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Inhibition of Glucosyltransferase enzyme of *Streptococcus mutans* by natural products: A Literature Review

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Abstract

Streptococcus mutans is acid producing, acid tolerant bacteria that is involved in the multifactorial process of dental caries. *Streptococcus mutans* is considered one of the most cariogenic bacteria of the oral flora capable of causing dental caries alone. This was attributed to its ability to produce extracellular polysaccharides that form the oral biofilm through their glucosyltransferase enzymes. Scientists have searched for a method to selectively target these bacteria or their enzymes in an attempt to prevent caries occurrence. This was previously done through the use of artificial products as Chlorhexidine gluconate, however, most artificial products have undesirable side effects. Therefore, researchers are nowadays researching natural products for their antibacterial properties and their ability to inhibit glucosyltransferase enzymes of *Streptococcus mutans* without the unnecessary side effects. Hence, the aim of this literature review was to focus on the natural products and their ability to inhibit *Streptococcus mutans* and its glucosyltransferase enzyme.

1. Introduction

All of the surfaces of the oral cavity are covered by biofilm formed by the microorganisms that inhabit it in a state of symbiosis. Oral diseases develop when this state of balance is disturbed causing dysbiosis [1–3]. Dental caries is a widespread multifactorial disease caused by caries causing bacteria that dominate the oral biofilm in the occurrence of dysbiosis. Among the most commonly involved caries causing bacteria is *Streptococcus mutans* which dominate the oral biofilm when carbohydrate intake increases leading to a drop in pH [4–7].

In order to achieve long term caries prevention, the target has changed from non-specific bacterial elimination to specific targeting of bacterial virulence factors rendering them non cariogenic [5,7,8]. Glucosyltransferase enzymes (GTFs) are considered the main virulence factor of *Streptococcus mutans* by giving it the ability to produce extracellular polysaccharides (EPS). *S. mutans* are one of the main producers of extracellular polysaccharides which help the bacteria attach to each other and the tooth structure giving bulk to the oral biofilm, especially the water insoluble glucans [6,9–11]. The increasing antimicrobial resistance and

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other undesired side effects have encouraged scientists to search for alternatives to the artificial products as Chlorhexidine gluconate despite their proven antibacterial properties and other benefits [10,12,13].

Therefore, this literature review aims to provide a screening of the natural products and extracts, with antibacterial properties and ability to inhibit the virulent GTFs of *S. mutans*, researched by scientists as an alternative to artificial products.

2. Review of Literature

S.mutans is one of the most researched bacteria for its role in dental caries. They are acid producing and acid tolerant bacteria that are part of the normal oral flora. They dominate the oral flora after an increase of carbohydrate intake that cause a decrease in pH favoring acidic conditions [4–7]. However, what makes them more virulent is not their ability to produce acids or tolerate acidic conditions, it is their GTFs that is considered their main virulence factor. *S. mutans* produce 3 genetically different glucosyltransferase enzymes that overlap in their function to create extracellular polysaccharides and the formation of biofilm. This has directed the scientists to selectively target GTFs through artificial or natural products [14–16]. Among the artificial products excessively researched was Chlorhexidine gluconate which is the gold standard in treating many oral diseases to which all new products are compared despite its undesirable side effects [17]. Several plant species have been found to have multiple medicinal values through the production of secondary metabolites [18,19]. About 81 culinary and human consumable plants have been reported to have inhibitory effect against *Streptococcus mutans* [20].

2.1 Streptococcus mutans:

Different bacteria were reviewed for the ability of different bacteria to induce initial carious lesions, using microhardness testing and polarized light microscopy, where they observed the ability of *Streptococcus mutans* to produce non cavitated carious lesions alone. They stated the significant role of *Streptococcus mutans* in caries production and suggested its use for in vitro caries induction [21,22]. Furthermore, the significant role of *Streptococcus mutans* in the caries process was reported where its production of extracellular polysaccharides is its main virulence factor by creating a niche for the adherence of other acidogenic bacteria and creating the suitable environment for acid production on the tooth surface [23,24]. A systematic review stated that plant extracts are most commonly tested against *Streptococcus mutans* in in vitro studies [25].

