

Evaluation of the Anti-inflammatory Effect of Nanocinnamon Gel on Oral Health

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الخلاصة

الأهداف: تهدف الدراسة الى تقييم الخواص الفيزيوكيميائية و تنمية تاثير الجزيئات النانوية من هلام القرفة الفموي على صحة الفم . **المواد وطرائق العمل :** تم تحضير هلام القرفة النانوي الفموي بتركيز (2٪) من مسحوق القرفة النانوي ودراسة بعض خصائصه (الانتقال الالكتروني المجهرية, الاشعة تحت الحمراء و قياس الباهة الحامضية)وتقييم تاثيرها على التهاب اللثة . جرت الدراسة على (٤٥) مريض بالتهاب اللثة المزمن تتراوح أعمارهم بين (١٨-٥٠) سنة, قسموا الى ثلاثة مجاميع كل مجموعة تضم خمسة عشر مريضا , تم اخذ قياس معامل الكلس ,معامل اللثة ومعامل النزف السريري للتهاب المزمن للثة لكل مجموعة قبل اخذ العلاج وبعد ٧ أيام و ٢١ يوم من العلاج, المعالجة كانت تتضمن علاج ميكانيكي لتنظيف وتلميع الأسنان في العيادة ثم العلاج الدوائي ,فالمجموعة الاولى تتعرض للعلاج الميكانيكي فقط , المجموعة الثانية علاج ميكانيكي واستخدام هلام الكلوروهيكسيدين الموضعي اما المجموعة الثالثة فعلاج ميكانيكي ثم استخدام هلام القرفة النانوي الموضعي, يستخدم العلاج مرتين في اليوم يبقى عشر دقائق على الاقل لمدة ثلاث اسابيع . تم تحليل البيانات باستخدام البرامج الاحصائية: كروسكل للأختبارات اللامعلمية. **النتائج:** أظهرت النتائج ان مؤشر الكلس او الترسيبات على اللثة انخفض معنويا في المجموعة الثالثة بعد ٢١ يوم من العلاج ,بالأضافة الى انخفاض مؤشر التهاب اللثة انخفاضا معنويا في المجموعة الثالثة بعد ٧ و ٢١ يوم من العلاج. **الاستنتاجات:** أن جزيئات نانوية من هلام القرفة الفموي أظهرت تأثيرها ضد التهاب اللثة المزمن وتقليل مؤشراتها السريرية .

ABSTRACT

Aims: This study aimed to evaluate the physicochemical characteristics and anti-inflammatory effects of nanocinnamon gel on oral health. **Materials and Methods:** prepared nanocinnamon gel 2% concentration from nanocinnamon powder and study some of its properties (TEM , IR , pH) and evaluate its effects on gingivitis. The study was carried out on the randomized clinical trial of chronic gingivitis comprises of 45 patients of age between (18-50) years old. They were divided into three groups, fifteen for each group and have been measured the plaque index, gingival index and bleeding for each group at baseline, after 7 and 21 days of treatment, treatment involved mechanical therapy by scaling and polishing at dental clinic and drug treatment in which the first group applied to the mechanical treatment alone, , second group received chlorhexidine gel topically and third group received nanocinnamon gel topically , the treatment used twice daily at least ten minute for three weeks. Data were analyzed using kruskal wallis -test for nonparametric data. **Results:** the results showed that plaque index were decreased significantly in nanocinnamon group after 21 days of treatment . Gingival index levels decrease significantly in nanocinnamon group after 7 and 21days of therapy. **Conclusion:** Noancinnamon gel has anti-inflammatory effect that decrease clinical parameter of gingivitis.

Key words: Cinnamon nanoparticles, chlorhexidine, gel, dental plaque, chronic gingivitis

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INTRODUCTION

Gingivitis is the most visible sign of periodontal disease, it is characterized by inflammation of the gingival tissues and the most common cause of gingivitis was plaque, thus removal of plaque and prevention of gingivitis is the mainstay in the prevention of periodontal diseases^[1]. The therapeutic mouthwashes or gel contain chemical active ingredients that help control bad breath, plaque and gingivitis. Chlorhexidine is the gold standard for the prevention of dental plaque, however, it has some side effects such as altered taste sensation, staining of the teeth, and the tongue^[2]. Since the search for alternative products and natural phytochemicals isolated from plants as used in herbal medicines is considered a good alternative to synthetic chemicals especially for prolonged use in periodontal disease and routine application^[3].

