Research Article

Evaluation of the anti-bacterial effect of quercitrin in comparison with chlorhexidine in dental implants: an in vitro study

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Abstract: Background: Dental implants have been used to replace lost teeth over the past ten years because of their high success rate. Studies have shown that both Gram-positive and Gram-negative bacteria can colonize and form biofilms on the surface of an implant. Chlorhexidine acts on the inner cytoplasmic membrane to reduce plaque accumulation, making it an antiplaque and antigingivitis agent. The current study aims at elucidating and comparing Quercitrin with the well-known antibacterial chlorhexidine in their antibacterial ability to improve the dental implant procedure. Materials and methods: From each primary positive culture on blood, UTI chromogenic agar, and Mannitol salt agar media, a single colony was taken and identified, stained with Gram's stain, and examined under a light microscope. Results: The results revealed that the minimum bactericidal concentration (MBC) and the minimum inhibition concentration (MIC) of chlorohexidine were the same as 3.12 µg/mL for all isolated bacteria that have been used in this study, which was the lowest concentration used that showed a statistically significant difference. The MIC of Quercitrin for the bacteria *Streptococcus. mutans*, *S. aureus*, and *P. gingivalis* was 1600 µg.ml-1 and 800 µg.ml-1 for the *E. faecalis*, while the MBC for *S. mutans*, *S. aureus*, and *P. gingivalis* was 3200 µg.ml-1 and for the *E. faecalis was* 1600 µg.ml-1. Conclusion: In comparison with chlorhexidine, Quercitrin in a certain concentration has the same antibacterial effect, which could be a novel discovery to be used as a part of the dental implant industry as a peri-implant's vital item for inflammation's control and prevention.

Keywords: Anti-bacterial, chlorhexidine, dental implant, Quercitrin.

Introduction

Over the past ten years, dental implants have had a remarkable success rate of over 95% and have been widely used to replace lost teeth [1-3]. Biological complications, including peri-implantitis, have a 10–40% incidence rate despite the astounding success rates for dental implants [4,5]. Peri-implantitis is a bad result of bacteria spreading around the implants. It destroys the alveolar bone and the gum tissue that supports it. Peri-implantitis may happen soon after the placement of the implant, and it appears to progress in a non-linear pattern [6-8]. The development of a biofilm surrounding the surface of the implants and a severe inflammatory response of the soft tissue against bacterial infections are behind peri-implantitis, which can also damage the hard tissue and cause loss of bone mass and osteolysis [9-11].

Studies have shown that some Gram-positive bacteria, such as enterococci, Staphylococcus aureus Rosenbach, and Streptococcus mutans Clark, can live on implants and form biofilms on their surface. The main culprits behind the onset of this condition are Gram-negative bacteria, including Porphyromonas gingivalis and Aggregatibacter actinomycetemcomitans [12] [13].

Chlorhexidine is one of the antimicrobial agents. It is an agent that eliminates gingivitis and plaque by penetrating the inner cytoplasmic membrane [14-16]. Rinsing with 0.12% chlorhexidine gluconate once daily may be a significant bonus for oral health for patients with implants. However, when used as a

chemical agent, gel, or irrigation solution in a full-mouth disinfection approach, it did not offer extra microbiological and/or clinical benefits over mechanical treatment alone [17] [18].

Among the many bacterial types that Quercitrin may destroy are those that cause infections in the urinary tract, gastrointestinal tract, respiratory system, and skin [19-21]. The solubility of Quercitrin [20,22] and its interaction with the bacterial cell membrane [23], which is greatly influenced by the presence of Quercitrin's hydroxyl groups [24,] [25], have been associated with Quercitrin's antibacterial capacity.

The bactericidal effects of Quercitrin are often more effective against Gram-positive bacteria than Gram-negative ones [26] [27]. There is a chance that the differences in Quercitrin susceptibility are due, at least in part, to differences in the cell membrane composition between Gram-positive and Gram-negative bacteria. The effectiveness of some Quercitrin derivatives against Gram-negative bacteria was shown to be higher than that against Gram-positive bacteria [20,24]. A shift in its efficacy against some bacteria might result from phosphorylation or sulfation at different hydroxyl groups, which could alter Quercitrin's solubility [24] [28] .This research is fresh, unique, and significant since, as far as currently aware, no comparable investigations have been conducted in Iraq.

