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MANUFACTURING A NEW MEDICATED CHEWABLE GUM FROM NATURAL MATERIALS TO CONTROL PERIODONTAL PATHOGENS

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Abstract

Within their multispecies subgingival biofilm in deep pockets, periodontal pathogens are being protected from the attendance of antimicrobial agents, in addition to; the licensed safe concentrations of antibacterials are less effective against biofilm; which leads to unsuccessful treatment and recurrent infections. Therefore, as a first local effort, the medical aim of the present study was to apply the natural material, frankincense, to make a medical chewing gum and an intra-pocket antimicrobial delivery system as a hopeful solution for the ineffectiveness of antimicrobials to control periodontal pathogens. The ability of frankincense film to work as an antibiotic delivery tool was tested by agar diffusion procedure against three types of anaerobic pathogens isolated from periodontal pockets. The usefulness of the currently prepared medical chewing gum from frankincense and other natural additives to control periodontal infections was tested by measuring the level of bacterial hydrolytic enzymes in gingival pockets. The results proved the validity of frankincense film to be a natural delivery tool of antimicrobial ingredients by the denotation of inhibiting the growth on agar plate. The results also proved the validity of frankincense to formulate a medical chewable gum with profound efficiency in reducing the bacterial load inside the gingival tissues. The study claims for the practical application of frankincense in the field of medicines production as a gum base to produce a medical chewable gum and an antimicrobial delivery system. This application can be adopted by pharmaceutical factories and can be dependable by the Ministry of Health and dentists as an alternative to increasing the concentration or combination of chemical medicines**.**

Keywords: *medical chewing gum, antibiotic delivery systems, oral health.*

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Introduction

Periodontitis is one of the common human infections that resulted from the complex interactions between anaerobic oral species (Rams *et al.*, 2020), among them *Tannerella forsythia, Treponema denticola* and *Porphyromonas gingivalis* are the most virulent contributors (Al-Hamdoni and Al- Rawi, 2020[a]). The most remarkable attributes of the pathogenic events of these species are their assembly in a multi-species biofilm and the over production of hydrolytic enzymes which destroy the periodontal ligament and alveolar bone, and finally tooth fall (Kitano *et al.,* 2016).

Formation of a firmed multispecies SUB- GIGIVAL plaque will delay the treatment by blocking the access of immune factors and antibacterials (Dashper *et al.*, 2014; Chaudhary *et al.*, 2020). For curing of most periodontitis infections and best control of the pathogens, mechanical removal of the SUB- GIGIVAL plaque must be coupled with a course of antibiotics; and it is often preferable to use two types of antibiotics along with the topical mouthwashes, chlorhexidine gluconate (0.12%) (Bedran *et al.*, 2016; Ong *et al.*, 2017; Al- Hamdoni and Al-Rawi, 2020[b]). Nevertheless, toxicity, resistance of periodontitis bacteria, disagreeable taste and discoloration of the teeth are the most upsetting outcomes for the prolong use of these chemical therapies (Gajdács *et al.*, 2017; Rams *et al.*, 2020). Risk of pathogen resistance pay interest for discovering new antimicrobial agents, among which plant-derived materials with therapeutic benefits represent hopeful solution for this resistance; and in addition to, they are most friendly to human and environment, easily available and inexpensive (Nawab Al-Deen, 2017; Al- Hamdoni and Al- Rawi, 2020[b]).