Cinnamon (*Cinnamomum zeylanicum*) is a member of the Lauraceae family. It is one of the main medicinal plants and there is some studies have shown that cinnamon may have different biological activities include (antibacterial, antifungal, antiviral, antioxidant, anticancer, immunomodulatory, analgesic, and anti-inflammatory actions)^[4]. Nanoparticles (NPs) are tiny materials having size ranges from 1 to 100 nm and the novel formulations (nanogel) of nanoparticles are reported to have some advantages which include enhancement of solubility and stability, bioavailability, protection from toxicity, enhancement of

pharmacological activity, enhancement of stability, improved tissue macrophages distribution, sustained delivery, and protection from physical and chemical degradation, also it can be prevented development of drug-resistance microbes^{[5][7]}. Therefore the aim of this study was to prepare a nanocinnamon gel 2% concentration, to study some of its physiochemical properties (TEM, IR, pH) and also to evaluate its anti-inflammatory effect on periodontal parameters in oral health such as plaque index, gingival index and bleeding index scores.

MATERIALS AND METHODS

The protocol of our study was reviewed and approved by the scientific committee of Nineveh Health Directorate at Al-Noor Specialist Dental Center and University of Mosul/ College of Dentistry/ Department of Basic Sciences (No. D.B.S./4/2432019-6) during the period between October 2019 and January 2020. Each participant was given verbal and written information that described the nature of the study, and each signed an informed consent form before registration in the study.

Preparation of cinnamon nanoparticles and nanocinnamon gel 2%

Oral gel was prepared as a concentration of 2% according to the pilot study. Cinnamon was collected from supermarket (Sri Lankan origin). Nanoparticles of cinnamon were prepared by Mechanical Attrition method to obtain partial size

between 1-100 nanometer (nm)^[9]. Preparation of natural product was conducted by taking 100 grams of cinnamon crust then it was cleaned, wash with water and dried in the shade with the presence of air. The crust was broken into small pieces then ground. These preparation of nanocinnamon partials have been tested by a Transmission Electron Microscopy (philips CM10, Holland) in Al - Nahrain University /college of Medicine in Baghdad and obtained size between 10-35 nm. Gel was prepared by mixing carboxy methylcelluse, sodium citrate, propylene glycol, and (2) gm of nanocinnamon powder, and added distilled water up to 100 ml^[8]. All the ingredients mixed with continues stirring on a hot-plate at 37c° for a few minutes until obtained a homogenous gel. Finally, the mixture was poured in many plastic containers, closed and labeled with the name of the product and stored at room temperature.

Morphology of powder nanoparticle

Transmission Electron Microscopy (TEM) was carried out to visualize the size, shape and morphology of the cinnamon powder nanoparticles.

Fourier Transmittance Infra Red (FTIR)

The infrared spectra recorded the vibration of bonding atoms for pure nanocinnamon powder and nanocinnamon gel in the region (400- 4000cm-1) wavenumber.

pH Determination of Nanocinnamon Gel

Nanocinnamon gel pH was determined by putting the electrode of pH meter inside the container which contains a few amount of the preparation. The determination of pH value was done immediately after preparation and three months interval.