Peri-implantitis can contribute to implant loss. The formation of biofilm in the tissues surrounding dental implants leads to peri-implantitis, which in turn triggers inflammation of the peri-implant mucosa and, eventually, the gradual loss of the supporting tissue [7] [29] [30]. The bacterial species linked to peri-implantitis are diverse and include Porphiromonas gingivalis, Salivarius salivarius, and Prevotella intermedia [30,31]. Researchers found a higher proportion of *P. gingivalis*, Tannerella forsythia, and Treponema denticola in peri-implantitis samples. Some researchers also found pathogens like Pseudomonas aeruginosa and Staphylococcus aureus, which act opportunistically during the infectious process. This biofilm complex also includes viruses and fungi [32-34].

Chlorhexidine has significantly less cytotoxicity. It can't, however, break down necrotic pulp tissue, and its effectiveness against gram-negative bacteria is rather low. Therefore, researchers continue to strive for the ideal irrigating solution for endodontic therapy in primary and permanent teeth [35] [36]. In an effort to enhance the dental implant process, the goal of the current study was to clarify and compare the antibacterial properties of Quercitrin and the widely recognized antibacterial chlorhexidine.

Materials and Methods

Gram-negative and gram-positive bacterial isolates were obtained from the mouth cavities of different patients who routinely visit different dental clinics. Blood agar, Mannitol Salt agar, UTI Chromogenic agar, Brain Heart Infusion broth, Brain Heart Infusion agar, and Muller Hinton broth were used for bacterial cultures. Chlorhexidine and Quercitrin were purchased from HiMedia, USA.

Identification of bacterial isolates

A single colony was cultured on differential and selective media, including Blood agar, UTI chromogenic agar, and Mannitol salt agar. Depending on phenotypic features such as colony size, color, borders, shape, pigments' nature, texture, and elevation, the bacterial strains were identified and stained with Gram's stain for light microscopy. The identification and purification of each isolate were carried out following standard microbiological methods (37,38), and confirmed by VITEK 2 to attain the very last diagnostic.

Culture and media preparation

All culture media were prepared following the manufacturer's recommendation. All media were sterilized in an autoclave at 121 ◦C for 15 minutes (39).

Blood agar: The blood agar medium (HiMedia M089-500G/ USA) was prepared by dissolving 40 g of blood agar base in 1000 ml of distilled water. The medium was autoclaved at 15 psi and 121 ºC for 15

min, then cooled to 50 ºC and 5% of fresh human blood was added. For the cultivation of the bacterial isolates and to determine the bacterial isolate's ability to cause blood hemolysis, this medium was used as an enrichment medium.

HiMedia M118-100/USA served as the mannitol salt agar in this study. It served as a selective medium for staphylococcus species differentiation and isolation. Staphylococcus and Micrococcus prefer the media containing 7.5–10 NaCl, while Staphylococcus exhibits a differential response (39).

UTI chromogenic agar: Forty-three grams of Chromogenic UTI Medium (HiMedia M1418-hicrome-uti-agar/USA) were suspended in 1L of distilled water, then mixed and autoclaved for 15 minutes at 121°C. The UTI was cooled down to 50°C and then poured into sterile Petri dishes.

Brain Heart Infusion Agar: Forty-three grams of Brain Heart Infusion Agar (HiMedia M211-100G/USA) were suspended in 1L of distilled water, then mixed and autoclaved for 15 minutes at 121°C. The UTI was cooled down to 50°C and then poured into sterile Petri dishes.

Müller Hinton Broth: Twenty-one grams of Müller Hinton broth powder (HiMedia M 391-500G/USA) were suspended in 1L of distilled water. The mixture was autoclaved for 15 minutes at 121°C.

Müller Hinton Agar: Thirty-eight grams of Müller Hinton agar powder (HiMedia M173-500G/USA) were suspended in 1L of distilled water. The mixture was autoclaved for 15 minutes at 121°C.

Gram stain solution: To study cell arrangement and morphology and to differentiate between Gram-positive and Gram-negative bacteria, the gram stain solution was used (40). Four solutions were incorporated into the Gram stain mixture, which was supplied by SynBio Technologies (USA). These solutions are: crystal violate, iodine, absolute alcohol, and safranine.

