

Glycemic Gums: Unveiling the Phytochemical Connection Between Diabetes and Oral Health: A Review

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Abstract

Hyperglycemia, a pathological condition, predominantly defines diabetes mellitus, a persistent and complex metabolic dysfunction. It has a significant impact on oral health, as seen by conditions including periodontal disease, xerostomia (dry mouth), and increased susceptibility to infections. The intricate bidirectional relationship that exists between oral health and the metabolic disorder diabetes has been thoroughly documented, where it has been observed with poor oral hygiene worsening glycemic management and vice versa. Recently, there has been a change in focus toward the utilization of phytochemicals, the bioactive substances found in plants, as an additional treatment strategy for addressing issues related to dental health and diabetes. Phytochemicals exhibit antimicrobial, anti-inflammatory, and antioxidant characteristics that are critical for battling oral infections as well as reducing the inflammatory processes associated with diabetic periodontitis. Evidence shows that these substances contribute to enhanced insulin sensitivity and glycemic management, in addition to their beneficial effects on dental health, such as suppressing inflammation and oxidative stress. This review investigates some complex interactions between diabetes and oral hygiene, as well as the role of inflammatory mediators, cellular oxidative stress, and dysfunction of the salivary gland. It explores the dual role of phytochemicals such as alkaloids, flavonoids, tannins, resveratrol, and saponins in the context of oral health care for diabetic individuals.

Keywords: Diabetes Mellitus, Glycemic Control, Oral Health, Oxidative Stress, Periodontal Disease, Phytochemical.

Introduction

Diabetes mellitus (DM) represents a multifaceted metabolic disorder distinguished by hyperglycemia, which is a consequence of inadequate insulin secretion or impaired insulin action. Type 1, Type 2, and diabetes during pregnancy are the three categories into which the condition is classified. Each has distinct pathophysiological mechanisms and treatment implications. With the presence of type 2 diabetes (T2DM), it majorly elevates the risk of

numerous issues, such as cardiovascular diseases, with the presence of type 2 diabetes (T2DM) and obesity being major causes [1]. The disease's prevalence has been rising globally, in part because of the obesity pandemic and aging-related demographic shifts [2].

Oral health is an important part of overall well-being, but many people throughout the world continue to suffer from a variety of debilitating oral disorders. The term "mouth

illnesses" describes a wide range of issues that affect the oral cavity and significantly damage an individual's well-being and standard of living. Dental caries, periodontal disease, and various mucosal illnesses are common oral diseases that can manifest either primary issues or as indications of underlying systemic conditions [3]. Leukoplakia, OSMF, and OSCC patients at high risk of malignant transformation may be identified using circulating exosomal miRNAs miRNA 21, miRNA 184, and miRNA 145 as plasma biomarkers [4]. Moreover, over 23% of people have dry mouth, which can aggravate conditions like oral candidiasis, particularly in those with weakened immune systems [4]. Calotropin targets apoptosis, glycolysis, metastasis, and proliferation in HSC-3 oral cancer cells, showing promise as a treatment [5].

The Interplay between Diabetes Mellitus and Oral Health

Diabetes mellitus, a persistent metabolic disorder defined by deregulated carbohydrate metabolism, has long been acknowledged as a substantial risk factor for different oral health issues. Comprehensive research has been undertaken on the intricate relationship between these two conditions, elucidating the complex relationship between oral diseases in individuals with diabetes. Moreover, continuous hyperglycemia that is linked to diabetes may impair immune responses, making patients more susceptible to infections such as periodontal disease and candidiasis [7]. Research indicates that those with type 2 diabetes have a 1.46-fold higher probability of reporting deficient oral health relative to individuals without the disease, with 37% of diabetic patients reporting poor oral health [8]. Salivary MMP-9 levels that are elevated in OSCC and severe dysplasia point to a possible involvement for this protein in tumor invasion, metastasis, and malignant transformation [9].

Diabetes-related changes to the oral environment, which include altered composition and reduced salivary flow, are linked to the emergence and persistence of a number of oral health issues, emphasizing the need for comprehensive care for oral health. Different genetic alterations in OSCC grades are revealed by NGS, which advances minimal intervention techniques and helps with individualized therapy planning [10]. Overall, the relationship between diabetes mellitus and dental health underscores the necessity for coordinated treatment techniques to properly manage both conditions.