Present study

A pilot study was done on 3 patient groups to limit the minimum effective concentration of nanocinnamon gel ,therefore the results showed that nanocinnamon gel 2% is the most effective concentration without side effects and high bioavailability. This randomized clinical trial carried out on 45 patients with chronic gingivitis of aged between (18-50) year. The inclusion criteria obtained via a questionnaire included no mouth or systemic disease, non-smoker, non-pregnant , probing depth ≤ 3mm, good oral hygien and non-sensitive to cinnamon. unstimulated saliva was collected for each individual and at least 2 hours after any food intake to exclude the food stimulatory effect on salivary secretions. The individual asked to wash his mouth three times with 30ml distilled water to ensure complete removal of any remnant food or debris. We included three groups, each group consists of 15 patients .The plaque, gingival and bleeding indicies scores for all groups were measured before and after different time intervals of treatment (baseline, 7 days and 21days) Treatment involved mechanical therapy by scaling and polishing at dental clinic and chemical

treatment in which the first group prescribe control group which is treated by mechanical therapy alone, the second group treated with chlorhexidine gel. After brushing, each individual in group 2 and 3, were instructed to apply chlorhexidine gel 0.2% and nanocinnamon gel 2% topically respectively on the inflamed gingiva for at least 10 minutes twice a day for three weeks and there after rinsed with water to clear any residual medication^[10]. Gingival clinical parameters are assessed at different time intervals (Baseline, 7 days and 21 days).

Measuring of Plaque Index: (Silness and Loe, 1964)^[25]

Plaque Index for the tooth is the moderate accumulation of soft deposit within the gingival pocket, or the tooth and gingival margin which can be seen with the naked eye. According to the Plaque index:

Score 0 - tooth surface is clean

Score 1 - tooth looks clean but materials can be removed from the gingival
Score 2 - visible plaque on the tooth

Score 3 - tooth surface covered with abundant plaque.

Measuring of Gingival Index: (Loe and Silness, 1963)^[24]

The severity of gingivitis is assessed separately at the four smooth surfaces of the teeth, wherever it is massaged with the side of the periodontal probe. According to the gingival index:

Score 1 - no bleeding

Score 2 - bleeding occurs

Score 3 - ulceration and spontaneous bleeding

Measuring of bleeding index: (Muehleman, 1977)^[26]

The bleeding intensity of gingival tissue is recorded after inserting a periodontal probe into the gingival sulcus at the base of the papilla on the mesial aspect, and then moved coronally to the papilla tip. According to the bleeding index:

Score 0 - no bleeding

Score 1 - A single discrete bleeding point

Score 2 - A single line of blood appear or several isolated bleeding points

Score 3 - The interdental triangle fills with blood shortly after probing.

RESULTS

Morphology and structure of the nanoparticles of cinnamon were determined by transmission electron microscopy (TEM) which demonstrated the spherical shape of nanoparticles of cinnamon and confirmed the nanometric particle diameter between (10-35) nanometer.^[11]

The vibrational response was represented in Figure (1) of pure cinnamon nanoparticle powder measurement via infrared beam, while Figure (2) showed the vibrational response of nanocinnamon gel 2%, the results in Figure (1) and (2) showed there are an identical diagram and this means they have the same chemical structure.

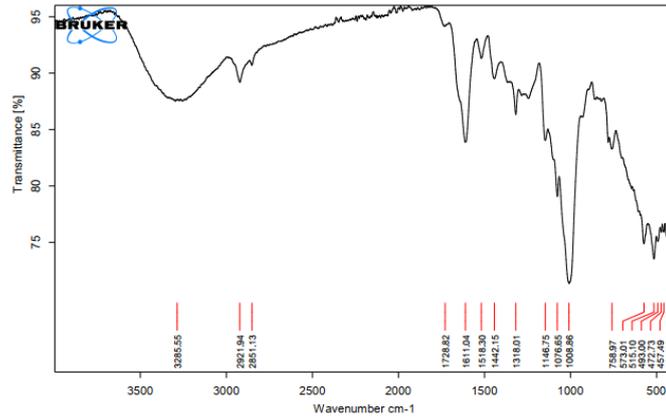


Figure (1): Pure cinnamon nanoparticle powder measurement by FTIR (Infra-red) spectroscopy