Chlorhexidine and Quercitrin: Chlorhexidine (HiMedia PCT1146-25G/USA) was prepared in concentrations of 3200, 1600, 800, 400, 200, 100, 50, 25, 12.5, 6.25, 3.12 μg.ml-1, and Quercitrin (HiMedia RM6191-25G/USA) in concentrations of 3200, 1600, 800, 400, 200, 100, 50, 25, 12.5, 6.25, 3.12 μg.ml-1.

Antibacterial Assay of Chlorhexidine and Quercitrin Using the Microdilution Method

The antibacterial activity of Chlorhexidine and Quercitrin was measured using the broth microdilution technique as described by (41). For the determination of the Minimum Inhibitory Concentration (MIC) and Minimum Bactericidal Concentration (MBC) of these two materials towards oral pathogenic bacteria, three Gram-positive bacteria (Streptococcus mutans, Staphylococcus aureus, and Enterococcus faecalis) and one Gram-negative bacteria (Porphyromonas gingivalis) were cultivated in Brain Heart Infusion Broth (BHIB) and incubated in anaerobic conditions at 37 C for 24 h. Firstly, serial dilutions of Chlorhexidine and Quercitrin were carried out in 50μL of sterilized Müller-Hinton broth in the wells of a 96-well microplate (Thermo Scientific™/USA) to get the following concentrations: 3200 μg.mL-1, 1600 μg.mL-1, 800 μg.mL-1, 400 μg.mL-1, 200 μg.mL-1, 100 μg.mL-1, 50 μg.mL-1, 25 μg.mL-1, 12.5 μg.mL-1, 6.25 μg.mL-1, 3.12 μg.mL-1, respectively. 50 μL of bacterial suspension with a 1106 CFU/mL concentration was transferred to each well containing Chlorhexidine and Quercitrin separately. The inoculated 96-well microplate was incubated in anaerobic conditions at 37°C for 24 hours. The MIC for each strain was determined by observing the wells, with the first well having no bacterial growth. The MBC was identified by transferring 10 μL from wells containing no growth and culturing them on Brain Heart Infusion Agar (BHIA). The clear plates represent the minimum bactericidal concentrations that reduce 3 logs of bacterial growth. By using an ELISA plate reader (BioTek, USA) at 630 nm, the absorbance of the samples was measured.

Statistical analysis

For data analysis, Prism 9 (GraphPad Software, USA) and SPSS (Statistical Package for Social Science, version 21) were utilized. For the purpose of descriptive analysis, the findings are shown as bar charts with mean values and standard deviations. A one-way ANOVA and the post-hoc Tukey's HSD test were used. P-values of more than 0.05, less than 0.05, and less than 0.01 indicated non-significant, significant, and highly significant differences, respectively.

Results

The culture revealed four different kinds of bacteria. The *Prophyromonas gingivalis* showed smooth, shiny, and convex colonies on blood agar, as shown in Figure (1.a), The *Streptococcus mutans* appeared in blood agar as small and pinheaded colonies, as shown in Figure (1.b). *Staphylococcus aureus* produced yellow colonies with yellow zones, as shown in Figure (1.c)). *Enterococcus faecalis* (Figure. 1.d).

