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SYSTEMATIC REVIEW

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Antibacterial Efficacy of Conventional Versus Herbal Products on *Streptococcus mutans* in Adult Population- a Systematic Review & Meta-analysis

Eficácia antibacteriana de produtos convencionais e fitoterápicos frente a *Streptococcus mutans* em adultos - uma revisão sistemática e meta-análise

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ABSTRACT

Background: Dental caries is challenging infectious disease, which is wide spread and difficult to control. Although it's multifactorial, microorganisms especially cariogenic *Streptococcus mutans* plays a wide role in initiation and progression of dental caries. **Objective:** The present review mainly aimed to evaluate and assess the antibacterial efficacy of herbal versus conventional products on *Streptococcus mutans*. Data Sources: A search was execute in electronic database (i.e., PUBMEDCENTRAL, COCHRANE, LILAC, SCIENCEDIRECT, GOOGLE SEARCH) using following search terms alone and in combination by means of PUBMED search builder from January 1990 up to July 2019. Study Eligibility Criteria: Studies were stipulate if they met the following criteria: In vivo studies comparing herbal and conventional products on anticariogenic or antibacterial activity on *Streptococcus mutans* were selected. Participants and Intervention: Adult patients aged from 18-65 years with dental caries undergoing intervention of herbal products. Study Appraisal and Synthesis **Material and Methods:** Out of 225 studies collected from databases, only 6 studies were included and other 6 were collected by hand search. Finally 12 included studies were analyzed out of which 5 studies were considered for meta-analysis. **Results:** The results unveil that natural

RESUMO

Introdução: A cárie dentária é um desafio para as doenças infecciosas, que são amplamente disseminadas e de difícil controle. Embora seja multifatorial, os microrganismos cariogênicos, em especial o *Streptococcus mutans*, desempenham um amplo papel na iniciação e progressão da cárie dentária. **Objetivo:** A presente revisão teve como objetivo principal avaliar a eficácia antibacteriana de produtos fitoterápicos em comparação com produtos convencionais frente a *Streptococcus mutans*. Os dados foram obtidos através de uma pesquisa executada em um banco de dados eletrônico (PUBMEDCENTRAL, COCHRANE, LILAC, SCIENCEDIRECT, GOOGLE SEARCH) usando termos isoladamente ou associados, por meio do construtor de pesquisa PUBMED, de janeiro de 1990 a julho de 2019. Foram selecionados estudos que atendessem aos seguintes critérios de elegibilidade: estudos in vivo comparando produtos à base de plantas e produtos convencionais sobre a atividade anticariogênica ou antibacteriana de *Streptococcus mutans*. Os participantes envolvidos consistiam de pacientes adultos de 18 a 65 anos com cárie dentária submetidos a intervenção de produtos fitoterápicos. **Material e métodos:** de 225 estudos coletados de bancos de dados eletrônicos, apenas 6 estudos foram incluídos e outros 6 foram selecionados por pesquisa manual. Finalmente, 12 estudos incluídos foram analisados, dos quais 5 foram considerados para meta-análise. **Resultados:** Os resultados revelaram que os

products exerted virtually homogeneous antibacterial effect against *Streptococcus mutans* when compared with the counterpart. **Limitations:** Review was assessing on patients with dental caries and studies previously assessed did not mention about the caries risk. Prevalence varies based on caries risk assessments. Study was concentrating only on single species *Streptococcus mutans*. But ideally caries is multifactorial. **Conclusion:** Although natural products were effective, the present systematic review does not furnish concrete evidence to a show increased antibacterial efficacy of natural products as compared to conventional products.

KEYWORDS

Antibiotics; Chlorhexidine; Dental caries; Herbal; *Streptococcus mutans*.

produtos naturais exerceram efeito antibacteriano homogêneo contra o *Streptococcus mutans* quando comparados com a contraparte. **Limitações:** A revisão avaliou pacientes com cárie dentária e os estudos prévios não mencionavam o risco de cárie. A prevalência varia com base nas avaliações de risco de cárie. O estudo se concentrou apenas em uma única espécie de *Streptococcus mutans*, mas a cárie dentária é de origem multifatorial. **Conclusão:** Embora os produtos naturais tenham sido eficazes, a presente revisão sistemática não fornece evidências concretas para mostrar um aumento da eficácia antibacteriana dos produtos naturais em comparação com os produtos convencionais.

PALAVRAS-CHAVE

Antibióticos; Clorexidina; Cárie dentária; Ervas, *Streptococcus mutans*.

