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# Periodontal Health and Disease in Glutathione Peroxidase

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## Abstract

Periodontal diseases are chronic, multifactorial inflammatory diseases that affect more than 10% of the world population. There are two general forms of periodontal diseases including gingivitis (reversible inflammation and confined with gingiva form) and periodontitis (irreversible, destruction form). Several studies have reported that periodontal disease was associated with a decreased antioxidant capacity and elevated oxidative damage within the oral cavity. Glutathione peroxidase (GSH-Px) is an important enzymatic antioxidant that protects periodontal tissues against oxidative stress. Hitherto, there is contradictory evidence concerning the relationship between the levels of GSH-Px and the periodontal status. Various studies have demonstrated that GSH-Px levels in different biological fluids increased, decreased, or are unaltered in individuals with periodontal disease. This discrepancy might be explained either by different determination protocols/assays applied among the studies or various dynamic processes of the periodontal disease progression. In this section, GSH-Px levels are summarized in the periodontal health and disease including the presence and absence of systemic disease, medication, wound healing, and smoking.

**Keywords:** glutathione peroxidase, periodontitis, gingivitis, gingival crevicular fluid, salivary

## 1. Introduction

The periodontium is a private connective tissue consisting of a gingiva, cementum, periodontal ligament, and alveolar bone supporting the tooth in the socket [1]. Periodontal disease is a widespread, chronic multimicrobial immunoinflammatory illness which began with the complex coaction between the host's immunoinflammatory responses and pathogenic bacteria in the dental tissue [2]. There are two general forms of periodontal diseases including gingivitis (confined with gingiva form) and periodontitis. Gingivitis is a localized inflammation of the gingiva, which is began by pathogens in the microbial dental plaque on the tooth and gingiva [3]. Gingivitis causes reversible inflammation in the periodontal tissues [3]. Periodontitis, the destructive form of periodontal disease, leads to the destruction of the gingiva, alveolar bone, and periodontal ligament and is responsible for causing tooth mobility and early tooth loss [3, 4]. Periodontitis leads to irreversible local periodontal tissue destruction [5]. Periodontal diseases are the most common chronic diseases impacting 10–15% of population worldwide [6, 7].

Microbial dental plaque, mostly gram-negative anaerobic or facultative pathogens inside the subgingival biofilm, is the principal etiological factor in periodontal diseases [8]. Robust evidence in the etiology of periodontal diseases has been shown

responsible for periodontopathogens including *Aggregatibacter actinomycetemcomitans* (Aa), *Porphyromonas gingivalis* (PG), *Tannerella forsythia* (TF), and *Treponema denticola* (TD) [9]. It is stated that “red complex” pathogens (PG, TD, and TF) are frequent in individuals with periodontitis [10]. The plurality of periodontal tissue devastation is brought about by an unsuitable host response to those pathogens and their products (lipopolysaccharides and proteases) [11]. The coaction between pathogenic bacteria and the host’s immune response is participated by chemokines, the produce of pro-inflammatory cytokines, and an exaggerated immune response, entailing an increase in the number and activity of polymorphonuclear leukocytes (PMNs) [12]. PMNs are the main mediators of host response averse to the bacteria [13].

PMNs create the first advocacy of cellular host defenses averse to pathogenic microorganisms in the gingival sulcus [14]. PMNs defend the host against bacteria in two pathways, including oxygen-dependent and non-oxygen-dependent mechanisms [15]. The oxygen-dependent pathway contains the production of reactive oxygen species (ROS), which causes the destruction of periodontal tissues [16]. Although the main reason for the production of ROS by PMNs is the killing of bacteria, excessive production of ROS in the extracellular space causes the destruction of tissues [8, 14, 16]. The overproduction of ROS leads to tissue damage through different mechanisms including lipid peroxidation, DNA and protein damage, and the stimulation of pro-inflammatory cytokine [1, 16]. Several studies have shown the relationship between ROS and periodontal disease [5, 16–18]. Oxidative stress (OS), an imbalance between the pro-oxidant and antioxidant system, is involved in the bone resorptive process during periodontal disease [19]. Various studies have shown that OS is involved in the pathophysiological mechanisms of periodontitis [1, 17, 18, 20, 21]. Recently Sreeram et al. have described it as follows: “Periodontitis is an inflammatory condition leading to increased OS” [22].