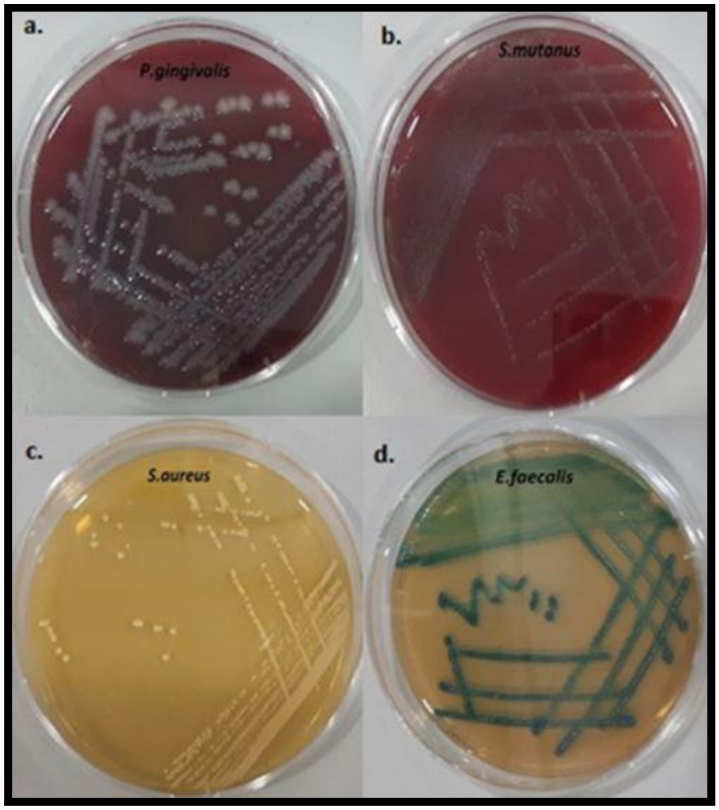

Figure 1: Colonies on incubated bacteria (a.) *prophyromonas gingivalis* (b.) *Streptococcus mutans* (c.) *Staphylococcus aureus* (d.) *Enterococcus faecalis*

Gram staining for these species showed one-gram negative species, while the others were positive gram species as listed in **Table 1.**

Table 1: bacterial gram stainin.

Bacterial species	Gram stain
P. gingivalis	Gram Negative
S. mutans	Gram Positive
S. aureus	Gram Positive
E. faecalis	Gram Positive

The antibacterial effect of Chlorhexidine and Quercitrin on *S. mutans, S. aureus, E. faecalis* and *P. gingivalis* by using the micro dilution method is shown in Figure. 2.

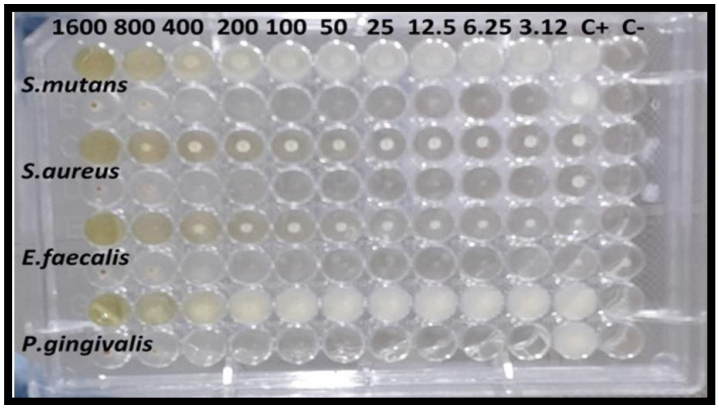

Figure 2 Determining the MIC of Quercitrin and Chlorohexidine using micro dilution method (96 well plates)..

The results of the absorbance are shown in Figure 3, Table 2. The results of Minimum Inhibition Concentration (MIC) of Chlorohexidine and Quercitrin on all isolated bacterial are shown in Figure 4, **Table 3,** and **Table 4**.

Table 2. Determining the MIC and MBC of Quercitrin and Chlorohexidine using ELISA plate reader Method.

	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
CALL	0.069	0.090	0.400	0.498	0.604	0.622	0.617	0.598	0.621	0.573	0.570	0.048
Calc00 Well RSLT	SMP1	SMP9	SMP17	SMP25	SMP33	SMP41	SMP49	SMP57	SMP65	SMP73	SMP81	SMP89
CALL	0.074	0.057	0.051	0.248	0.049	0.046	0.048	0.059	0.518	0.579	0.620	0.044
Calc00 Well RSLT	SMP2	SMP10	SMP18	SMP26	SMP34	SMP42	SMP50	SMP58	SMP66	SMP74	SMP82	SMP90
CALL	0.055	0.088	0.364	0.471	0.508	0.631	0.595	0.557	0.590	0.594	0.574	0.045
Calc00 Well RSLT	SMP3	SMP11	SMP19	SMP27	SMP35	SMP43	SMP51	SMP59	SMP67	SMP75	SMP83	SMP91
CALL	0.078	0.055	0.049	0.051	0.046	0.051	0.053	0.389	0.607	0.584	0.564	0.045
Calc00 Well RSLT	SMP4	SMP12	SMP20	SMP28	SMP36	SMP44	SMP52	SMP60	SMP68	SMP76	SMP84	SMP92
CALL	0.051	0.052	0.054	0.061	0.089	0.105	0.157	0.162	0.159	0.161	0.142	0.047
Calc00 Well RSLT	SMP5	SMP13	SMP21	SMP29	SMP37	SMP45	SMP53	SMP61	SMP69	SMP77	SMP85	SMP93
CALL	0.076	0.056	0.051	0.045	0.045	0.045	0.045	0.102	0.157	0.157	0.161	0.048
Calc00 Well RSLT	SMP6	SMP14	SMP22	SMP30	SMP38	SMP46	SMP54	SMP62	SMP70	SMP70	SMP86	SMP94
CALL	0.048	0.061	0.379	0.630	0.639	0.695	0.702	0.717	0.720	0.703	0.659	0.047
Calc00 Well RSLT	SMP7	SMP15	SMP23	SMP31	SMP39	SMP47	SMP55	SMP63	SMP71	SMP79	SMP87	SMP95
CALL	0.077	0.068	0.050	0.046	0.047	0.046	0.045	0.044	0.586	0.640	0.628	0.048
Calc00 Well RSLT	SMP8	SMP16	SMP42	SMP32	SMP40	SMP48	SMP56	SMP64	SMP72	SMP80	SMP88	SMP96