Drug delivery systems that feed sufficient quantities of antimicrobials into dental pockets were introduced as a more effective method to combat the multispecies plaque and successful treatment (Ismail *et al.*, 2019). Because of its popular use, the efforts of specialists were directed to employing chewing gum as a drug- delivery tool (Mehta *et al.*, 2017). The drug substance is loaded on a natural or synthetic polymer which acts as a carrier that delivers the therapeutic agent during chewing to ensure the presence of the influential dose as long period as possible (Wessel *et al.*, 2016). For instance, Ondansetron is loaded to prevent nausea and vomiting, anti-histamine H1 receptor antagonist as an anti-allergic, fluoride or xylitol as a prophylaxis to combat dental carries, nicotine for smoking stopping, aspirin as an analgesic, caffeine to increase alertness (Kumar *et al.*, 2014; Lakshmi *et al.*, 2014; Bhatt *et al.*, 2015; Mehta *et al.*, 2017). For most synthetic polymers, the accurate structure remains unknown, they require lot of manipulations and several components must be added to reach acceptable taste and desired benefit (Mehta *et al.,* 2017; Hagbani and Nazzal, 2018). On the other hand, the natural gum base, like juletong or Chicle which are extracted from Sapodilla tree are not easily obtained and are expensive (Jain *et al.*, 2019). As a first pioneer research in Iraq, the medical aim of the present study was to employ the natural material, frankincense, to make a medical chewing gum and an intra-pocket antimicrobial delivery film as a confident solution to control periodontal pathogens.

Materials and Methods

Prepare a film of antibacterial agents:

Frankincense solutions at 40- 60% (W/V) were made in warmed water at 80°C and volumes of 10- 25 µl were taken from each concentration and dried over Falcon nylon to select the suitable one to make a film. Then different concentrations of aluminum potassium sulfate or Chlorhexidin rinses or Ciprofloxacin antibiotic were mixed with these solutions to make a film of antimicrobial agents. Agar- diffusion method was applied to show the ability of this film to inhibit the growth of three types of potent periodontitis causatives, *Tannerella forsythia*, *Treponema denticola* and *Porphyromonas gingivalis* (Al-Hamdoni and Al-Rawi, 2020[b]).

Manufacturing a new chewable gum from natural materials:

The constituents and weights are shown in table (1). The precise weight of each component was documented after several times of trial and the production steps were planned depending on Hagbani, and Nazzal, (2018). Frankincense was soaked overnight in warm water. Calcium carbonate was dissolved in sterilized distilled water shortly before use. After softening the frankincense on a water bath for 15 min and mixing, the other constitutes were added in the following order: glycerin and sunflower oil and mix for 10 min, calcium carbonate and mix for 5 min, sucralose and ascorbic acid and mix for 5 min and when a thick consistent mass was formed, the heating source was turned off and peppermint oil was added and mixed for 5 min. The gum pieces were formed (500 mg), enclosed in Falcon nylon and aluminum foil and stored at 10-20°C.

Table (1): The weights of the constituents used in the study to make medicinal chewing gum

Constituents	Weights (mg)
Frankincense as a chewable mass and antibacterial	**400**
Calcium carbonate as a filler	**30**
Sucralose as a sweetener	**26.5**
Sun flower oil as a softening	**15**
Glycerin as a plasticizer	**15**
Peppermint oil as a flavor	**5**
Ascorbic acid as an antioxidant	**2**

Demonstration the effectiveness of the frankincense medicinal chewing gum:

The effectiveness of the current medicinal product was tested by measuring the level of enzymatic activity of bacteria in the gingiva fluid using APIZYM system (BioMérieux® SA, France). Patients included in the test gave a verbal agreement after get a full description about the test in the Teaching Hospital of the College of Dentistry in the University of Mosul. They were divided into two groups: the negative control group was treated by mechanical cleaning only and the test group (from relatives) using medical chewing gum. Ten gingival pocket fluid samples were taken at zero time and after 7 days. The sample was tested in the APIZYM strip and the enzymatic activity was evaluated as a score from 0 to 5, which is related to the microbial load according to the company's directions (API® ZYM RÉF 25200 Kit leaflet, https://www.biomerieux.com).

Results and Discussion

The results showed that the formulated film of frankincense can release its antimicrobial content and prevent the growth of the three types of bacteria, as it was indicated by the formation of the zone of growth inhibition around the film. The diameter of inhibition was increased if other antimicrobial agents were added to the film (figure 1). These results propose the usefulness of the aqueous extract of frankincense to formulate an antimicrobial delivery film.