Diabetes Mellitus and Its Impacts on Gum Health: The Role of Inflammatory Mediators and Cellular Oxidative Stress

The pathophysiology of gum disease, especially periodontitis, which is defined by constant swelling in the periodontal tissue, is significantly influenced by inflammatory mediators [11]. Moreover, periodontitis worsens the regulation of blood sugar levels, creating a reciprocal relationship in which persistent inflammation brought on by gum disease may worsen diabetes [12]. The association between the severity of periodontitis and glycemic status has been discovered to be influenced by white blood cell count (WBC) and C-reactive protein (CRP), suggesting that inflammation is a key mechanism linking these two illnesses [13]. In order to improve the course of gum disease and diabetes, it is essential to reduce inflammation.

Moreover, diabetes and elevated oxidative stress are associated. Stress due to oxidation occurs when there is a discrepancy between the body's ability to remove free radicals and the way they are produced [14]. An accumulation of reactive oxygen species (ROS) triggers a number of pathways that cause dysregulated autophagy and enhanced pro-inflammatory mediators, which can lead to issues including diabetic neuropathy and periodontitis [15]. Research has indicated that oxidative stress

causes periodontal ligament cells to lose their capacity to regenerate by breaking down their telomeres. It also accelerates the death of periodontal cells, which exacerbates bone loss [16]. For this reason, the management of oxidative stress is necessary to prevent gum disease.

Herbal Remedies for Oral Health Associated with Diabetes Mellitus

Natural substances derived from plants, or phytomedicines, have become a promising treatment and prevention option for oral diseases. Furthermore, the antibacterial properties of medicinal herbs including *Plantago major*, *Ficus religiosa*, and *Glycyrrhiza glabra* inhibit the formation of plaque and periodontal diseases. The anti-inflammatory and antioxidant properties of these herbs provide them viable substitutes for conventional treatments in promoting overall oral health [17]. miRNAs are important in OPMDs because they may be used as therapeutic targets and diagnostic indicators [18].

Herbal treatments have demonstrated great potential in preventing gum disease and tooth decay, especially among diabetics who were more susceptible to oral health issues. Herbal remedies originating from traditional sources, such as aloe vera, tulsi, and garlic, have demonstrated anti-diabetic and antioxidant properties. These properties can improve oral health by reducing issues associated with diabetes [19]. Herbs such as *Withania somnifera*, *Trigonella foenum-graecum*, and *Moringa oliefera* have anti-hypoglycemic properties that can lower the risk of problems and help regulate blood sugar levels, including dental health concerns, in people with diabetes [20]. Diabetes can be treated with black garlic. Polyphenols, flavonoids, tannins, and ajoene found in black garlic have the ability to reduce blood glucose and increase blood insulin levels in diabetics [21]. Overall, these herbal solutions offer an integrated strategy for maintaining oral

health in the context of diabetes. Targeting important apoptotic pathways and causing apoptosis in KB cells, β -Sitosterol has great therapeutic promise against oral cancer [22].

The Role of Phytochemicals in Oral Health Related to Diabetes Mellitus

Alkaloids

Alkaloids are useful in the management of oral infections associated with diabetes, particularly diabetes-related periodontitis (DP). Due to heightened inflammatory responses and compromised immunological responses that may worsen the symptoms of diabetes mellitus, people with poorly controlled diabetes are more susceptible to developing diabetes-related periodontitis (DP). Alkaloids, produced from several medicinal plants, demonstrate antidiabetic activities by modulating glucose metabolism and increasing insulin sensitivity via mechanisms such as boosting insulin production and decreasing insulin resistance [23]. Alkaloids have a strong therapeutic potential in treating oral infections in individuals with diabetes, which calls for more research in clinical settings.