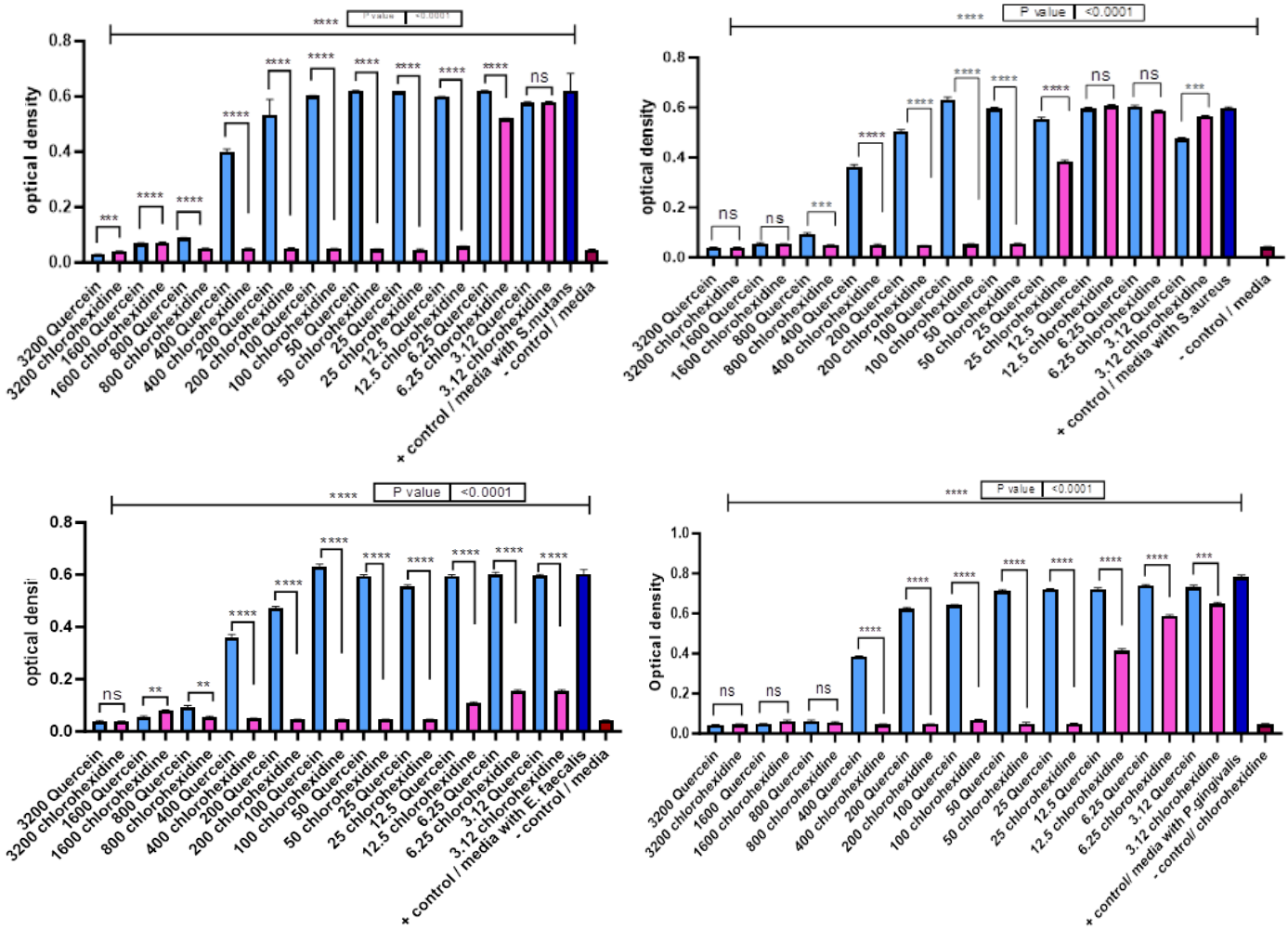

Figure 3: The antibacterial effect of Chlorhexidine and Quercetin on A) S .mutans, B) S.aureus, C)E. faecalis, and D) P. gingivalis by using an ELISA plate reader

Table 3: Antibacterial effect of Chlorohexidine

Bacterial strain	MIC (µg.ml^{-1})	MBC (µg.ml^{-1})
S. mutans	3.12	3.12
	3.12	3.12
	3.12	3.12
S. aureus	3.12	3.12
	3.12	3.12
	3.12	3.12
E. faecalis	3.12	3.12
	3.12	3.12
	3.12	3.12
P. gingivalis	3.12	3.12
	3.12	3.12
	3.12	3.12