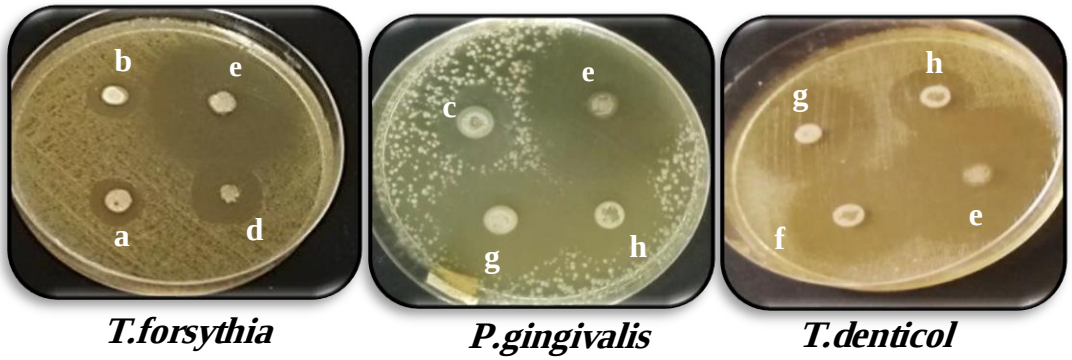

Figure 1: Disc- like film of frankincense alone (a) or with aluminum potassium sulfate (b), Ciprofloxacin (CIP) (c), Chlorhexidin (CHX) (d), aluminum potassium sulfate and CIP and CHX (e), aluminum potassium sulfate and CIP (f), aluminum potassium sulfate and CHX (g) or CIP and CHX (h).

The current study chose natural ingredients available locally to make medical gum with a low cost. The easy chewed gum piece with 500 mg and with an acceptable flavor is shown in Figure 2. Each piece contains 80% chewable mass of frankincense, 15% plasticizer, 15% softener, 6% filler, 5.3% sweetener, 0.3% antioxidant, and 1% flavor materials. Our medical product was effective in reducing the microbial load in gingival fluid in the test group who used it one hr. by three times daily for one week.

According to the results of APIZYM test, the effectiveness was proved as the enzymatic activities of bacteria were recorded at 0-1 score after use (figure 3 III) while they were at 3-5

score at the zero time (figure 3I) and in the negative control (figure 3 II) after one week. Therefore, our medicinal product can be used as a natural medicinal product alternative to chemical treatments for combating periodontal pathogen.

Figure 2: The Formulated medicinal frankincense gum

Figure 3: Microbial hydrolytic enzymes measured by APIZYM stipe at zero time (I) and after 7 days in the control group (II) and in the test group (III). Stipe cupules contain the substrates of the bacterial enzymes. In cupule 1, normal saline was added (the negative control). In cupules 2 to 20, 20 µl of the sample was added.

We utilized the advantage of the aqueous solution of frankincense to form disc like film, and the advantage of the synergistic interaction between frankincense and the other antibacterial substances proved in our previous study (Al-Hamdoni and Al- Rawi, 2020[b]). This film which can acts as a drug delivery system, released its active ingredients causing a growth inhibition zone. This film can be put inside the pocket to deliver the antimicrobial contents directly inside the pocket, so that the causative pathogens will encounter high levels of