Alkaloids in Treating Xerostomia in Diabetic Patients

Specific alkaloids such as Vindoline, jatrorrhizine, and catharanthine all have mechanisms that effectively control diabetes mellitus and treat xerostomia. Both Vindoline and Catharanthine have hypoglycemic action, which lowers blood sugar levels by promoting glucose metabolism and insulin production. They may help to preserve salivary flow and lessen the symptoms of xerostomia by controlling blood sugar levels [24]. Jatrorrhizine, which is present in many medicinal plants, inhibits α -glucosidase. Lower postprandial blood sugar levels result from this activity, which delays the digestion and absorption of carbohydrates. Glycemic management can improve salivary gland function generally, which may help with

xerostomia [25]. Cavitated carious lesions may harbor *H. pylori*, increasing caries severity and promoting *Streptococcus mutans* dominance [26].

Alkaloids in Treating Periodontal Disease in Diabetic Patients

A bioactive ingredient in chilli peppers called capsaicin has demonstrated promise in the treatment of periodontal disease, particularly in diabetics. Periodontal treatment, which encompasses mechanical therapies and potentially adjunctive agents such as capsaicin, may contribute to the reduction of inflammatory cytokines and enhancement of glycemic control in diabetic patients [27]. Berberine (BBR) has been identified as a potential therapeutic agent for periodontal disease, especially in diabetic patients, owing to its diverse mechanisms of action. It demonstrates significant anti-inflammatory effects, decreasing pro-inflammatory mediators like TNF- α and IL-1 β , which play a critical role in the development of periodontitis [28]. BBR promotes the osteogenic differentiation of human periodontal ligament stem cells through modulation of the canonical Wnt/ β -catenin pathway, mitigating the adverse effects of advanced glycation end products (AGEs) commonly found in diabetes [29]. Collectively, these findings suggest that BBR could be an effective adjunctive treatment for periodontal disease in diabetic patients, addressing both inflammation and bone metabolism.

Alkaloids in Treating Oral Infection in Diabetic Patients

Boldine, a natural antioxidant produced from the *Chilean boldo* tree, has potential therapeutic advantages for treating oral infections in diabetic patients by addressing both oxidative stress and inflammatory reactions associated with diabetes. It has antibacterial characteristics, which are critical in treating infections, especially those in the oral cavity [30]. Sanguinarine, a benzophenanthridine

alkaloid produced from *Sanguinaria canadensis*, possesses considerable antibacterial and anti-inflammatory characteristics, making it a good choice for treating oral infections. Sanguinarine's broad-spectrum antibacterial characteristics make it efficient against pathogenic germs, increasing the efficiency of standard antibiotics like polymyxin B against Gram-negative bacteria [31]. Thus, integrating sanguinarine into treatment regimens could be beneficial for managing oral infections in diabetic individuals.

Flavonoids

Flavonoids are important in the treatment of oral infections, especially in diabetics, who are more vulnerable to such illnesses due to changed oral microbiota and increased oxidative stress. According to research, flavonoids have antibacterial characteristics that can resist pathogens often present in oral infections, such as *Staphylococcus* spp. and *E. coli*, which are prominent in diabetes mellitus patients [32]. Additionally, flavonoids have antioxidant and anti-inflammatory properties, which are vital in mitigating the challenges associated with diabetes, including tooth health issues [33]. By boosting antioxidant defences, reducing inflammation, and promoting oral tissue repair, flavonoids help mitigate these effects. Moreover, their ability to regulate blood sugar may help minimize dental issues associated with diabetes [34]. Overall, flavonoids represent a promising avenue for therapeutic intervention in the context of diabetes-associated oral infections. During orthodontic treatment stages, there is a negative correlation between salivary 1-25dihydroxycholecalciferol and IL-17A levels, indicating that vitamin D administration may hasten tooth movement while minimizing tissue injury [35].

Flavonoids in Treating Xerostomia in Diabetic Patients

A natural flavonoid with a variety of therapeutic benefits, kaempferol has demonstrated potential in treating xerostomia, especially in diabetic patients. Because of its strong anti-inflammatory properties, kaempferol may help diabetes patients produce more saliva by minimizing inflammation-induced damage to the salivary glands [36]. Kaempferol may help preserve the integrity of salivary glands by lowering oxidative damage, which would enhance saliva production. Because improved glycemic management is linked to fewer symptoms of xerostomia, kaempferol's effects on insulin sensitivity and glucose metabolism can also indirectly promote salivary gland function [37]. Hesperidin, a flavonoid found in citrus fruits, has shown potential in addressing xerostomia, particularly in diabetic patients. Hesperidin may prevent damage to the salivary glands by lowering oxidative stress, which is increased in diabetic situations. According to clinical research, hesperidin reduces inflammatory indicators like IL-6 and hs-CRP, which may lessen salivary gland inflammation. Hesperidin's role in enhancing salivary gland function through its anti-inflammatory and antioxidant effects suggests it could be beneficial for diabetic patients suffering from dry mouth [38].