Table 4: Antibacterial effect of Quercetin

Bacterial strain	MIC (µg.ml^{-1})	MBC (µg.ml^{-1})
S. mutans	1600	800
	1600	800
	1600	800
S. aureus	1600	800
	1600	800
	1600	800
E. faecalis	800	1600
	800	1600
	800	1600
P. gingivalis	1600	800
	1600	800
	1600	800

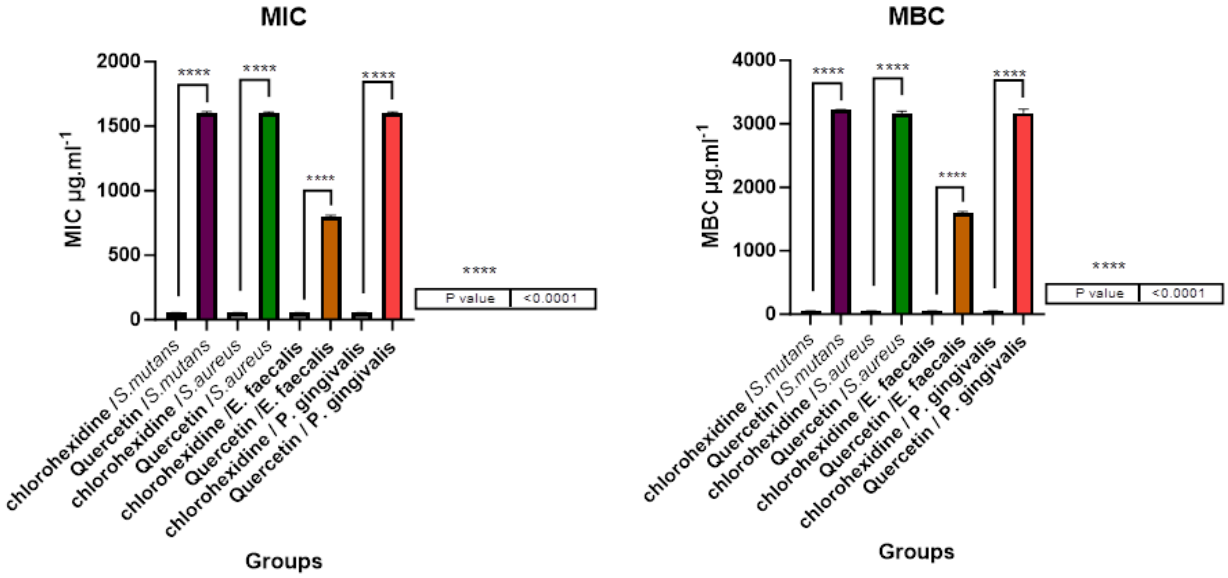

Figure 4: The results of Minimum Inhibition Concentration (MIC) and the Minimum Bactericidal Concentration (MBC) of Chlorohexidine and Quercetin on all isolated bacterial.

