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COMPARING CHLORHEXIDINE MOUTHWASH WITH NATURAL MOUTHWASHES IN PREVENTION AND TREATING GINGIVITIS: A SYSTEMATIC REVIEW

Master's Thesis

Supervisor

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DEPARTMENT OF DENTAL AND ORAL PATHOLOGY

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Master's Thesis

The thesis was done

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Kaunas, 2017

EVALUATION TABLE OF THE MASTER'S THESIS OF THE TYPE OF SYSTEMIC REVIEW OF SCIENTIFIC LITERATURE

Evaluation: ....

Reviewer: ....
(scientific degree, name and surname)

Reviewing date: ....

No.	MT parts	MT evaluation aspects	Compliance with MT requirements and evaluation		
			Yes	**Partially**	**No**
1	**Summary (0.5 point)**	Is summary informative and in compliance with the thesis content and requirements?	0.3	0.1	0
2		Are keywords in compliance with the thesis essence?	0.2	0.1	0
3	**Introduction, aim and tasks (1 point)**	Are the novelty, relevance and significance of the work justified in the introduction of the thesis?	0.4	0.2	0
4		Are the problem, hypothesis, aim and tasks formed clearly and properly?	0.4	0.2	0
5		Are the aim and tasks inter-related?	0.2	0.1	0
6	**Selection criteria of the studies, search methods and strategy (3.4 points)**	Is the protocol of systemic review present?	0.6	0.3	0
7		Were the eligibility criteria of articles for the selected protocol determined (e.g., year, language, publication condition, etc.)	0.4	0.2	0
8		Are all the information sources (databases with dates of coverage, contact with study authors to identify additional studies) described and is the last search day indicated?	0.2	0.1	0
9		Is the electronic search strategy described in such a way that it could be repeated (year of search, the last search day; keywords and their combinations; number of found and selected articles according to the combinations of	0.4	0.1	0

		keywords)?			
10		Is the selection process of studies (screening, eligibility, included in systemic review or, if applicable, included in the meta-analysis) described?	0.4	0.2	0
11		Is the data extraction method from the articles (types of investigations, participants, interventions, analysed factors, indexes) described?	0.4	0.2	0
12		Are all the variables (for which data were sought and any assumptions and simplifications made) listed and defined?	0.4	0.2	0
13		Are the methods, which were used to evaluate the risk of bias of individual studies and how this	0.2	0.1	0

		information is to be used in data synthesis, described?			
14		Were the principal summary measures (risk ratio, difference in means) stated?	0.4	0.2	0
15		Is the number of studies screened: included upon assessment for eligibility and excluded upon giving the reasons in each stage of exclusion presented?	0.6	0.3	0
16	**Systemization and analysis of data (2.2 points)**	Are the characteristics of studies presented in the included articles, according to which the data were extracted (e.g., study size, follow-up period, type of respondents) presented?	0.6	0.3	0
17		Are the evaluations of beneficial or harmful outcomes for each study presented? (a) simple summary data for each intervention group; b) effect estimates and confidence intervals)	0.4	0.2	0
18		Are the extracted and systemized data from studies presented in the tables according to individual tasks?	0.6	0.3	0
19	**Discussion (1.4 points)**	Are the main findings summarized and is their relevance indicated?	0.4	0.2	0
20		Are the limitations of the performed systemic review discussed?	0.4	0.2	0

21		Does author present the interpretation of the results?	0.4	0.2	0
22	**Conclusions (0.5 points)**	Do the conclusions reflect the topic, aim and tasks of the Master's thesis?	0.2	0.1	0
23		Are the conclusions based on the analysed material?	0.2	0.1	0
24		Are the conclusions clear and laconic?	0.1	0.1	0
25	**Referenes (1 point)**	Is the references list formed according to the requirements?	0.4	0.2	0
26		Are the links of the references to the text correct? Are the literature sources cited correctly and precisely?	0.2	0.1	0
27		Is the scientific level of references suitable for Master's thesis?	0.2	0.1	0
28		Do the cited sources not older than 10 years old form at least 70% of sources, and the not older than 5 years – at least 40%?	0.2	0.1	0
Additional sections, which may increase the collected number of points					
29	**Annexes**	Do the presented annexes help to understand the analysed topic?	+0.2	+0.1	0
30	**Practical recommendations**	Are the practical recommendations suggested and are they related to the received results?	+0.4	+0.2	0
31		Were additional methods of data analysis and their results used and described (sensitivity analyses, meta-regression)?	+1	+0.5	0

32		Was meta-analysis applied? Are the selected statistical methods indicated? Are the results of each meta-analysis presented?	+2	+1	0
General requirements, non-compliance with which reduce the number of points					
33	**General requirements**	Is the thesis volume sufficient (excluding annexes)?		15-20 pages (-2 points)	<15 pages (-5 points)

34		Is the thesis volume increased artificially?	-2 points	-1 point	
35		Does the thesis structure satisfy the requirements of Master's thesis?		-1 point	-2 points
36		Is the thesis written in correct language, scientifically, logically and laconically?		-0.5 point	-1 points
37		Are there any grammatical, style or computer literacy-related mistakes?	-2 points	-1 points	
38		Is text consistent, integral, and are the volumes of its structural parts balanced?		-0.2 point	-0.5 points
39		Amount of plagiarism in the thesis.	>20% (not evaluated)		
40		Is the content (names of sections and sub- sections and enumeration of pages) in compliance with the thesis structure and aims?		-0.2 point	-0.5 points
41		Are the names of the thesis parts in compliance with the text? Are the titles of sections and sub-sections distinguished logically and correctly?		-0.2 point	-0.5 points
42		Are there explanations of the key terms and abbreviations (if needed)?		-0.2 point	-0.5 points
43		Is the quality of the thesis typography (quality of printing, visual aids, binding) good?		-0.2 point	-0.5 points
*In total (maximum 10 points):					

*Remark: the amount of collected points may exceed 10 points.