Antioxidant defense mechanisms (nonenzymatic and enzymatic antioxidants) eliminate ROS and inhibit their detrimental consequences on the host [23]. Antioxidant enzymes protect tissues against the destructive effects of ROS created by different metabolic processes, modulating the dimension of inflammatory response [18, 24]. The defense mechanism averse to ROS involves three antioxidant pathways including intracellular, extracellular, and membrane antioxidants [25]. The main system is intracellular ROS cleaning enzymes: superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GSH-Px) [25]. GSH-Px, as a selenium-containing peroxidase, is a major group of enzymes that eliminate hydrogen peroxide created by SOD in the cytosol and mitochondria by oxidizing reduced glutathione to its oxidized form [22, 26]. GSH-Px is one of the enzymes that has a significant role in host defense averse to oxidative stress in cytosol [1, 18]. GSH-Px1 inhibits cytotoxic peroxide-induced oxidative damage, protein degeneration, and lipid peroxidation [27].

Traditional diagnosis of periodontal disease is based on clinical (gingival index (GI), bleeding on probing (BOP), clinical attachment level (CAL), probing pocket depth (PPD)) and radiographic parameters [22]. Traditional clinical measurements that are used for periodontal diagnosis are frequently of only restricted usefulness inasmuch as they are indicators of previous periodontal disease rather than present disease activity [28, 29]. Knowing the disease activity will enable early detection of the disease [21]. Moreover, the levels of oxidative stress parameters in saliva and gingival crevicular fluid (GCF) may show the activity and severity of periodontal disease [29].

Saliva is used as an easily collected diagnostic fluid that makes it possible to determine the levels of biomarkers in the evaluation of the disease condition [30]. By the way, GCF is a biological fluid in the gingival sulcus that derives from blood plasma and consists of metabolic elements of pathogens and host cells, which are explained

as transudates or exudates [31]. Thereby, disease diagnosis via analysis of saliva and GCF is suitable for individuals [21]. Since the half-life of ROS is very short, they cannot be determined easily. Thus, ROS-induced demolition products and the activity of enzymatic and nonenzymatic antioxidants are optimal candidates to assess the consequences of OS-connected events in the pathological process of chronic periodontitis [21]. On the other hand, antioxidants (enzymatic and nonenzymatic antioxidants) in the saliva preserve the unity of oral tissues by neutralizing ROS [14].

In this section, GSH-Px levels are summarized in the periodontal health and disease including the presence and absence of systemic disease, medication, wound healing, smoking.

## **2. Glutathione peroxidase and periodontal disease**

Wei et al. [32] examined the role of glutathione peroxidase in the pathogenesis of periodontal diseases. They reported higher total amount of GSH-Px in GCF samples from patients with gingivitis and periodontitis compared to healthy subjects [32]. Moreover, they determined that the total amount of GSH-Px was significantly higher in periodontitis patients than in gingivitis patients [32]. Also, there is a positive and significant correlation between the total amount of glutathione peroxidase and interleukin (IL)-1 $\beta$  and plaque index (PI) in GCF of the individuals with periodontal disease [32]. Besides, Panjamurthy et al. [33] assessed the levels of GSH-Px in patients with chronic periodontitis (CP) and determined that GSH-Px activities in the plasma, erythrocyte lysate, and gingival tissues were significantly increased in patients with periodontitis compared to healthy subjects. In addition, Borges et al. [34] analyzed the GSH-Px activities in the gingival tissue of individuals with CP. They determined a significant increase in GSH-Px activities in the individuals with CP when compared to the control group [34]. They noticed that an increase in GSH-Px may indicate possible antioxidant suppression in the destroyed ROS products in the gingival tissue [34]. Moreover, Arunachalam et al. [35] stated that the GSH-Px levels in the plasma of patients with aggressive periodontitis increased compared with the healthy individuals. Conversely, Sreeram et al. [22] and Aziz et al. [36] reported that serum GSH-Px activity in individuals with CP decreased when compared with the control groups.