Discussion

Bacterial Isolates Identification

The culture revealed four different kinds of bacteria, which were the most common bacterial growths found among the isolates. Prophyromonas gingivalis is one of the bacterial isolates that shows smooth, shiny, and convex colonies on blood agar. The bacteria show a white colony rather than its normal black color on blood agar, as shown in Figure (1.a), which sometimes refers to the mutation that some of the P. gingivalis strains exhibit no pigmentation on blood agar. These strains have a nonsense mutation in the wbpB gene, which is responsible for the pigment-less phenotype of the strain [42] [43].

The Streptococcus mutans exhibited gamma hemolysin on blood agar; the colonies form irregular, heaped, rough colonies resembling frosted glass, mostly crumbly; whole colonies can be picked from the agar [44-46]. as shown in Figure (1.b). On mannitol salt agar, Staphylococcus aureus produced yellow colonies with yellow zones, as shown in Figure (1.c) because mannitol can be fermented by S. aureus, and an acidic byproduct was formed, which caused the phenol red to turn yellow in the agar [47] [48]. Enterococcus faecalis (Figure. 1.d) produced green-colored colonies on UTI chromogenic agar due to ß-glucosidase production. Green to blue-colored colonies were produced by vancomycin-resistant E. faecalis on chromogenic agar due to a substrate's hydrolysis that detects α-glucosidase activity [49] [50]. Gram staining for these species showed one-gram negative species, while the others were positive gram species, as listed in Table 1

In the oral cavity, diverse colonization species are found, depending on the conditions or even the region of this cavity, and according to the microorganism's biochemical characteristics and metabolism, the microorganisms are distributed. One essential component of all microbial sites is the salivary microbiome. Although in all oral sites there is an overlap of all species, the species of Streptococcus mutans, Prevotella spp., Neisseria spp., and Gemella spp. are more frequently found in the saliva [51-53]. Nevertheless, it was found that bacteria present on the tongue are not primarily the same as those located on the hard palate. S. salivarius and Rothia spp. Colonize mainly the surfaces of the tongue or

tooth; the hard palate is colonized only by Simonsieur spp.; and the subgingival and gingival tissues are typically colonized by Treponema spp [33] [54] [55].

Antibacterial Assay of Chlorhexidine and Quercitrin Using the Microdilution Method and the ELISA Plate Reader Method.

The antibacterial effect of Chlorhexidine and Quercitrin on S.mutans, S. aureus, E. faecalis, and P. gingivalis by using the microdilution method is shown in Fig. 2, and the absorbance of the samples is shown in Table 2. The results revealed that the Minimum Inhibition Concentration (MIC) and the Minimum Bactericidal Concentration (MBC) of Chlorohexidine were at the same concentration of 3.12 μg/mL for all isolated bacteria that have been used in this study, as shown in Table 3, which was the lowest concentration used. On the other hand, the MIC of Quercitrin for S. mutans, S. aureus, and P. gingivalis was 1600 μg.ml-1, and 800 μg.ml-1 for the E. faecalis, while the MBC for S. mutans, S. aureus, and P. gingivalis was 3200 μg.ml-1, and for the E. faecalis, 1600 μg.ml-1, as shown in Table 4.

The results confirm that chlorohexidine is a highly effective substance against oral cavity microbiomes and pathogens at the lowest concentration that has been used. Quercitrin was revealed to have the same antibacterial activity as Chlorohexidine by using it at higher concentrations. The use of Chlorohexidine in oral healthcare and dentistry continues to be common and widespread. This includes the caries, dental plaque, and oral hygiene management; peri-implant, gingivitis, and periodontitis disease; oral surgery, root canal therapy, and associated complications; oral mucosal disease; and as a practice to reduce the aerosolization of microbes during dental procedures [56] [57]. For instance, chlorhexidine, as a mouthwash in dentistry, has a full-mouth effect on fungi, viruses, and bacteria that cause different oral infectious diseases and not only has locally antimicrobial effects [58-60]. Quercitrin also has many pharmacological effects, such as anti-tumor, anti-oxidation, anti-inflammation, hypolipidemic, and hypoglycemic [61-63]. On the other hand, failures of an implant system that cause diseases are still continuously reported. For instance, as a result of a multifactorial process, peri-implantitis takes hold in the oral cavity, where the overproduction of reactive oxygen species (ROS) seems to play the dominant role [64.65]. Peri-implantitis is triggered by anaerobic, microaerophilic, or gram-negative bacteria, as well as the development of an inflammation outbreak that can lead to the production of ROS. As soon as it formed, the ROS triggered a vicious circle by promoting the production of pro-inflammatory cytokines [66] [67]. According to the results of [68], in the case of peri-implantitis, it significantly reduces saliva's overall antioxidant capability. In order to create innovative, inherently antioxidant Quercitrin-based biomaterials that might be used in both dentistry and medicine as bone implant replacements and components for dental implants [69-72].