Reviewer's comments: _____

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Reviewer's name and surname   Reviewer's signature

TABLE OF CONTENTS

SUMMARY

Objective: Aim of systematic review was to search and analyze the publications related to selected topic and compare the efficacy, safety, antiplaque and anti-gingivitis properties of natural mouthwashes with chlorhexidine mouthwash. Also to find out how many mouthwashes from natural products can be used in prevention of gingivitis, which of them can be as effective as chlorhexidine mouthwash in treating of gingivitis and clarify whether the natural mouthwash is more effective than chlorhexidine.

Material and methods: A systematic review was carried out to identify relevant studies reporting data on comparing antiplaque and anti-gingivitis properties of natural mouthwashes with chlorhexidine mouthwash. The data was extracted from the selected articles that fulfilled all selection criteria. The following key words or their combinations were used during searching: chlorhexidine mouthwash, natural mouthwash, prevention gingivitis. The search was performed through PubMed/ MEDLINE, Wiley Online Library and was restricted to English language articles, published from 2012 to 2017.

Results. A total of 108 of articles were identified after initial search and 19 publications were enrolled in this systematic review.

Conclusion. This systemic review revealed that it is a big variety of natural mouthwashes that can be as effective or even better as chlorhexidine mouthwash in prevention and treating gingivitis. Also it was confirmed, that natural mouthwashes have a smaller amount of side effects than chlorhexidine. Taking into consideration that mouthwashes that now are commonly used for prevention and treatment of gingivitis are chemically based, expensive, have a lot of side effects, it is important to find out easily available, low-priced, effective natural mouthwash. It could help to reach better prevention and prevalence of oral diseases.

Key words: chlorhexidine mouthwash, natural mouthwash, prevention gingivitis.

Abbreviations:

CLX/ CHX – chlorhexidine; MW – mouthwash

PI- plaque index; VPI- visible plaque index

GI – gingival index; BLI / GBI - gingival bleeding index; MGI- modified gingival index

OHI- S - oral hygiene index-simplified

BA – biofilm accumulation; PD – pocket depth

INTRODUCTION

Periodontal disease is a polimicrobial oral infection elicited by a complex group of bacterial species. [1] Periodontal inflammation diseases is one of the main global oral health burdens and characterized by both infection and proinflammatory evens [2] and increase risk of developing subclinical atherosclerotic and coronary heart disease [3], rheumatoid arthritis [4]. This is the reasons for increased attention for prevention and treatment of this diseases.

People who have poor oral hygiene are in higher risk for oral diseases. To maintain good oral hygiene it is necessary to take good home-based care and do it regularly. Properly performed mechanical home biofilm control is the most important prevention strategy for periodontal diseases, but proper mechanical control is not performed effectively by the majority of the population, mostly because of lack of motivation and of manual dexterity. [5]

Oral microbiota of the mouth is the most diverse microbial community in the human body and plays a decisive role in the emergence and evolution of gingival pathology. Dental plaque, deposition of microorganisms embedded in extracellular matrix, initiates dental caries and periodontal disease. The bacteria that cause plaque are microorganisms that form the biofilm such as *Streptococcus Mutans* and other anaerobes (*fusobacterium* and *actinobacteria*), which adhere to the tooth surface when this process is started. Accumulation of the plaque around the teeth borders and gingiva, causes and inflammation of the tissue. A specific shift in the quantity and diversity of the microbial community developed on dental and mucosal surfaces, could lead to the occurrence of chronic inflammation mediated by the overproduction of pro-inflammatory cytokines. [6] Characteristics of gingivitis are red, puffy appearance of gums and bleeding when brushing or flossing. In early stages of gingivitis if the plaque is removed this process can be reversible. Removal of dental plaque by mechanical or chemical means is the key intervention in prevention of dental caries and gingivitis. [7]

Gingivitis is the mildest form of periodontal disease and it affects about 50% - 90% of adults worldwide. [8] In Lithuania there is no researches of periodontal diseases prevalence at state level. It is why we can only rely on regional studies. In Lithuanian regions periodontal disease affects about 95,7% in the adult population. [9] The best way for prevention of gingivitis is regular and well hygiene, and the best way of treatment in the start. Another very effective method of plaque removal and maintaining proper oral hygiene is with the use of antimicrobial mouthwashes.