Tsai et al. [37] aimed to determine the GSH-Px levels in saliva before and after periodontal treatment in patients with CP. They did not find a significant difference in the activities of GSH-Px in saliva between periodontally diseased and healthy subjects and even between prior to and after treatment in periodontitis patients [37]. On the contrary, Çanakçı et al. [20] and Miricescu et al. [38] found that the GSH-Px activities in saliva of patients with periodontitis were significantly lower than the controls. In accordance with Tsai et al. [37], Çanakçı et al. [20] suggested that there were no significant correlations between salivary GSH-Px capacities and periodontal status. Contrary to Tsai et al. [37], Novaković et al. [14, 39] evaluated the GSH-Px activity in saliva of the CP patients before and after nonsurgical treatment and concluded that there was a significant increase in these levels after therapy. Novaković et al. [14] argued that the increase in GSH-Px activity in saliva can be explained by the reduction in periodontal tissue inflammation after nonsurgical therapy. Novaković et al. [39] indicated that salivary GSH-Px could be used as a reliable biomarker in evaluating periodontal status and therapy outcome. A recent meta-analysis declared that there are no significant differences in the salivary GSH-Px levels between the patients with CP and periodontally healthy individuals [21]. These meta-analysis results coincide with other studies that have determined an increase or decrease in salivary GSH-Px levels [21]. The authors claimed that this

disagreement might be connected to the various dynamic processes of the periodontitis progression [21].

Almerich-Silla et al. [17] showed the association between GSH-Px levels and the presence of different periodontal pathogens (PG, Aa, TD, and TF). They reported that GSH-Px levels were elevated in the existence of all bacteria types, except PG genotypes III and IV, and also the presence of different types of bacteria has a positive relationship with GSH-Px [17]. The authors advised that determination of GSH-Px levels and periodontal bacteria can be an important tool to control the progression of periodontal disease [17].

Until today, there is contradictory evidence concerning the relationship between the levels of GSH-Px and the periodontal status. Various studies have demonstrated that GSH-Px levels in different biological fluids increased, decreased, or are unaltered in individuals with periodontal disease. This discrepancy might be explained by different determination protocols/assays applied among the studies. On the other hand, a more persuasive change in GSH-Px activity in GCF than in saliva is observed [40]. GCF is more specific for periodontal inflammation than saliva, and also, saliva and serum GSH-Px levels may be affected by systemic conditions.

Replace the entirety of this text with the main body of your chapter. The body is where the author explains experiments, presents and interprets data of one's research. Authors are free to decide how the main body will be structured. However, you are required to have at least one heading. Please ensure that either British or American English is used consistently in your chapter.

## **2.1 Plasma glutathione peroxidase and periodontal disease**

Patel et al. [8] examined the levels of plasma glutathione peroxidase (eGPx) in GCF before and 6–8 weeks after periodontal therapy in patients with periodontal disease. They ascertained that eGPx levels in GCF were significantly elevated progressively from health to gingivitis and periodontitis [8]. The study suggested that increased eGPx level in GCF from inflamed gingiva may indicate the increased ROS generation at the diseased site [8]. Also, the authors determined that the mean concentration of eGPx in GCF in CP group showed a significant reduction after the treatment and thus stated that increased eGPx concentration is associated with the severity of periodontal disease [8]. Similar to the previous study, Patel et al. [41] determined an increase of the eGPx concentrations in GCF and serum progressively from health to gingivitis and periodontitis groups and a decrease of these levels after nonsurgical periodontal therapy. Thus, the authors declared that the increase in GCF and serum eGPx can be considered as a marker of oxidative stress caused by periodontal infection [41]. Moreover, they noted that the significant increase in serum eGPx concentration in the periodontal disease can be possibly because of the overflow from the diseased periodontal tissues or increased production of eGPx by kidney proximal tubules in response to systemic oxidative stress caused by periodontal disease [41].