Flavonoids in Treating Periodontal Disease in Diabetic Patients

A natural flavonoid called quercetin has shown promise in the treatment of periodontal disease, especially in diabetic individuals, by reducing inflammation and accelerating the healing process. In human gingival fibroblasts, quercetin has been demonstrated to decrease inflammatory cytokines, including IL-6 and IL-8, which are frequently increased in diabetes situations [39]. According to in vivo research, quercetin supplementation lowers the production of gingival cytokines and the infiltration of inflammatory cells, which lessens

the loss of alveolar bone [40]. Isoflavones, notably those found in soy, have demonstrated promise in the treatment of periodontal disease, particularly in those with diabetes. Isoflavones can lower inflammatory indicators, including interleukin-17 (IL-17), that are linked to the loss of periodontal tissue. Isoflavones increase the production of tight junction proteins, which enhance the oral epithelial barrier and may lessen inflammation and bacterial invasion [41]. While isoflavones present promising benefits, further research is needed to fully understand their efficacy and mechanisms in diabetic patients with periodontal disease.

Flavonoids in Treating Oral Infection in Diabetic Patients

Many fruits and vegetables contain anthocyanins, which show significant potential in treating oral infections, especially in diabetics. Because of their potent antioxidant properties, anthocyanins help lower oxidative stress, which is frequently higher in diabetes patients [42]. According to systematic studies, taking anthocyanin supplements greatly helps diabetic people and may help avoid problems like dental infections. Clinical studies have demonstrated that glycemic control, which is essential for treating diabetes-related oral health problems, may be significantly improved with dosages of anthocyanin around 320 mg per day [43]. Conversely, while anthocyanins show promise, the variability in individual responses and the need for standardized dosages highlight the necessity for further research to fully understand their role in treating oral infections in diabetic patients.

Tannins

Many medicinal plants include tannins, a kind of polyphenolic compound with potent antibacterial properties that can help treat oral infections, particularly in those with diabetes. Because diabetes lowers immune responses and alters the oral microbiome, which can result in an imbalance favouring pathogenic species,

evidence suggests that diabetes increases sensitivity to periodontal disorders [44]. Plants like *Quercus robur* and *Agrimonia eupatoria* generate tannins, which have demonstrated promise in treating many ailments by inhibiting the growth of microorganisms and reducing inflammation [45]. Recent studies have demonstrated that tannin-rich hydrogels can enhance healing in diabetic oral mucosal defects [46]. Thus, incorporating tannin-rich extracts into oral care regimens could be a promising strategy for enhancing oral health in this population.

Tannins in Treating Xerostomia in Diabetic Patients

Gallotannins, especially those obtained naturally, have demonstrated potential in the treatment of xerostomia, particularly in those with diabetes. Gallotannins may increase saliva production by influencing the expression of aquaporin-5, a protein essential for salivary gland water transport. They can raise the amounts of α -amylase, an enzyme that helps produce saliva but is frequently reduced in diabetes situations [47]. These substances can reduce oxidative stress, which is a major contributing cause to complications associated with diabetes [48]. Gallotannins may enhance salivary gland function and relieve dry mouth by promoting tissue healing and lowering inflammation.

Tannins in Treating Periodontal Disease in Diabetic Patients

Ellagitannins, a family of bioactive polyphenols, have shown promise in controlling periodontal disease, particularly in diabetic individuals. Ellagitannins and their metabolites can lower inflammation, which is a major contributing cause of diabetes and periodontal disease [49]. In diabetic patients, periodontal therapies, including scaling and root planing, have been demonstrated to improve glycemic control; these benefits can be amplified by ellagitannins' anti-inflammatory

properties. Better insulin sensitivity may result from less periodontal inflammation, which would further support ellagitannins' function in controlling problems associated with diabetes [50]. For diabetic individuals with periodontal disease, adding ellagitannins to functional food may offer a double advantage, addressing both metabolic regulation and dental health [49].