In regards to mouthwashes there are two main types, firstly cosmetic and secondly therapeutic. There are therapeutic mouth rinses that help decrease and control gingivitis, bad breath and tooth

decay. Although has no mechanism of action in preventing or controlling plaque, thus making it only cosmetic. Therapeutic mouthwash, on the other hand, contains active ingredients that promote and support the reduction of gingivitis, bad breath, tooth decay and plaque. [10]

According to a comparable study between 0,2% and 0,12% chlorhexidine mouth rinse, it has been well known to be the gold standard of mouth rinses. A study was performed to analyze the efficiency of these concentrations on gingival indices and the level of dental staining. They confirmed that it is better to prescribe lower concentrations of chlorhexidine, because the higher the concentration is does not act more effective in controlling gingivitis and dental plaque. [11]

As mentioned before chlorhexidine is the gold standard although it comes with several drawbacks, changing color of teeth, irritation, mouth dryness, salivary stones. Thus finding the best alternative natural mouthwash is important. In literature it was found a big variety of natural products which can be used in making mouthwashes which has antimicrobial effect: neem, turmeric (curcumin), anacardium occidentale, terminalia chebula, aloe vera, magnolia extract, dedroponax morbitera leveille extract, blackberry extract, lemongrass oil, bacharis dracunculifolia, green tea, triphala, azadirachta indica, schinus terebinthitolius, matricaria chamomile, punica granatum, acacia arabica. Apart from these mentioned even mouthwashes made of coconut oil, honey, chitosan can act as a suitable replacement for chemical mouthwashes. After observing the natural mouthwashes such as Aloe vera, green tea, matricaria chamomile and etc., it can be said that they have major positive aspects, fewer side effects, lower cost and easy availability. [12]

Aim:

To search and analyze the publications related to selected topic and compare the efficacy, safety, antiplaque and anti-gingivitis properties of natural mouthwashes with chlorhexidine mouthwash.

Tasks:

1. To search, gather and evaluate available data for analysis according to the conclusion and exclusion criteria.

2. To determine variety of natural mouthwashes that can be used in prevention of plaque and gingivitis.

3. To identify which of the natural mouthwashes can be as effective in treating of gingivitis as chlorhexidine mouthwash.

4. To determine whether there is more effective mouthwash made from natural products compared to chlorhexidine.

1.SEARCH MATERIAL AND METHODS

1.1 Literature search strategy

Literature search for this systemic review was selected through PubMed/ MEDLINE, Wiley Online Library. In both databases variety number of articles can be found according the key word/ phrase that should be typed in the search box. Key words that were used: chlorhexidine mouthwash, natural mouthwash, prevention gingivitis. Databases were searched for English language articles, published from 2012 to 2017. This comprehensive search was designed to include any published articles that evaluated the effects of natural mouthwash compared to chlorhexidine mouthwash. In the search results it were found 108 publications (abstracts). If full articles were not accessible without purchasing, they were excluded. 38 articles were read and analyzed, of which 19 met the eligibility criteria with the subject of this review. After exclusions that have been made, articles related to the theme and fulfilled selection criteria were qualified and analyzed. One investigator carried out the selection and evaluation of articles.

According to the PRISMA guidelines, was conducted an electronic search using PubMed/MEDLINE, Wiley Online Library databases to locate articles about antiplaque and anti-gingivitis properties of natural mouthwashes compared to chlorhexidine. (Figure 1)

1.2. Inclusion and exclusion criteria

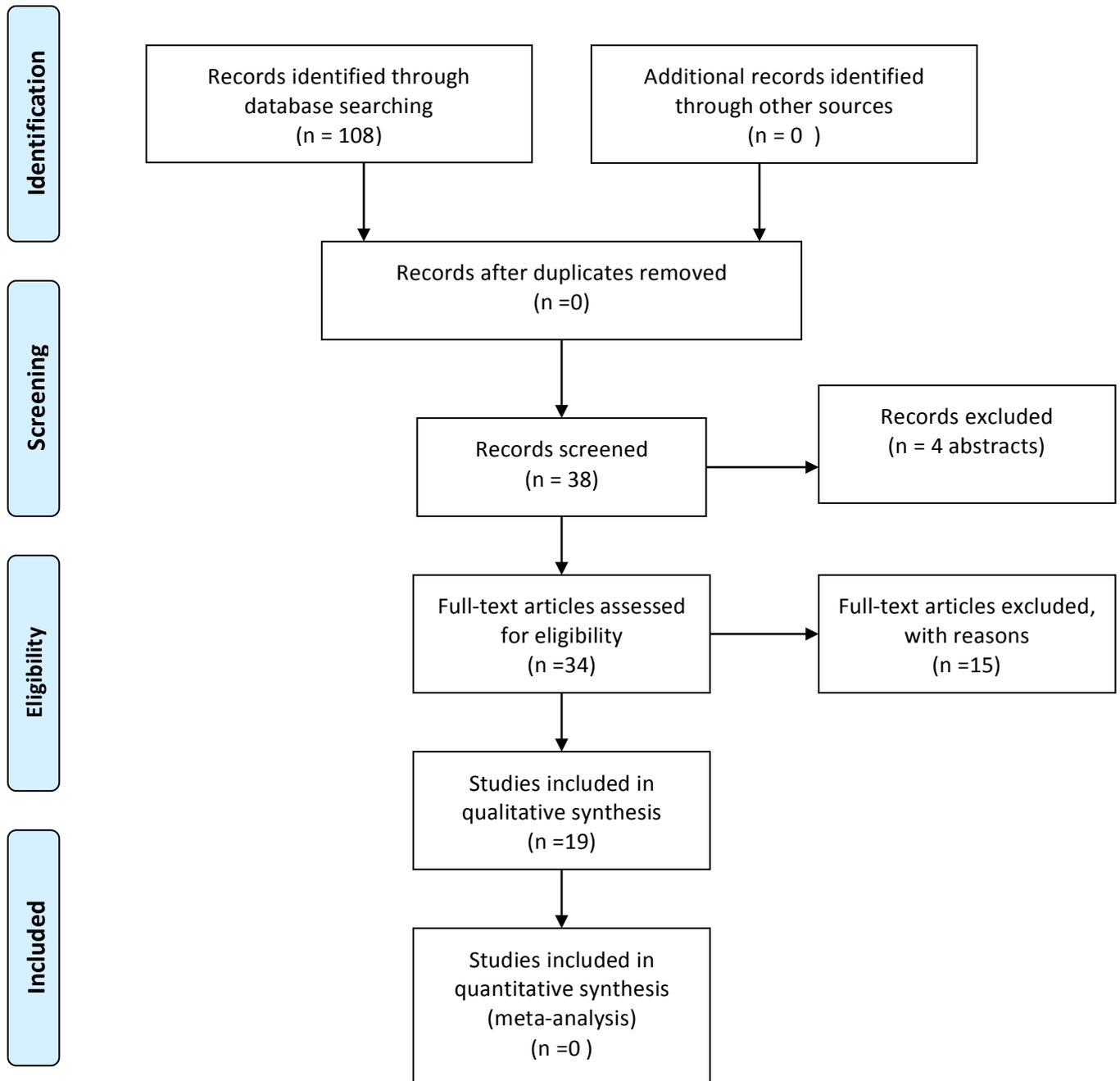### 1.2.1 Inclusion criteria for the selection were the following:

- Publications written in English language.

- Studies performed on humans only.

- Full text articles.

- Articles familiar to topic "Chlorhexidine and natural mouthwash".

- Articles that specify the mouthwash, not the other texture (gel, powder or etc.) for oral care.

- Articles where chlorhexidine mouthwash is compared with mouthwash from natural products for prevention and treating of gingivitis.

- Randomized controlled clinical trials or controlled clinical trials.

1.2.2 Exclusion criteria for the selection were the following:

 - Abstracts.

- Systematic review and review articles.

- Studies performed in laboratory.

- Studies where commercial essential oils compared to chlorhexidine.

Figure 1. PRISMA flow diagram illustrates by a flow chart the process of filtering.

Identification

Records identified through
database searching
(n = 108)

Additional records identified
through other sources
(n = 0)

Screening

Records after duplicates removed
(n =0)

Records screened
(n = 38)

Records excluded
(n = 4 abstracts)

Eligibility

Full-text articles assessed
for eligibility
(n =34)

Full-text articles excluded,
with reasons
(n =15)

Included

Studies included in
qualitative synthesis
(n =19)

Studies included in
quantitative synthesis
(meta-analysis)
(n =0)

2. SYSTEMIZATION AND ANALYSIS OF DATA

This systematic review included 19 articles published between 2012 and 2017. All 19 of included studies were randomized. The sample size of the studies ranged was from 30 to 390, while participant's age varied from 9 to 65 years old. The most common age groups were between 18-25 years. The most prevalent size of sample varied from approximately from 30 to 90 participants. Study duration was from 4 till 60 days, most common duration 21 days. Based on the literature, results focused on the following aspects: to determine variety of natural mouthwashes that can be used in prevention of plaque and gingivitis (Table 2); to identify which of the natural mouthwashes can be as effective in treating of gingivitis as chlorhexidine; review anti-inflammatory properties of analyzed natural products who can be effective in treating gingivitis (Table 3); to reveal the whether there are more effective mouthwash made from natural products compared to chlorhexidine.

Table 1. Main characteristics of analyzed studies.

Researchers	Number of subjects/ Age (years)/ Study duration	Evaluating by	Study details	Outcome
Gupta D. et al., 2014 [13]	108/ not given (students)/ 30 days	PI, GI	Group 1 = 4% Ocimum sanctum mouthwash Group 2 = 0.12% Chlorhexidine Group 3 = the placebo control group and saline water was given as the mouthwash	There was a significant decrease in the plaque and gingivitis in both the Ocimum sanctum and chlorhexidine groups at 15 days and 30 days ($P <$ 0.05). There was no significant difference between Ocimum sanctum based mouth rinse and chlorhexidine for any clinical parameters.
Mali A. M et al., 2012	60/15 years and above/ 21	PI, GI	Group A = 2% Chlorhexidine	The PI and GI were reduced during the study in both groups, but no statistically

