. 2022. Resveratrol decreases local inflammatory markers and systemic endotoxin in patients with aggressive periodontitis. *Medicine (Baltimore)* **101(25)**:e29393 DOI 10.1097/MD.0000000000029393.

Zhang B, Yang Y, Yi J, Zhao Z, Ye R. 2021. Hyperglycemia modulates M1/M2 macrophage polarization via reactive oxygen species overproduction in ligature-induced periodontitis. *Journal of Periodontal Research* **56(5)**:991–1005 DOI 10.1111/jre.12912.

Zhang Y, Yuan X, Wu Y, Pei M, Yang M, Wu X, Pang Y, Wang J. 2020. Liraglutide regulates bone destruction and exhibits anti-inflammatory effects in periodontitis in vitro and in vivo. *Journal of Dentistry* **94(9)**:103310 DOI 10.1016/j.jdent.2020.103310.

Zhao YZ, Du CC, Xuan Y, Huang D, Qi B, Shi Y, Shen X, Zhang Y, Fu Y, Chen Y, Kou L, Yao Q. 2024. Bilirubin/morin self-assembled nanoparticle-engulfed collagen/polyvinyl alcohol hydrogel accelerates chronic diabetic wound healing by modulating inflammation and ameliorating oxidative stress. *International Journal of Biological Macromolecules* **261(1)**:129704 DOI 10.1016/j.ijbiomac.2024.129704.

Zhao Y, Zheng Z, Zhang M, Wang Y, Hu R, Lin W, Huang C, Xu C, Wu J, Deng H. 2021. Design, synthesis, and evaluation of mono-carbonyl analogues of curcumin (MCACs) as

potential antioxidants against periodontitis. *Journal of Periodontal Research* **56(4)**:656–666 DOI 10.1111/jre.12862.

Zhou J, Shi P, Ma R, Xie X, Zhao L, Wang J. 2023. Notopterol inhibits the NF-κB pathway and activates the PI3K/Akt/Nrf2 pathway in periodontal tissue. *The Journal of Immunology* **211(10)**:1516–1525 DOI 10.4049/jimmunol.2200727.

Zhou X, Yuan W, Xiong X, Zhang Z, Liu J, Zheng Y, Wang J, Liu J. 2021. HO-1 in bone biology: potential therapeutic strategies for osteoporosis. *Frontiers in Cell and Developmental Biology* **9**:791585 DOI 10.3389/fcell.2021.791585.

Zhou MM, Zhang WY, Li RJ, Guo C, Wei SS, Tian XM, Luo J, Kong LY. 2018. Anti-inflammatory activity of Khayandirobilide A from Khaya senegalensis via NF-κB, AP-1 and p38 MAPK/Nrf2/HO-1 signaling pathways in lipopolysaccharide-stimulated RAW 264. 7 and BV-2 cells. *Phytomedicine* **42**:152–163 DOI 10.1016/j.phymed.2018.03.016.

Zhu X, Fan WG, Li DP, Kung H, Lin MC. 2011. Heme oxygenase-1 system and gastrointestinal inflammation: a short review. *World Journal of Gastroenterology* **17(38)**:4283–4288 DOI 10.3748/wjg.v17.i38.4283.

Zhu B, Wu J, Li T, Liu S, Guo J, Yu Y, Qiu X, Zhao Y, Peng H, Zhang J, Miao L, Wei H. 2024. A glutathione peroxidase-mimicking nanozyme precisely alleviates reactive oxygen species and promotes periodontal bone regeneration. *Advanced Healthcare Materials* **13(4)**:e2302485 DOI 10.1002/adhm.202302485.

Żukowski P, Maciejczyk M, Waszkiel D. 2018. Sources of free radicals and oxidative stress in the oral cavity. *Archives of Oral Biology* **92(3)**:8–17 DOI 10.1016/j.archoralbio.2018.04.018.