## **2.2 Glutathione peroxidase and periodontal wound healing**

Sakallıoğlu et al. [25] investigated GSH-Px profiles in the 30-day recovery period (at days 3, 12, 21, and 30) in an acute incisional wound model created with muco-periosteal periodontal flaps in dogs. They determined that GSH-Px levels increased significantly on the 3rd day of recovery period and then decreased insignificantly on the 12th day and increased insignificantly on the 21st day [25]. Later, GSH-Px levels decreased significantly on the 30th day compared to the 21st day of the recovery period, and these levels are lower than the baseline [25]. It is suggested

that GSH-Px plays a significant role in the eradication of ROS in the recovery period of periodontal repair [25]. Moreover they argued that GSH-Px can neutralize to the noxious effects of OH in a normal periodontal mucoperiosteal or gingival wound healing [25].

### **2.3 Glutathione peroxidase, smoking, and periodontal disease**

The etiology of periodontal disease is multifactorial, and periodontal pathogenesis processes are replaced by environmental and acquired risk factors such as smoking [42]. Tobacco smoking is one of the principal modifiable risk factor associated with chronic destructive periodontal disease [36]. It has been reported that the prevalence of periodontitis was three to six times higher in smokers than nonsmokers [16]. Possible negative effects of smoking on periodontal tissues may include altered neutrophil function, decreased IgG production, vascular alterations, increased prevalence of perio-pathogens, altered fibroblast attachment and functions, decreased lymphocyte proliferation, difficulty in eliminating pathogens by mechanical therapy, and negative local effects on cytokinesis and growth factor production [36]. Smoking influences oxidative stress in the body by promoting oxidative burst in neutrophils and causes an imbalance between antioxidants and ROS [43].

Guentsch et al. [16] evaluated both GSH-Px activities in saliva and serum in patients with periodontitis and the effects of periodontal treatment and smoking on these parameters. They reported an elevated GSH-Px activity in saliva in both the nonsmoking and smoking periodontitis groups compared to the periodontally healthy control groups and that these levels, which increased in both periodontitis groups, decreased after treatment [16]. However, the authors did not find a significant difference in serum GSH-Px values of both smokers and nonsmoker individuals with periodontitis and those who are periodontally healthy [16]. It is suggested that elevated GSH-Px levels in the saliva of periodontitis patients indicate to adversely affect antioxidant mechanisms leading to tissue damage of the continuous ROS production in periodontal inflammation [16]. Also, it is shown that smoking increased the GSH-Px levels in patients with periodontitis [16]. On the contrary, Aziz et al. [36] argued that smokers with CP have shown decreased GSH-Px activity in serum when compared to nonsmoker controls.

Hendek et al. [18] examined the effects of initial periodontal therapy on GSH-Px levels in serum, saliva, and GCF samples in smokers and nonsmokers with CP. They found that there was no significant difference among all groups for GSH-Px enzyme activity in serum, while GSH-Px enzyme activity in saliva and GCF was higher in smokers and nonsmokers with CP than periodontally healthy nonsmokers but statistically insignificant in GCF [18]. In addition, authors declared that there was no significant difference in the GSH-Px enzyme activity in GCF, serum, and saliva after periodontal therapy in both periodontitis groups [18]. Their data speculated that elevated GSH-Px activity in periodontitis patients may be a result of tissue repair and adaptive mechanisms against inflamed periodontal tissues in response to oxidative stress [18]. Conversely, Naresh et al. [43] found that the levels of GSH-Px in the saliva of smokers and nonsmokers with CP were decreased when compared with the healthy group and mean GSH-Px levels were lowest in smokers with CP. They stated that exposure to smoking may reduce salivary GSH-Px levels [43].