[14]	days		Group B = 0,1% Turmeric mouthwash	significant difference was found between the two groups.
Gomes C. E. B. et al., 2016 [12]	30/18-32 years/ 30 days	PLI, BLI	Group 1 = 10% Anacardium Occidentale (AO) Linn. Group 2 = 0.12% Chlorhexidine Group 3 = the placebo control group	There was a significant reduction ($P < 0.05$) on plaque and gingivitis at day 30 in CLX ([PLI = 0.47 ± 0.16; -30%]; [BLI = 0.15 ± 0.09; -55.8%]) and AO ([PLI = 0.49 ± 0.21; -31%]; [BLI = 0.13 ± 0.10; -56.6%]) groups, but no statistically significant difference was observed among them ($P > 0.05$).
Balappanavar A. Y. et al., 2013 [15]	30/ 18-25 years/ 21 days	PI, GI, OHI-S, salivary pH	Group A = 0,2% Chlorhexidine Group B = 2% Neem Group C = 0,5% tea	Mean plaque and gingival scores were reduced over the 3 weesks trial period for experimental and control groups. Anti-plaque effectiveness was observed in all groups and the highest being in group C ($P < 0.05$). Neem and tea showed comparative effectiveness on gingiva better than chlorhexidine ($P < 0.05$). The salivary pH rise was sustained and significant in Group B and C compared to Group A.
Kaur H. et al., 2014	30/ 18-25 years/ 15 days	PI	Group A = 0,25% green tea catechin mouthwash	Green tea catechin MW and chlorhexidine MW have

[16]			Group B = 0,12% Chlorhexidine	comparable results in plaque reduction. But the difference between plaque scores, were not statistically significant ($P > 0.05$).
Radafshar G. et al., 2015 [17]	40/ 18-25 years / 28 days	PI, GI, GBI	Group A= green tea extract containing 1% tannin Group B = 0,12% Chlorhexidine	Significant in-group differences, but not between-group differences, were observed in all indices after 1 and 4 weeks compared to baseline.
Priya B. M et al., 2015 [18]	30/ 18-24 years/ 30 days	PI, GI, BI	Group A= green tea Group B = 0,12% Chlorhexidine	There was a significant decrease in plaque index, gingival index, and bleeding index in both the groups. However, green tea mouthwash resulted in a statistically significant decrease in bleeding index compared to chlorhexidine group. There was no significant difference in tooth and tongue stain in both the groups.
Vangipuram S. et al., 2016 [19]	390/ 18-40 years/ 30 days	PI, GI	Group 1 = Aloe Vera Group 2 = 0,12 % Chlorhexidine Group 3 = the placebo control group	There was significant reduction ($p<0.05$) in the mean scores of all the parameters with Aloe Vera and chlorhexidine group. No significant difference ($p<0.05$) was observed between Aloe Vera and

				chlorhexidine group.
Chandrahas B. et al., 2012 [20]	148/ 18-25 years/ 22 days	PI, MGI, BI	Group A = 100% Aloe Vera Group B = Placebo group Group C = 0,2% chlorhexidine	Mouthwash containing Aloe vera showed significant reduction of plaque and gingivitis but when compared with chlorhexidine the effect was less significant.
Kumar G. R et al., 2014 [21]	300/ not given/ 4 days	GI, PI	Group A = Aloe Vera Group B = 0,2% chlorhexidine Group C = Placebo group (saline water)	The results showed that Aloe vera mouth rinse is equally effective in reducing plaque as chlorhexidine compared to placebo. There was a significant reduction on plaque in Aloe vera and chlorhexidine groups and no statistically significant difference was observed among them (p>0.05).
Yetura S. K et al., 2015 [22]	90/ over 18 years/ 15 days	PI, GI	Group A = Aloe Vera Group B = chlorine dioxide Group C = chlorhexidine	A significantly higher reduction (plaque and gingival scores) was found in chlorhexidine when compared with the Aloe vera group.
Dany S. S et al., 2013	60/ 25-45 years/ 21 days	PI, GI	Group A = 0,25% lemongrass oil	Lemongrass oil mouthwash group showed highest reduction in GI and PI at

[23]			mouthwash Group B = oral prophylaxis Group C = chlorhexidine 0,2%	both 14th and 21st day, which was statistically significant (p≤0.05).
Rahimabadi M.S et al., 2016 [24]	80/ 20-65 years/ 14 days	GBI, MGI, PD, PI	Group A= Golnaar (Punica granatum) Group B = 0,2% Chlorhexidine	There were no significant differences between Golnaar and chlorhexidine in primary outcome measures except for modified gingival index for which Golnaar mouthwash had a superiority after 2 weeks when comparing with chlorhexidine (P= .039).
Goes P. et al., 2016 [25]	30/ 10-40 years/ 15 days	VPI, GBI	Group A = placebo Group B = 1% Matricaria chamomile L (MTC) Group C = chlorhexidine 0,12%	The CHX and MTC groups did not differ with respect to VPI index ($P > 0.05$). GBI did not differ between participants receiving CHX and MTC mouthwashes ($P > 0.05$).
Gupta D. et al., 2013 [26]	78/ 19-25 years/ 14 days	PI, GI	Group 1 = 10% Terminalia chebula Group 2 = 0,12% Chlorhexidine Group 3 = Saline water	The clinical parameters were significantly reduced by both chlorhexidine and Terminalia chebula mouth rinse although no significant difference was seen between the two groups (P > 0.05).