effective antimicrobial agents for adequate period. In contrast, the concentration of the systemic antibiotics that reaches the gingival fluid may be lower than the effective concentration in the serum (Shawky *et al.*, 2015); and also, the effect of the topical mouth disinfectant is only at or shortly after the time of application when they are in higher concentrations; but their concentration will decrease with rinsing, and also they do not reach the deeper sites in the pocket (Kumar *et al.*, 2010; Bogdanovska *et al.*, 2012). Therefore, drug delivery systems have been introduced as a mean to overcome the limited exposure to the effective level of antimicrobial agents, reduce the amount of the total dose needed and side effects, and maintain the effective concentration in sufficient quantity and for a longer time (Mehta *et al.*, 2017; Tsaousoglou *et al.*, 2014). For instance, Chitosan, Xanthan gum, Locust bean gum were described as antibiotic- delivery systems against *Staphylococcus aureus* (Mahadlek *et al.*, 2010; Shukla *et al.*, 2010); polymers of Ethyl cellulose and Bioadhesive hydroxyl propyl methyl cellulose to make film of Metronidazole (Kumar *et al.*, 2010). Chemical polymers were also used to prepare gel of herbals against some bacterial species tested by the team of Vinita (2013). The team of Algarni (2015) described the preparation of Methylocellulose gel which contains two or three types of antibiotics to be more effective against endodontic pathogens. The current study presents a natural, easily available and low- cost procedure to prepare a system for delivering antimicrobial materials into the tooth pocket.

The current study represented the first local effort investigates the advantage of medical chewing gum to control periodontal infections. The study chose natural, safe, and locally available with low- cost material for the formulation. The frankincense resins act as chewable mass which releases its active substances (antimicrobial and anti- inflammation components) during chewing. Frankincense as a natural substance can be used without fear when its components are absorbed via the mouth mucosa or swallowed. It was described to be safe compounds for use by the Food and Drug Administration (FDA) Organization (Raja *et al.*, 2011). In addition to, previous studies proved that 300- 400mg of frankincense are not toxic and safe for human, and also 800 mg/ kg of body three times daily have no histological or biochemical side effects (Abdel- tawab *et al.*, 2011). However, the frankincense is a hard piece and has a bitter taste and after short time unpleasantly it sticks to the tooth; therefore, to improve its properties, glycerin and sun flower oil were added to soften the mass and control its stickiness in order to keep the piece of gum in the mouth for a longer period. As filler matter to modulate the fabric of the gum piece, calcium carbonate was added. Sweeteners and flavor were added in the amount that gave an acceptable taste. Sucralose used to sweeten our medicinal product is one of the sugary substitutes and was classified among the alternatives to industrial sugars with no calories, is not nutritional so do not fermented into acid nor cause tooth decay (Jayadevan *et al.*, 2019). Ascorbic acid, the antioxidant, helped maintain the product's qualities preserved at 10-20°C during 15-day.

Measuring the level of hydrolysis enzymes of bacteria in the pocket fluid gave supportive proof for the eligibility of the treatment by the produced medical gum in reducing the microbial load compared to the treatment with mechanical cleaning only. This measurement was carried

out using the APIZYM system which indicates directly the quantity of the bacterial enzyme as a color intensity scored between 0- 5, and then indirectly the level of the bacterial load. The current results provide an easy and inexpensive method for making medicinal frankincense gum, which can be made at home to gain the benefits of the frankincense components as a therapeutic or preventive material. This chewing gum represents a hopeful natural medicinal substance for controlling oral infections as its use showed a significant reduction in the level of all degrading enzymes. Therefore, substitute the popular chewing gum with medicinal frankincense gum will give benefits in reducing the majority of oral pathogens. In addition, by absorbing the active substances of frankincense through the mouth or ingestion, the benefits will reach other areas in the body

Conclusions

Our study, for the first time in Iraq succeeded in making a natural delivery tool from frankincense which can be put inside the tooth pocket to release its antibacterial content in sufficient quantity. In addition to, the addition of synergistically acting antimicrobials into this film enhances the inhibitory effect on pathogens instead of increasing the concentration or using two types of chemical medicines. Our study also as a first attempt in the country succeeded to formulate frankincense medical gum from available and cheap ingredients, which has proven its efficiency in reducing the bacterial load inside the oral tissues. The practical application of the current study for the production of medical chewing gum with therapeutic and economic efficacy can be implemented in pharmaceutical factories at the level of country as it is safe for human administration, cheap and from available natural materials. This medical gum can be dependable by the Ministry of Health and dentists as an alternative to chemical treatments. Also, frankincense can be used in the field of producing medicines delivery tools.

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