Toguç et al. [44] investigated the impact of smoking status on the GSH-Px levels in the gingival tissue and blood in subjects with CP. When blood GSH-Px levels are evaluated, the lowest values were observed in the smoker patients with CP compared to nonsmoker patients with CP and in the nonsmoker control group compared to nonsmokers and former smokers with CP [44]. Besides, elevated GSH-Px levels in gingival tissue have been determined in the control group when compared

with all CP groups [44]. When gingival tissue GSH-Px levels are evaluated among all CP groups, the lowest values were found surprisingly in nonsmokers [44]. Moreover, they found that there were strong negative correlations between gingival tissue GSH-Px levels and smoking duration and yearly cigarette consumption [44]. Thus, they stated that the reduced local GSH-Px levels in the periodontitis patients may increase with smoking, and the reason for this increase may be the result of a protective and adaptive mechanism developing in the tissue [44].

## **2.4 Glutathione peroxidase, systemic diseases, and periodontal disease**

Periodontal disease has been associated with several systemic illnesses, including atherosclerosis, cardiovascular disease, rheumatoid arthritis, diabetes mellitus, adverse pregnancy outcomes, and Alzheimer's disease [12].

### *2.4.1 Diabetes mellitus*

Diabetes mellitus (DM) is a major risk factor for periodontal diseases, and periodontitis is noted as the sixth complication of DM. It has been shown with increasing evidence that the prevalence, progression, and severity of periodontitis increase in individuals with diabetes, especially uncontrolled, compared to individuals with no diabetes [45, 46]. There is a bilateral relationship between periodontal disease and DM. Various mechanisms have been suggested to clarify this relationship including the formation of advanced glycation end products (AGEs), changes in collagen metabolism and immune function, and recently an increased oxidative stress [47].

Arana et al. [48] evaluated the levels of GSH-Px in the saliva of patients with diabetes mellitus type 2 (DM2) and healthy nondiabetic patients in the presence of periodontal disease. They determined that the salivary GSH-Px levels in the diabetic group with good metabolic control was significantly higher than the control group and the diabetic group with poor metabolic control, and also patients with poor metabolic control in comparison with the control group and well-controlled diabetic groups have worst periodontal health and lowest saliva GPx levels [48]. Authors suggested that poor metabolic control in DM2 patients is associated with lower levels of salivary GSH-Px and worse periodontal health [48]. On the other hand, Duarte et al. [47] evaluated the gene expression of GSH-Px1 in the gingival tissue of poorly and well-controlled type 2 diabetic subjects with CP. They found that the periodontitis groups presented higher expression of GSH-Px1 than the periodontally healthy control [47]. It is advocated that GSH-Px1 was enhanced by periodontitis, independently of the diabetic status of the patients [47].

### *2.4.2 Cardiovascular disease*

A recent review has shown a positive relationship between periodontitis and cardiovascular diseases [49]. It is determined that periodontal inflammation increases the development and progression of atheroma plaques via systemic bacteremia and lesion from the interaction of the intima with perio-pathogens entering the circulation [49]. Therefore, it is noted that the presence of periodontitis may be a risk factor for cardiovascular diseases [50]. Moreover, oxidative stress plays an important role in the pathogenesis of both periodontal disease and cardiovascular diseases [51].

Punj et al. [1] investigated the levels of glutathione peroxidase in serum and saliva of CP patients with and without ischemic heart disease (IHD). They stated that salivary GSH-Px levels were increased in the IHD + CP, IHD + H, and CP groups when compared with the healthy controls, whereas the serum GSH-Px levels were increased in the healthy group when compared with IHD + CP, IHD + H,

and CP groups [1]. Authors indicated that this situation could probably be a result of a curative increase of GSH-Px to the oxidant stress in diseased states [1]. They emphasized that increased oxidative stress in the presence of chronic periodontitis may cause endothelial dysfunction of the blood vasculature, predisposing to atherosclerotic plaque formation and increasing predisposition to ischemic heart disease [1]. Köse et al. [52] examined the influences of periodontitis on levels of cardiac oxidative stress. Authors found that GSH-Px levels in the heart ventricular tissue of the rats with experimental periodontitis were higher than that of control group but statistically insignificant [52]. They argued that this increase could be associated with adaptive response [52]. Moreover, they speculated that oxidative stress in the cardiac tissue may be the result of an increase in the amount of ROS rather than a decrease in antioxidant levels [52].