Mamgain P. et al., 2016 [27]	60/ >18 years/ 21 days	GI, PI	Group A = Tripfala and Ela Group B = 0,2% Chlorhexidine	No statistical significant difference for intergroup comparison was found.
Pradeep A. R. et al., 2016 [28]	90/ 25-40 years/ 60 days	PI, GI, OHIS, microbiological colony counts	Group I = Placebo mouthwash Group II = Triphala Group III = 0,12% Chlorhexidine	A significant difference was noticed with respect to reduction in PI, GI, OHI-S, and microbiologic counts in group I compared with groups II and III. However, no significant differences were found between groups II and III for any parameters at any time intervals.
Naiktari R. S. et al., 2014 [29]	120/ 20-65 years/ 15 days	PI, GI	Group A = Distilled water Group B = 0,2% Chlorhexidine Group C = Triphala mouthwash	No significant difference when the efficacy of triphala was compared with 0.2% chlorhexidine. However, a statistically significant difference was observed in PI and GI when both group B and group C were compared with group A and also within groups B and C, after 15 days ($P < 0.05$).
Freires I. D. A. F. et al., 2013, [30]	54 / 9-13 years / 10 days	GI, BA	Group 1 = 0,3125% Schinus terebinthifolius mouthwash (ST) Group 2 = 0,12%	It was found that both ST and CHX were able to significantly reduce GI levels after 10 days ($P <$

			Chlorhexidine	0.001) and there was no significant difference between them ($P > 0.05$). CHX was the only product able to significantly reduce BA after 10 days when compared to baseline ($P < 0.05$).

2.1. Variety of natural mouthwashes

One of this, systemic review objectives, is, to determine variety of natural mouthwashes that can be used in prevention of plaque and gingivitis. After analysis of 19 articles, it was found 12 types of natural mouthwashes that have been discovered to be effective in prevention of gingivitis. (Table 2)

All authors except one (Yetura S.K. et al., 2015), who researched Aloe Vera mouthwash, found out that these natural mouthwashes have equal or better effect on reducing plaque and gingivitis as chlorhexidine and can be good alternative to this chemical mouthwash.

Table 2. Variety of natural mouthwashes that can be used in prevention of gingivitis

Natural mouthwash	Origin of product	Effectiveness in comparing with chlorhexidine	Amount of studies
Ocimum sanctum (herbal tea)	Ocimum tenuiflorum (synonym Ocimum sanctum), commonly known as holy basil, is an aromatic plant in the family Lamiaceae which is native to the Indian subcontinent and widespread as a cultivated plant throughout the Southeast Asian tropics.	Equally effective in reducing plaque and gingivitis. [13]	1

Turmeric 	Turmeric is a rhizomatous herbaceous perennial plant (Curcuma longa) of the ginger family, Zingiberaceae. It is native to southern Asia.	Have comparable anti-plaque, anti-inflammatory and anti-microbial properties. [14]	1
Anacardium occidentale 	Anacardium occidentale (AO) Linn. (cashew), a member of the family Anacardiaceae and presently cultivated in many regions of the world, is a tropical tree originally indigenous and commonly found in the Northeast of Brazil.	Was effective antiplaque, anti-gingivitis agent in the same way as chlorhexidine. [12]	1
Neem 	Azadirachta indica, also known as Neem is a tree in the mahogany family Meliaceae. It is one of two species in the genus Azadirachta, and is native to India and the Indian subcontinent including Nepal, Pakistan, Bangladesh, and Sri Lanka. Neem trees now also grow in islands located in the southern part of Iran. Its fruits and seeds are the source of neem oil.	Better effectiveness on gingiva. [15]	1
Green tea 	Green tea is made solely with the leaves of *Camellia sinensis* that have undergone minimal oxidation during processing. It is a member of the Theaceae family and native to China and southern Asia, is cultivated in many countries around the world, including Iran.	Equally effective and one study showed better effectiveness on gingiva. [15,16,17,18]	4
Aloe vera 	Aloe Vera is a succulent, cactus like plant belonging to the Aloe cease family (subfamily of the Asphoelaceae).	Equally effective, but one study showed significantly higher reduction in plaque	4

		and gingival scores with chlorhexidine then with Aloe vera. [19,20,21,22]	
Lemongrass oil	Lemongrass belongs to the section of *Andropogan* called *Cymbopogam* of the family *Germineae;* and from it the lemongrass oil is extracted. It grows in tropical and subtropical regions, such as in India, Cambodia, Malaysia, Indonesia, Sri Lanka, China, and Guatemala.	Showed higher reduction in plaque index and gingival index. [23]	1
Punica granatum var pleniflora (Golnaar)	Punica granatum var. pleniflora (Golnaar in Persian) is a subspecies of pomegranate. The Golnaar is the male plant of pomegranate that only has the blooms with no fruit generation.	Equally effective in reducing plaque and gingivitis. [24]	1
Matricaria chamomile	Matricaria chamomilla wild chamomile or scented mayweed, is an annual plant of the composite family Asteraceae.	Equally effective in reducing plaque and gingivitis. [25]	1
Terminalia chebula Extract	Terminalia chebula, commonly known as black or chebulic myrobalan, is a species of Terminalia, native to South Asia from India and Nepal east to southwest China (Yunnan), and south to Sri Lanka, Malaysia, and Vietnam.	The same effectiveness reducing microbial plaque, gingival inflammation and neutralizing salivary pH. [26]	1