2.2 Chlorhexidine:

Chlorhexidine gluconate is a broad-spectrum antimicrobial agent with prolonged effect that can decrease biofilm formation and is effective against *Streptococcus mutans*, however it is not without side effects such as staining of teeth and oral mucosa and altering the taste sensation [26–28]. Moreover, chlorhexidine gluconate has been reported to have the ability to protect enamel against caries and increase its microhardness. So, chlorhexidine gluconate was used as a positive control in several studies with the aim of finding a natural alternative with similar superior effect without the undesirable side effects [29,30]. Regarding the concentration of the chlorhexidine gluconate, different concentrations were tested and it was found that 0.12% is the most effective in its antibacterial properties, inhibition of glucosyltransferase and decreasing enamel decalcification [31–33]. Several researchers have reported the superior ability of chlorhexidine gluconate alone without any combinations with other products to inhibit *S. mutans* and its glucosyltransferase enzyme [34]. Similar to other medications, choosing the proper dose of the chlorhexidine gluconate is of significant effect although, even the sub-lethal doses can also inhibit *S. mutans* [35].

2.3 Natural products:

A large number of diverse plant species have been used for medicinal purposes all around the world while being effective and biocompatible as they are a rich source of bioactive components that can help treat acute and chronic diseases with the significant benefit of minimal side effects [36–38]. Various natural products have been reported to have the ability to remineralize initial carious lesions as an alternative to fluoride, as grape seed extract, licorice root and green tea which can inhibit glucan production by inhibiting glucosyltransferase enzyme. They stated that grape seed extract can encourage the formation of hydroxyapatite by supporting collagen cross-links [39–41].

Several researchers have reported the multiple therapeutic benefits of the Mediterranean grown *Rosmarinus officinalis* such as anti-inflammatory, antioxidant, antibacterial, anti-fungal, antiviral and even anti-cancer potential among many other benefits [40,42–45]. Moreover, researchers have reported the ability of rosemary to remineralize initial caries lesions while others have reported the ability of rosemary to inhibit glucosyltransferase and subsequent glucan production of *Streptococcus mutans* and *Streptococcus sorbinus*

respectively [20,46–50]. Rosemary has been reported to have antibacterial properties against several cariogenic bacteria including *S. mutans* in addition to inhibiting its biofilm formation ability wither through their water or alcoholic extracts [50–52]. The alcoholic extracts of thyme, mint, garlic, cinnamon, chamomile, tea tree, clove, spearmint, sage, and rosemary were compared in their ability to inhibit *S. mutans* in comparison to the gold standard chlorhexidine gluconate. Several extracts managed to inhibit *S. mutans* with rosemary showing superior results [53]. Other researchers reported the ability of *Rosmarinus officianalis* L., *Salvia officianalis* L., unfermented cocoa, red grape seed, peppermint, sandalwood, lavender and green tea to not only inhibit glucosyltransferase enzyme of *S. mutans* and subsequent biofilm formation but also its ability to produce acids [54,55]. Others observed the benefits of combining more than one natural extract where Chamomile, liquorice, marigold, and lavender can augment or antagonize each other according to the second component of the mixture. They observed that propolis, cinnamon, and cloves can augment each other, while sweet flag, dog rose, and oregano can antagonize each other. They highlighted the superior ability of combining cloves, cinnamon, propolis, and lavender to inhibit the tested bacteria [56]. It was also observed that the concentration of the extract is of great significance to its effect, where higher doses can generate greater effect. That suggests that finding the proper dose is of great importance for long term effect [18,57,58]. The form of the extracts has also been investigated from water to alcoholic extracts or mouthwashes or varnishes to determine the most effective method of application [59–61].