### *2.4.3 Pregnancy*

Various studies have proven a possible bidirectional association with periodontal disease and pregnancy [53]. It is supported that periodontal diseases are related with adverse pregnancy effects [54]. One of the possible mechanisms underlying this interaction stated that there may be oxidative stress-related inflammation pathways in case of pregnancy and periodontal disease [5, 27]. Oxidative stress is a principal supporting factor in the pathogenesis of preeclampsia and periodontal disease [27]. Çanakçı et al. [40] evaluated the GSH-Px levels in serum, saliva, and GCF in preeclamptic and normotensive pregnant women with and without periodontal disease. They determined that the GSH-Px activities in the serum and GCF of the periodontally healthy normotensive women were higher than that of preeclamptic and normotensive women with periodontal disease and periodontally healthy preeclamptic women [40]. There was no significant differences in saliva GSH-Px activities among all groups [40]. They declared that systemic and local GSH-Px activities reduced with the effect of periodontal disease in addition to the impact of preeclampsia [40]. Similarly Shetty et al. [27] observed that the GSH-Px activity in serum and saliva elevated in normotensive pregnant women with healthy periodontium when compared with preeclampsia pregnant women with and without periodontitis, and also preeclamptic women with periodontitis group have the lowest values but statistically nonsignificant. They indicated that periodontal diseases which cause a reduction in antioxidant levels could be a likelihood risk factor for severity, progression, and even initiation of preeclampsia [27].

Gümüş et al. [5] examined the salivary GSH-Px levels of the pregnant and postpartum women and their link with clinical parameters of periodontal inflammation and disease severity. They assigned that the GSH-Px levels were increased in the postpartum group when compared with pregnant and nonpregnant groups and in the nonpregnant group when compared with pregnant group [5]. Furthermore, they found that salivary GSH-Px levels were positively correlated with PD and BOP and total bacterial numbers in the postpartum group and with PD, CAL, BOP, or PI in the nonpregnant women group [5]. Conversely authors did not find association between GPx levels and periodontal disease status in pregnant women [5]. It is determined that salivary GSH-Px levels, which were at low levels during pregnancy, increased in the postpartum [5]. They speculated that this may be due to a healing mechanism against the exposure of tissues to excessive ROS during pregnancy [5].

## **2.5 Glutathione peroxidase, medication, and periodontal disease**

Drug-induced gingival enlargement is previously reported as side effect of immunosuppressive agents such as cyclosporine A (CsA) and tacrolimus, calcium

channel blockers such as amlodipine and nifedipine, and anticonvulsant drugs such as phenytoin [55]. It has been stated that overgrowth develops due to the increase in collagen accumulation and decrease in collagenase enzyme activity after drug use [55]. Gingival and periodontal inflammation may increase, as excessive gingival enlargement will complicate oral hygiene practices [55]. Sobeniec et al. [56] evaluated the GSH-Px activity in serum and saliva in patients with periodontal disease treated due to epilepsy. They determined that serum and saliva GSH-Px activities decreased in these patients with excessive gingival enlargement when compared with the control group [56]. On the other hand, Sardarian et al. [26], an *in vitro* study, determined that the low concentration of CsA (0.1 mg/mL) had no effect on GSH-Px activity in the oral epithelium while the activity was significantly increased at higher concentrations (1 mg/mL). They argued that GSH-Px activity increased to eliminate increased ROS in the oral epithelium after treatment with CsA [26].

In an experimental study, rats were infected with multibacterial inoculum containing PG, TD, and TF, as an oral lavage every other week for 12 weeks [12]. Afterward, daily subcutaneous injections of enoxacin, bis-enoxacin, alendronate, or doxycycline were administered for 6 weeks after 6 weeks of multibacterial infection in rats [12]. Subsequently, they evaluated the levels of GSH-Px in the serum of the infected, treated, and sham-infected rats [12]. Consequently, it is determined that serum levels of GSH-Px increased in rats infected with periodontal bacteria when compared with sham-infected rats and reduced in treated rats compared to infected and untreated rats [12]. Authors stated that elevated GSH-Px activity protects the periodontal tissues averse to oxidative stress [12].