Triphala and Ela	Triphala ("three fruits") - is an Ayurvedic herbal rasayana formula consisting of equal parts of three myrobalans, taken without seed: Amalaki (Emblica officinalis), Bibhitaki (Terminalia belerica) and Haritaki (T. chebula).	Equally effective in reducing plaque and gingivitis in all three studies. [27,28,29]	3
Schinus terebinthifolius	Schinus terebinthifolius, popularly known as Brazilian pepper tree, is native to South America and belongs to the plant kingdom, division Tracheophyta, class Agnoliopsida, order Sapindales, and family Anacardiaceae.	There was no significant difference between them reducing gingiva index levels. [30]	1

2.2 Natural mouthwashes that are as effective in treating gingivitis as chlorhexidine mouthwash

To determine which mouthwashes can be alternative replacement for chlorhexidine in treating gingivitis, in 14 studies [12, 14, 17-19, 22-30] choosing (inclusion) criteria for participants invited to participate, was – subjects with gingivitis. Two of these studies participants were undergoing orthodontic treatment [22, 25] and in one study - patients with diabetes mellitus [24].

Evaluation of the results for scoring of supra-gingival plaque was done by Quigley–Hein plaque index and for scoring of gingival inflammation (gingivitis) by Gingival Index of Loe and Silness. The most amount of authors were using this PI and GI, so results can be compared. Thus, according to these researches [14, 17-19, 23, 24, 26-30], PI and GI were reduced during the studies, but no statistically significant differences were found in comparing natural mouthwash with chlorhexidine. Therefore, it can be said that Turmeric, green tea (two authors confirmed that: Radafshar G. et al., 2015; Priya B. M et al., 2015); Aloe Vera, Lemongrass oil, Terminalia chebula extract, Triphala (two authors confirmed that: Mamgain P. et al., 2016; Pradeep A.R. et al., 2016), Schinus

terebinthifolius mouthwashes can be used as alternative to chlorhexidine mouthwash in treating gingivitis. Even study of Rahimabadi M.S. et al. [24] with patients who have diabetes mellitus, proved that mouthwash made of natural product (in this case Punica granatum var pleniflora (Golnaar)) can be as effective as chlorhexidine in treating gingivitis. Two studies with orthodontic patients also proven that Aloe vera and Matricaria chamomile mouthwashes can be suitable replacement for chlorhexidine. [22, 25]

Although chlorhexidine mouthwash is considered the gold standard for biofilm control and gingivitis treatment, it has side effects such as allergic reactions, burning sensation, change in taste, supra-gingival calculus deposition, mucosal erosion and tooth staining. In analyzed studies revealed that people who precipitant in researches did not reported side effects or reports were lower compared to chlorhexidine. [12, 14, 17, 25, 26, 29]

Anti-inflammatory properties of analyzed natural products that can be effective in treating gingivitis are shown in Table 3.

Table 3. Anti-inflammatory properties of natural products

Natural product	Mode of action
Turmeric	Turmeric has definite antimicrobial property. Turmeric influence BAPNA values (permits the detection of microorganisms possessing trypsin-like enzymes such as *T.forsythensis, Treponema denticola* and *P. gingivalis*). [14]
Green tea	The main active ingredients responsible for the effects of green tea are polyphenols. Plant polyphenols are commonly known as tannins, which have bacteriostatic and bactericidal activity against *Streptococcus mutans, Staphylococcus aureus* and it is methicillin resistant strains, as well as multidrug resistant *Pseudomonas aeruginosa*. Green tea is an antioxidant and has anti-inflammatory properties. Antioxidants play an important role in the control of gingival inflammation by inhibiting the oxidative stress. [17, 18]

Aloe vera	Aloe vera has anti-microbial potential against *Streptoccocus pyogenes* and *Streptococcus faecalis*. Three aloesin derivatives from aloe (isorabaichromone, feruoylaloesin, and p-coumaroylaloesin) showed potent free radical and superoxide anion-scavenging activities. [19]
Lemongrass oil	One of the non-enzymatic antioxidants found in every cell of the body is Glutathione, also known as sulfhydryl glutathione (GSH) is important in the role of protection against oxidative stress. Gargling with 2% and 4% concentrations of lemongrass essential oil increases salivary GSH levels in moderate gingivitis patients. So it can speed-up gingivitis healing process. In inflammatory process like gingivitis GSH not only acts as an anti-oxidant but also an immune function modulator. [23]
Punica granatum (Golnaar)	Punica granatum has potential mechanisms such as providing better perfusion of the gingival tissue and hardening it, affecting plaque bacterial flora, having anti-inflammatory effect on the gum, exerting antioxidative influence, reversing back the swollen and edematous gingiva to normal conditions. It may be effective for gingival and periodontal impairments. [24]
Terminalia chebula	Terminalia chebula has antibacterial and antiviral effect against *Helicobactor pylori*, *Xanthomonas campestris pv. citri* and *Salmonella typhi*. Terminalia chebula contains almost 32%–34% tannins and other minor constituents are polyphenols such as corilagin, galloyl glucose, punicalagin, terflavin A and maslinic acid. Tannins release gallic acid which have an antimicrobial and astringent effect. [26]
Triphala	Triphala has a strong inhibitory effect on polymorphonuclear leukocyte-type matrix metalloproteinase, which plays an important role in periodontal tissue destruction, therefore it suggests effectiveness in treatment of periodontal diseases. [28]

Schinus terebinthifolius	The antimicrobial activity of the hydroalcoholic extract of S. terebinthifolius was evaluated against *S. mutans*, *S. mitis*, *S. sobrinus*, *S. sanguis,* and *Lactobacillus casei*. On these microorganisms bacteriostatic and bactericidal activity was confirmed. [30]

2.3 More effective mouthwash made from natural product compared to chlorhexidine

In this systematic review was set two studies [15, 23] where natural product showed better effectiveness on gingiva.