Tannins in Treating Oral Infection in Diabetic Patients

Ellagitannins, a group of bioactive polyphenols, exhibit significant potential in treating oral infections. Their antimicrobial properties, coupled with anti-inflammatory effects, make them valuable in managing oral health complications associated with diabetes. Ellagitannins, such as punicalagin, have been shown to limit bacterial growth, especially pathogens linked to oral infections. They increase macrophage-mediated bacterial death, boosting the immune response to oral infections [51]. The conversion of ellagitannins to urolithins by gut bacteria enhances their bioavailability and therapeutic effects, potentially improving oral health outcomes in diabetic patients [49]. Ellagitannins show promise in treating oral infections.

Resveratrol

In diabetic individuals, resveratrol administration has shown promise in reducing inflammatory markers and promoting periodontal health, which may help to mitigate the severity of oral infections. Research shows that resveratrol significantly reduced blood levels of interleukin 6 (IL6) in diabetic patients with chronic periodontitis and improved pocket depth (PD) and clinical attachment loss (CAL) when used in addition to non-surgical periodontal treatment [52]. Moreover, novel drug delivery approaches, like resveratrol-grafted mesoporous silica nanoparticles, have been created to increase resveratrol's bioavailability and possibly boost its therapeutic efficacy in controlling

inflammation and glucose metabolism. This presents a promising approach to the treatment of diabetic periodontitis [53]. Overall, these data show that resveratrol may perform a beneficial role in reducing the severity of oral infections in diabetic patients.

Resveratrol in Treating Xerostomia in Diabetic Patients

Resveratrol, a polyphenolic compound, has shown potential in managing xerostomia (dry mouth) in diabetic patients. Because of its diverse biological characteristics, trans-resveratrol (t-RSV) has gained attention as a possible treatment for xerostomia, especially in diabetic patients. It has been discovered that trans-resveratrol increases salivary flow, which may lessen xerostomia symptoms in diabetics. Trans-resveratrol may improve the general quality of life for diabetes patients, who frequently deal with numerous problems, by reducing the symptoms of dry mouth [54]. Significant anti-inflammatory and antioxidant properties of t-RSV can help reduce inflammation and oxidative stress, which are frequently observed in diabetes patients. These qualities might lessen the symptoms of xerostomia by enhancing salivary gland function [55]. Future research should concentrate on how t-RSV directly affects xerostomia and salivary output in diabetes individuals.

Resveratrol in Treating Periodontal Disease in Diabetic Patients

Cis-resveratrol has emerged as a promising therapeutic agent for treating periodontal disease in diabetic patients due to its multifaceted anti-inflammatory and antioxidant properties. Because of its strong anti-inflammatory properties, cis-resveratrol can lessen the inflammatory response in diabetic periodontal tissues. It reduces pro-inflammatory cytokines, potentially improving periodontal health in diabetic patients [56]. According to research, resveratrol promotes

bone growth in high-glucose environments, which is essential for periodontal regeneration. It encourages osteoblast development and proliferation, which is necessary for the repair of diabetic periodontal tissues [57]. While cis-resveratrol shows potential in treating periodontal disease in diabetic patients, challenges such as bioavailability and the need for further clinical trials remain.

Resveratrol in Treating Oral Infection in Diabetic Patients

Trans-resveratrol has emerged as a promising therapeutic agent for treating oral infections. Research showed that trans-resveratrol at high doses worked well in microbiological tests, suggesting that it can be used to treat buccal candidiasis [50]. It has been demonstrated that tRSV injection increases the production of antibacterial proteins in the acquired enamel pellicle, potentially improving dental health and offering an infection-prevention benefit. Cis-resveratrol exhibits significant antibacterial properties that make it effective in treating oral infections. By increasing the production of antimicrobial proteins in the acquired enamel pellicle, resveratrol administration improves dental health [59]. Conversely, while cis-resveratrol shows promise in treating oral infections, its potential cytotoxic effects at higher concentrations necessitate careful consideration in clinical applications.