Host modulatory therapy (HMT) is a treatment method that aims to decrease tissue destruction and stabilize the periodontium by arranging the components of the host response [57]. HMTs may be categorized as anti-inflammatory drugs, bone-stimulating agents (bisphosphonates), and anti-proteinase agents, such as low-dose doxycycline (LDD) [58]. Caffeic acid phenethyl ester (CAPE) has antioxidant, antitumoral, anti-inflammatory, and immunomodulatory properties and inhibits ROS production during inflammatory processes [59]. Recently, it has been reported that CAPE can modulate the host response [60]. Yiğit et al. [19] evaluated the effects of LDD and CAPE on alveolar bone level and the plasma levels of GSH-Px activity in an experimental periodontitis rat model. They determined that GSH-Px levels in plasma increased in the CAPE + periodontitis group, but decreased in the periodontitis and periodontitis + LDD groups when compared to control group [19]. The authors stated that CAPE significantly increased GSH-Px levels and CAPE may have more antioxidant properties than LDD in periodontal inflammation [19].

A previous study showed the creation of fast reepithelization on the human gingival wounds of the topical application of 1% taurine (2-amino ethane sulfonic acid) [61]. Sree and Sethupathy [62] investigated the effect of taurine as an antioxidant in the management of patients with the chronic periodontitis. For this purpose, they evaluated GSH-Px levels in the plasma and gingival tissue before and after administration of taurine [62]. They reported that decreased GSH-Px levels in plasma and gingival tissue were determined after taurine administration [62]. It is suggested that taurine enhanced the antioxidant status of chronic periodontitis patients by affecting GSH-Px antioxidant levels [62].

While melatonin has a direct neutralizing effect against ROS, it has an indirect effect by increasing the effectiveness of GSH-Px [63]. Özdem et al. [64] investigated the GSH-Px levels in the heart tissues after melatonin application after induction of experimental periodontitis in the rats. They found that the GSH-Px levels in heart tissue were higher in the periodontitis + melatonin group compared to periodontitis + saline solution group and in the healthy + melatonin group compared to healthy + saline solution group, while there were no significant differences between

healthy + saline solution and periodontitis + saline solution groups [64]. In line with these results, the authors claimed that application of melatonin caused an increase in GSH-Px levels in the heart tissue either due to its antioxidant properties or by increasing the synthesis of antioxidant enzymes [64]. Furthermore, Kırzioğlu et al. [24] examined the effects of systemically administered rosuvastatin, which decreases the levels of ROS and increases antioxidant activity, on GSH-Px levels in the serum of the rats with experimental periodontitis. They reported there were no significant differences in the levels of GSH-Px among control, healthy + rosuvastatin, periodontitis, and periodontitis + rosuvastatin groups [24].

### 3. Conclusions

There is a growing evidence for the role of ROS in the pathogenesis of periodontal diseases. The short half-life of ROS limits its measurability in biological fluids in the periodontal disease. Therefore, it is stated that it is more reliable to measure the products of ROS-induced tissue damage and levels of antioxidants in the periodontal disease. One of the most frequently detected enzymatic antioxidants in periodontal disease is GSH-Px. Previous studies found that GSH-Px levels in different biological fluids increased, decreased, or are unchanged in individuals with periodontal disease compared to control groups. The reason for this contradiction might be linked to the difference in the analyses applied between studies and the presence of various dynamic processes in progression of periodontal disease. Nevertheless, the common result in the studies stated that GSH-Px protects periodontal tissues against oxidative stress and plays an important role in the progression of periodontal disease. Thus, it was emphasized that GSH-Px can be a reliable biomarker in biological fluids to evaluate periodontal status and results of periodontal treatment. However, further studies in long term using large population are needed in order to better understand how GSH-Px contributes to the development of periodontal diseases using knockout and knockdown techniques.

### Conflict of interest

The authors declare no conflict of interest.

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