2.4 Fungal Endophytes

2.4.1 Definition, classification and diversity

Endophytic fungi have been identified as microfungi that live inside the cells and/or between the cells of plant tissue asymptomatically without causing any detectable pathological symptoms [62–64].

Scientists recognized the presence of endophytic fungi asymptomatically in plants since the 1800s [65]. It is believed that there are more than 1 million species of endophytic fungi present when compared to the number of species of vascular plants present in ratio of 1:4–5 fungi per plant [66].

Endophytes have been linked with plants from the start of their evolution in a mutual symbiotic relationship. It is observed that divergent plants such as monocots, dicots, trees, gymnosperms and bryophytes contain endophytic fungi [67].

2.4.2 Biological Role of Fungal Endophytes

Endophytic fungi show various interactions with their host plants, the environment and human life. These peculiar interactions of the endophytes with their host plants and the environment help the endophytes produce several bioactive pharmaceutical metabolites. Consequently, endophytes can be regarded as sources for several active drugs [68].

Mostly, the interactions of endophytic fungi with their host plants are beneficial although researches haven't fully understood the behavior of endophytes with their hosts [10,69]. The endophytes produce metabolites which increase the ability of the plants to withstand biotic and abiotic stresses. These metabolites improve the plant growth either directly or indirectly [66,70].

2.4.3 Metabolites of Fungal Endophytes

Endophytes are regarded as sources for primary and secondary metabolites with various medicinal, industrial and agricultural uses [10,64,66,71–74]. The secondary metabolites of endophytes offer a cheaper and safer source for drugs while conserving the plants of medicinal values [75].

One of the main problems facing scientists is the toxicity of many newly discovered drugs. The endophytes produce bioactive metabolites which can be regarded as an alternative for some toxic drugs [76]. Endophytes produce various new compounds which can be used for their antibacterial, anti-fungal, antiviral, anti-inflammatory, anti-tumor effects [66,77,78]. Several researchers have reported the various pharmaceutical benefits of the secondary metabolites of endophytic fungi such as antioxidant, antibacterial, anti-inflammatory and even anti- cancer potentials among several others where they can produce the same bioactive compounds as their host plants which can be obtained by using only small amount of the tested plants eliminating the need to over harvest medicinal plants which exhausts our reservoirs of these beneficial plants and endangers their existence [79–81].

It has been reported that using a small portion of the root, stem or leaves of medicinal plants, several bioactive compounds can be extracted from their endophytic fungi. These bioactive compounds have the same action as the extracts of their host plants like inhibit Streptococcus mutans and their biofilm formation while being biosafe. These endophytic fungal extracts can specifically target glucosyltransferase enzyme and prevent the production of water insoluble glucan even

when compared to the gold standard chlorhexidine gluconate [82–8]

3. Conclusion

Caries prevention is a dream that researchers keep chasing. Nowadays, after the paradigm shift in the concept of caries production, the goal is selective targeting of caries causing bacteria or their virulence factors. Chlorhexidine is the gold standard artificial product with proven efficacy in inhibiting *Streptococcus mutans* and its glucosyltransferase enzyme with subsequent biofilm formation. However, its undesirable side effects from altered taste to disturbing the oral flora has driven the focus to more natural products. Nature has provided an unlimited resource of bioactive extracts with antibacterial and biofilm inhibition properties. Many natural products are now supported by rigorous research to support is ability to achieve gold standard activity. Due to the fear of depleting our planet's natural resources, researchers have discovered a method to produce the same natural bioactive compounds from small portions of the same plant through their inhabiting endophytic fungal extracts. Natural products can now offer an alternative method of caries prevention through inhibiting *S. mutans* and its glucosyltransferase enzyme without the undesirable side effects.

Authors' Contributions

Mona Tarek Balbaa, principal author.
Prof. Dr. Heba Mohamed Taher, Ass.Prof. Dr. Nermeen Kamal Hamza and Dr. Bassem Ayman Balbool managed manuscript revision.

All authors have read and approved the manuscript.

Conflict of interest

The authors declare that they hold no competing interests.

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