Conclusion

At a specific concentration, Quercitrin exhibits the same antibacterial effects on bacteria as chlorohexidine, presenting a promising discovery for the dental implant industry as a crucial component for peri-implant health and inflammation control and prevention.

Conflict of interest

The authors have no conflicts of interest to declare.

Author contributions

INS: study conception and design. HKH; data collection. INS and HKH: methodology HKH and AY: statistical analysis and interpretation of results. HKH: original draft manuscript preparation. INS, FHH, and AY: writing review and editing. Supervision: INS and FHH. After reviewing the results, all authors approved the final version of the manuscript for publication.

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73.

تقييم تأثير الكيرسيترين كمضاد بكتيري بالمقارنة مع الكلوروهيكسيدين في زراعة الأسنان

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المستخلص:

حققت زراعة الأسنان وعلى مدى السنوات العشر الماضية نسبة نجاح عالية وتم استخدامها على نطاق واسع لتعويض الأسنان المفقودة. ثبت أن البكتيريا إيجابية الجرام وسالبة الجرام تستعمر وتطور الأغشية الحيوية على سطح الغرسة. يقلل الكلوروهيكسيدين من تراكم البلاك عن طريق التأثير على الغشاء السيتوبلازمي الداخلي، مما يجعله عاملًا مضادًا للبلاك ومضادًا لالتهاب اللثة. تهدف الدراسة الحالية إلى توضيح ومقارنة الكيرسيترين مع المضاد الحيوي الكلوروهيكسيدين المعروف في قدرتهما المضادة للبكتيريا في تحسين إجراء زراعة الأسنان. تهدف الدراسة الحالية إلى توضيح ومقارنة الكيرسيترين مع الكلوروهيكسيدين المضاد للبكتيريا المعروف في قدرته المضادة للبكتيريا في تحسين اداء زراعة الأسنان .المواد وطرائق العمل: من كل وسط زرعي أولية للدم، وأجار UTI المولد للون، وأوساط أجار ملح المانيتول، تم أخذ مستعمرة واحدة وتحديدها، وصبغها بصبغة جرام وفحصها بالمجهر الضوئي . النتائج: أظهرت النتائج أن أقل تركيز مبيد للجراثيم (MBC) وأقل تركيز مثبط (MIC) للكلوروهيكسيدين كان بنفس التركيز 3.12 ميكروغرام.مل$^{-1}$على جميع البكتريا المعزولة التي تم استخدامها في هذه

الدراسة وهو أقل تركيز تم استخدامه .أقل تركيز مثبط من كيرسيتين للبكتيريا العقدية *S. aureus* و *P. gingival*is كان 1600 ميكروغرام مل-1، و 800 ميكروغرام مل- 1 لبكتيريا *E. faecalis*، في حين بلغت نسبة أقل تركيز مبيد للجراثيم لـ *S. mutans* و *S. aureus* و *P. gingivalis* 3200 ميكروغرام .مل-1، وللبكتيريا 1600 *E. faecalis* ميكروغرام.مل-1. الاستنتاجات: بالمقارنة مع الكلورهيكسيدين، فإن كيرسيتين بتركيز معين له نفس التأثير المضاد للبكتيريا، وهو ما يمكن أن يكون اكتشافًا جديدًا يمكن استخدامه كجزء من صناعة زراعة الأسنان كعنصر حيوي صحي حول الزرعات للسيطرة على الالتهابات والوقاية منها.