In the study where were compared the effectiveness of 0.5% tea, 2% neem, and 0.2% chlorhexidine mouthwashes on oral health for 3 week trial anti-plaque effectiveness was observed in all groups and the highest being in group of tee mouthwash ($P < 0.05$). Neem and tea showed comparative effectiveness on gingiva better than chlorhexidine (P < 0.05). [15]

The other study efficacy of 0.25% Lemongrass oil mouthwash revealed that lemongrass oil mouthwash showed highest at both 14th and 21st day, which was statistically significant (p≤0.05). [23]

3. Discussion

Variety of carried out studies revealed a big amount of natural mouthwashes, which can be suitable replacement for chlorhexidine mouthwash and can be used in therapeutic manner for prevention and treating gingivitis.

A lot of mouth rinses are available for the purpose to prevent and treat gingivitis and chlorhexidine has been proved as the most effective chemical agent in plaque control. Chlorhexidine is an antimicrobial agent and has high inhibitory effect on plaque formation and gingivitis. However, long term daily use of it is not recommended because it has been associated with a number of local side effects such as brownish discoloration of the teeth, restorative materials and the dorsum of the tongue in addition to interference with taste. [31] According to Najafi M.H. et al. comparative study of 0.2% and 0.12% digluconate chlorhexidine mouth rinses this two concentrations did not differ significantly from each other and also was found that the 0.2% chlorhexidine caused much more

staining on the teeth than 0.12%. [11] This systematic review shows that authors more often choose in researches to use 0,12% of chlorhexidine for comparing with natural mouthwashes.

Twelve different types of natural mouthwashes was observed in this review and all of them showed good effective against the plaque and gingivitis comparing to chlorhexidine. Aloe vera and green tea were studied more. The foundlings in this systemic review confirms findings of Sarin S. et al. [32] and Karim B. et al. [33] that mouthwash containing 2% of green tea, or Aloe vera mouthwash owns ability in reducing periodontal indices. Green tea mouthwash could be a safe alternative to chlorhexidine in conditions, such as inflammatory gingival disease in pregnancy or childhood, also for handicapped or people living in elderly care institutions. [15]

Of the articles selected for this systematic review it can be said that Turmeric, green tea, Aloe Vera, Lemongrass oil, Terminalia chebula extract, Triphala, Schinus terebinthifolius mouthwashes can be used as alternative to chlorhexidine mouthwash in treating gingivitis. Study of Rahimabadi M.S. et al. [24] with patients who have diabetes mellitus, proved that mouthwash made of natural product Golnaar can be as effective as chlorhexidine in treating gingivitis, also two studies with orthodontic patients [22, 25] also proved that Aloe vera and Matricaria chamomile mouthwashes can be suitable replacement for chlorhexidine. According to Aspalli S. et al. [34] herbal mouthwash is effective in treatment of plaque-induced gingivitis and can be effectively used as an adjunct to mechanical therapy and it has less side effects. The conclusion can be done that natural mouthwashes can be used in treating gingivitis also this systemic review confirms that they have a smaller amount of side effects.

In this review were two studies [15, 23] where it was discovered three types of natural mouthwashes (green tea, Azadirachta indica (neem), Lemongrass oil) that showed better reduction in gingival and plaque indexes compared to chlorhexidine. Dhingra K, Vanda K.L. [35] confirmed that neem mouthwash was as effective as chlorhexidine mouthwash in reducing plaque and gingival inflammation in gingivitis patients.

One of the findings of this study was that the studies that compared natural mouthwashes with chlorhexidine mostly take place in India and Brazil, in my opinion mainly because the alternative medicine is more popular there and they are more interested in finding new product as alternative to chemical mouthwash chlorhexidine.

Conclusion

This systemic review revealed that it is a big variety of natural mouthwashes that can be as effective or even better than chlorhexidine mouthwash in prevention and treating gingivitis. Also it was confirmed that natural mouthwashes have a smaller amount of side effects than chlorhexidine.

Taking into consideration that mouthwashes that now are commonly used for prevention and treatment of gingivitis are chemically based, expensive, have a lot of side effects, it is important to find out easily available, low-priced, effective natural mouthwash. It could help to reach better prevention and prevalence of oral diseases.

It is why, further clinical studies need to be done to compare natural mouthwashes with chlorhexidine and get more evidence about the efficacy, safety, antiplaque and anti-gingivitis properties.

Practical recommendations

Recommendations for doctors would be to prescribe in case of inflammatory gingival disease for children, pregnant woman, handicapped person, for people who live in elderly care institutions or for patients who have to use mouthwash for a longer period of time, natural mouthwash (for example Aloe vera or green tea) instead of chemical mouthwash chlorhexidine.

The study results supplement the knowledge on the natural mouthwash bactericidal activity and enable to create plan for timely prevention and treatment of inflammation disease of periodontium.

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