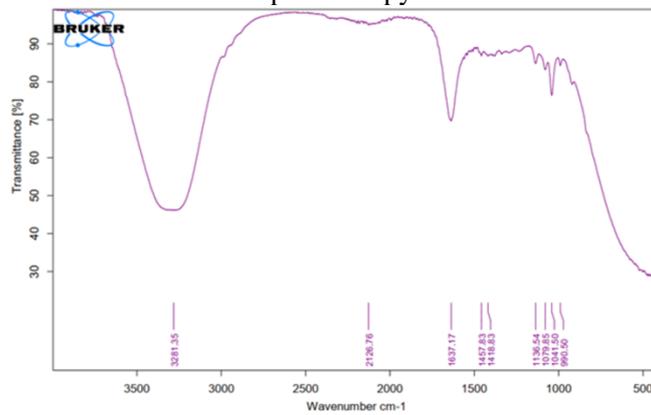


Figure (2): Nanocinnamon gel 2% measurement by FTIR (Infra-red) spectroscopy .

Determination the pH of nanocinnamon gel was done immediately after preparation and after three months represented (6.27 , 6.36)

respectively and for chlorhexidine gel was (7, 6.9) respectively according to time shown in Table (1).

Table (1): pH of nanocinnamon gel 2% and chlorhexidine gel 0.2%.

Material	pH at once	pH after 3 months
Nanocinnamon gel 2%	6.27	6.36
Chlorhexidine Oral gel 0.2%	7	6.9

Statistical analysis

Kruskal -Wallis H test in spss was applied among the data of the three groups at the indicated interval times of non parametric values.

The results of plaque index

The results showed that there is statistical significant difference of the levels of mean plaque index in nanocinnamon group at 21day with mean (0.40±0.27) in comparison to control and chlorhexidine

groups with mean(0.83±0.50)and(0.66±0.53) respectively as illustrated in Table (2) Figure (3).

Table (2): Kruskal H test of comparison the means of plaque index between three groups

<i>Follow-up period</i>	<i>Control group Mean±SD</i>	<i>Chlorhexidine Mean±SD</i>	<i>Nanocinnamon Mean±SD</i>	<i>Kruskal H test</i>	<i>df</i>	<i>p-value</i>
<i>Baseline</i>	2.17±0.62	2.04±0.64	2.09±0.59	0.122	2	0.941
<i>Day 7</i>	1.19±0.70	0.79±0.28	0.78±0.53	1.927	2	0.382
<i>Day 21</i>	0.83±0.50	0.66±0.53	0.40±0.27	7.104	2	0.029

Significant difference at $p \leq 0.05$

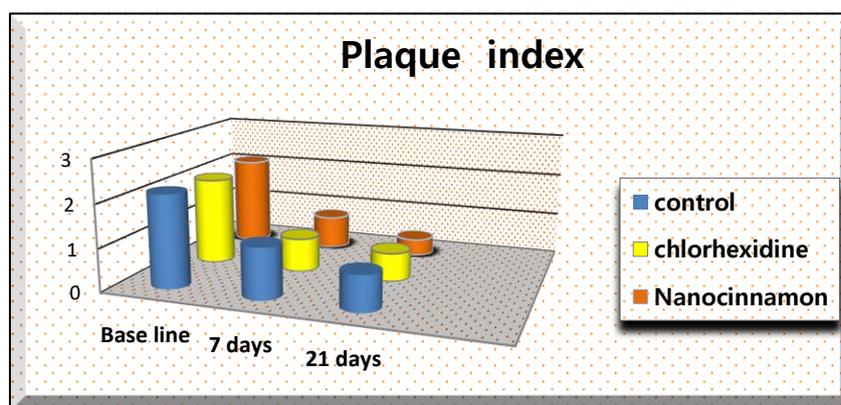


Figure (3): Comparison of plaque index at the indicated time intervals for the nanocinnamon , chlorhexidine and control group

Gingival index

The mean of gingival index in nanocinnamon group at baseline was decreased significantly after time interval therapy 7 day from (2.41±0.51) to

(1.17±0.47) and after 21days decrease to (0.41±0.2) respectively at $p\text{-value} \leq 0.05$. However there was significant difference in comparison to control and chlorhexidine group as illustrated in Table(3) , Figure (4).