Saponin

Numerous plants contain a form of glycosidic molecule called saponins, which has been shown to have significant therapeutic effects, including the potential to reduce oral infections linked to diabetes. Diabetes is known to exacerbate oral health problems such as xerostomia, periodontal disease, and oral infections. These circumstances may have a serious influence on overall health and glycemic control [60]. Studies reveal that saponins possess anti-inflammatory and

antioxidant properties that may aid in mitigating oxidative stress and inflammation linked to diabetes-related oral health issues. By reducing oxidative damage and increasing insulin sensitivity, saponins may benefit diabetic individuals' dental health [61]. Thus, incorporating saponins into treatment strategies may offer a promising approach to managing oral infections in individuals with diabetes mellitus.

Saponin in Treating Xerostomia in Diabetic Patients

Ginsenosides, the active compounds in ginseng, have shown potential in addressing xerostomia, particularly in diabetic patients. This condition, characterized by reduced salivary flow, can be exacerbated by diabetes due to its impact on oral health. Ginsenosides can boost immunological responses, which may improve oral health and lessen xerostomia-related inflammation. They have been demonstrated to enhance metabolic function and insulin sensitivity, which may aid in the management of xerostomia and other diabetes-related problems [62]. Ginsenosides might be included in therapy techniques for xerostomia in diabetic patients, possibly offering a natural alternative to conventional medications.

Saponin in Treating Periodontal Disease in Diabetic Patients

Soyasaponins have emerged as a potential therapeutic agent in managing periodontal disease, particularly in diabetic patients. Soyasaponins regulate the TLR4/MyD88 signaling pathway, which is important in

inflammatory reactions. They reduce MyD88 expression and TLR4 recruitment, resulting in lower levels of pro-inflammatory cytokines such as TNF α and IL-6 [63]. Soyasaponins, which have anti-inflammatory effects, may help reduce inflammation in periodontal disease, thereby improving glycemic control. Research suggests that substances like paeoniflorin, a monoterpene glycoside, have shown potential in lowering inflammation and bone loss in diabetic periodontitis animals [64]. Diabetes and periodontal disease are connected disorders that require collaborative care from dental and medical practitioners.

Saponin in Treating Oral Infections in Diabetic Patients

Quillaja saponins, which come from the *Quillaja saponaria* tree, are important for treating oral infections, especially in those with diabetes. The antimicrobial properties of these saponins can increase the efficacy of disinfectants against biofilms. Quillaja saponins have antibacterial properties against a variety of microorganisms, which may help diabetics who are more vulnerable to these issues from getting mouth infections [65]. The natural antibacterial properties of quillaja saponins can stop the growth of many bacterial types, particularly those linked to oral illnesses. They are useful in treating infections that are resistant to traditional treatments because of their capacity to break down biofilms, which increases the effectiveness of conventional disinfectants [66]. Quillaja saponins may be used in dental care products to promote better oral hygiene and lower the risk of infection.

Table 1. Functions of Phytochemicals in Diabetes Related to Oral Health

Phytochemical	Properties	Functions
Alkaloid	Antioxidant, Anti-inflammatory	Boosting insulin production and treatment of diabetes-related periodontitis [23]
Flavonoid	Antibacterial, Antioxidant and Anti-inflammatory	Regulate blood glucose levels, Boost antioxidant defences, reducing inflammation, promote oral tissue repair, and reduce the risk of plaque-induced gingival inflammation [33] [34]
Tannins	Antibacterial, Anti-inflammatory	Reduce blood glucose levels, Inhibiting the growth of microorganisms and reducing inflammation [45] [46]

Resveratrol	Anti-inflammatory	Reducing inflammatory markers, Control glucose metabolism [52]
Saponin	Anti-inflammatory and Antioxidant	Increasing insulin sensitivity and reducing oxidative damage [61]

Conclusion

In conclusion, untreated oral illnesses hinder the ability to manage diabetes, while poor glycemic control exacerbates dental issues like periodontitis. Phytochemicals provide potential therapeutic uses in the treatment of diabetes-related oral health problems due to their anti-inflammatory, antioxidant, and antibacterial properties. They not only assist in regulating blood sugar levels but also fight oxidative stress and lessen tissue inflammation in the mouth. For people with diabetes to maintain optimal

oral health, more research is required to fully understand the mechanisms of action and therapeutic potential of phytochemicals.

Conflict of Interest

The authors hereby declare that there is no conflict of interest.

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