Table(3): Kruskal H test of comparison the means of gingival index between three groups at indicated time interval

<i>Follow-up period</i>	<i>Control group Mean±SD</i>	<i>Chlorhexidine Mean±SD</i>	<i>Nanocinnamon Mean±SD</i>	<i>Kruskal H test</i>	<i>df</i>	<i>p-value</i>
<i>Baseline</i>	2.33±056	2.41±0.61	2.41±0.51	0.429	2	0.807
<i>Day 7</i>	1.84±048	1.48±0.75	1.17±0.47	6.286	2	0.043
<i>Day 21</i>	1.55±066	0.97±0.77	0.41±0.2	11.678	2	0.003

significant difference at $p\text{-value} \leq 0.05$

Anti-inflammatory effect of nanocinnamon gel on oral health

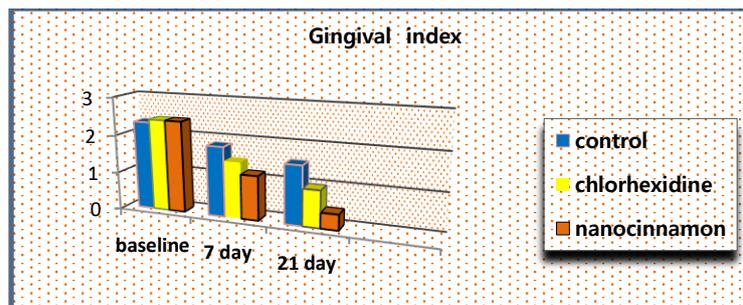


Figure (4): Comparison of gingival index between three groups at the indicated time intervals

Bleeding index

The mean of bleeding index between three groups showed statistical significant difference in nanocinnamon group after 21

day of treatment from (1.47±0.46) to (0.89±0.34) and (0.43±0.29) respectively at p-value ≤ 0.05 in comparison to control and chlorhexidine groups as illustrated in Table (4) Figure (5).

Table(4): Kruskal H test of comparison the means of bleeding index between three groups at indicated time interval

<i>Follow-up period</i>	<i>Control group Mean±SD</i>	<i>Chlorhexidine Mean±SD</i>	<i>Nanocinnamon Mean±SD</i>	<i>Kruskal H test</i>	<i>df</i>	<i>p-value</i>
<i>Baseline</i>	2.42±0.49	2.52±0.36	2.44±0.31	.331	2	.848
<i>Day 7</i>	1.52±0.5	1.58±0.45	1.05±0.51	5.038	2	0.068
<i>Day 21</i>	1.47±0.46	0.89±0.34	0.43±0.29	17.109	2	0.000

Significant difference at p-value ≤ 0.05

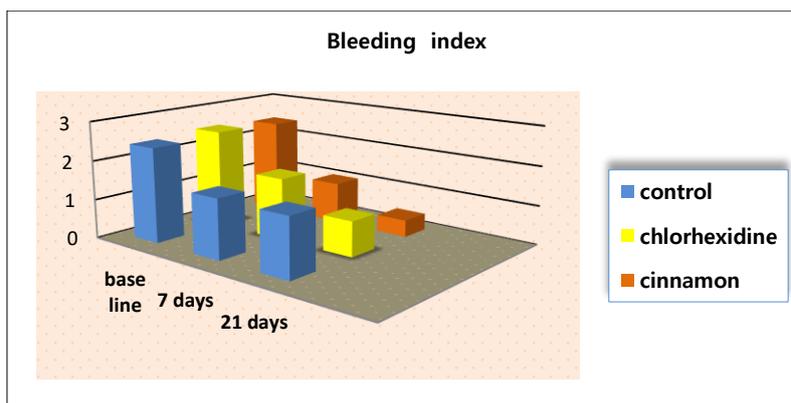


Figure (5): Comparison of bleeding index between treatment and control group at the indicated time intervals

DISCUSSION

When we compared (pure nanocinnamon and nanocinnamon gel) using FTIR

spectroscopy analysis, results demonstrated that, the two materials have the same chemical structure evidenced by the

identical diagram for the two materials with slight increase or decrease in frequency and intensity. We can see an increase in the activity for the cinnamon after adding it to a gel because the presence of the phenolic group. In addition to that, the disappearance of two peaks which that refer to aliphatic (C-H) group in a gel compared to the pure cinnamon, may be attributed to a gel concentration that was more than a pure cinnamon concentration^[13]. The pH of the gel was nearby to chlorhexidine gel and still the pH almost constant even with long period of preparation, indicating that nanocinnamon gel was pH stable even in long period^[14].

In our study, clinically significant reduction in gingival inflammation was seen in nanocinnamon gel group and chlorhexidine group as compared to control group in chronic gingivitis so that, the use of nanocinnamon gel 2 % as a adjunct to scaling and polishing have efficacy in reduction of dental plaque and gingival inflammation at the interval of therapy.

The effect of chlorhexidine on plaque and its property of slow release has made it as the panacea in the adjunctive treatment to gingivitis. Chlorhexidine being cationic prevents pellicle formation and is bacteriostatic at lower concentrations and bactericidal at higher concentrations^{[12][17]}.

In the present study, mean plaque index decreased among all groups at indicated interval of therapy, however it was significant difference in nanocinnamon

group after 21 days of treatment, the reduction could be explained to bactericidal property of the cinnamon, these results were agreement with Gupta and Jain who proved that both cinnamon and chlorhexidine were effective as anti-plaque and anti-gingivitis agents^[15]. A significant inhibitory effect on plaque accumulation appeared within group after treatment with nanocinnamon, chlorhexidine and control at all intervals in comparison with the baseline. In addition, Waty et al, proved that cinnamon is a potent antibacterial agent as mouthwash to inhibit *streptococcus mutans* growth^[16]. Adzakiyah *et al*, demonstrated that flavonoid compounds was another component of cinnamon which disrupt bacteria by destroying the cytoplasmic membrane and causing leakage of important metabolites that inactivate bacterial enzyme systems. However, cinnamon mimics various events that happen during the apoptosis process by causing a change in the function and structure of the cell membrane^[18]. Moreover, the level of gingival index score decreased in all treatment groups with statistically significant reduction in nanocinnamon treated group compared to chlorhexidine and control groups.

Bleeding index score decreased in all treatment groups with a statistically significant reduction in nanocinnamon group after 21 days of treatment compared to chlorhexidine and control groups, indicating that nanocinnamon having better

anti-inflammatory effects than chlorhexidine at 21 days. Results of present study were consistent with the results of Kumar et al, and Buggapati who have been proved that mouth rinse contain several herbal medicines such as cinnamon ,turmeric ,neem ,clove and aleovera have anti-inflammatory effects in dentistry, so that decrease of gingival bleeding and gingivitis and inhibition of the growth of the aerobic micro aerophilic and anaerobic bacteria^{[19][20][21]}.

The mechanism of cinnamon could be explained by its potent anti-inflammatory property, which inhibits of prostaglandin biosynthesis, nitric oxide production and cyclooxygenase-2(COX-2)enzyme^[22].

Gunawardena et al showed that 2-Hydroxycinnamaldehyde had the strongest inhibitory effect on NO production among the cinnamaledhyde derivatives through inhibition of NF-kappa B activation, and thus might be used as an anti-inflammatory agent^[23].In addition eugenol is one of the most components of cinnamon, could also inhibit 5-lipoxygenase enzyme in polymorphonuclear leukocytes and it can inhibit inducible nitric oxide synthesis (iNOS),and nitric oxide (NO) production^[22],. Polymorphonuclear lycocytes (PMNs) are the primary host defense modulator in gingival inflammation and reactive oxygen species (ROS) are generated by PMNs, as a result of the inflammatory tissue response mechanisms^[17].

CONCLUSION

Within the limitation of this trial,small doses of nanocinnamon gel were safe and effective on plaque and gingivitis with absence of burning sensation, dryness and staining of teeth as compared to standard chlorhexidine. When we used a novel drug delivery system showed much better absorption profile which enables them to cross the biological membrane, resulting in enhanced bioavailability. Both chlorhexidine and nanocinnamon groups had good patient compliance without adverse effects in both treatment groups .In future , others anti-inflammatoryeffects and antioxidant effects of nanocinnamon should be ascertained with further longitudinal studies.

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