INTRODUCTION

Dental caries is a dynamic phenomenon, resulting in the localized dissolution and destruction of dental hard tissues, by acidic byproducts, resulted from bacterial fermentation of carbohydrates [1]. Ecological plaque hypothesis states the important role of microbes as a key factor for dental caries causation [2]. Although caries is multifactorial, the main causative etiological factors include bacteria such as Streptococcus mutans and Lactobacillus [3].

Dental caries is ubiquitous in nature. It results from the interaction of the dietary constituents with the specific causative microbe [1]. Ideally, Plaque serves as a reservoir providing the homeostatic environment suitable for the destructive consequence [2]. Dental plaque transforms to a cariogenic plaque biofilm, once the bacteria tends to colonize on the surfaces of the substrate [2].

Streptococcus mutans are highly acidogenic and acid tolerant [4,5,6]. They serve as a key contributor for the caries progression [4]. These bacteria utilize the dietary sucrose, to synthesize the larger amounts of extracellular polysaccharides, followed by initial substrate adherence using glucan [4]. It is believed that, reducing the mass of Streptococcus mutans in the dental biofilm could lower the incidence of dental caries [7]. So, disengagement of Streptococcus mutans bacteria by usage of anti-adhesion agents without affecting their viability might serve as a valuable aid in clinically reducing the causative organisms at the root level [7].

Current caries combating strategies concentrate on usage of broad-spectrum antimicrobials for therapeutic advantage [8]. Although, they have a beneficial effect in short span, they impose bad impact on long run. Resistance of the microorganisms to antibiotics is the current issue that has to be addressed [9]. There is a growing evidence suggesting that the frequent usage of antibiotics induces resistance and threatens the effectiveness of the treatment [9,10].

Literature favors a wide range of natural plant extracts exhibiting antimicrobial properties and therapeutic benefits [11,12]. Considering this fact, many clinicians have shifted their interest

towards exploring the natural plant extracts [11]. Especially in dentistry, interest towards the usage of herbal products has increased.

Streptococcus mutans and Lactobacillus are the major microbes involved in the decalcification and tooth decay [13]. Ideally the caries combating strategies includes both mechanical and chemical plaque controlling methods, to prevent the disease progression [14]. So, basic mechanical plaque controlling methods alone may not be sufficient or effective to remove the cariogenic plaque. Adjunctive aids including chemical plaque controlling methods aid in better plaque removal [14].

So, considering all these facts, the present review was done to exploit and compare the benefits of various herbal formulations in reducing Streptococcus mutans levels in adult population.

METHODS

Rationale of the Systematic review

The aim of this systematic review was to assess the anti-bacterial effects of herbal products with the compared conventional product against Streptococcus mutans in adult population.

OBJECTIVES

The present systematic review included the articles published on both conventional versus herbal products used for management of caries associated bacteria. Search was carried out using multiple terms including various tooth-pastes and mouth washes from January 1990 to July 2019. This is a first ever study which concentrated on the clinical trials evaluated mainly the herbal and conventional tooth-pastes and mouthwashes on reducing the Streptococcus mutans levels in patients with dental caries.

PICO Question

Do herbal products bring about noteworthy antibacterial activity and reduction of Streptococcus mutans from saliva juxtapose to conventional products?

PICO Analysis

- Population - Adult patients with dental caries
- Intervention - Herbal products
- Comparison - conventional products
- Outcome - Reduction in Streptococcus mutans

Protocol for Registration:

The present study was registered and reviewed by the ethical committee of institutional Ethical Committee prior to the start of the research.

Eligibility Criteria:

Types of Studies

Randomized clinical trials, comparative clinical trials, prospective clinical trials in which natural and conventional tooth-pastes and mouthwashes have been compared.

Types of Participants

Patients between 18-70 years of age with dental caries.

Types of Interventions

Herbal products and conventional products.

Types of Outcome Measures

Antibacterial efficacy against Streptococcus mutans.

Exclusion Criteria

The following studies were excluded,

- In vitro studies
- Animal studies
- Pediatric studies
- Review articles

Information Sources

For identification of studies included or considered for this review, detailed search strategies were developed for the database searched. The search was carried out from January 1990 to July 2019. All possible databases were searched and for precise selection of studies hand search were also carried out by the assessors involved in the search.

Searched Databases

- PubMed
- PubMed Advanced Search
- SCIENCE DIRECT
- MEDLINE
- Google search

Language

Full text articles in English were only selected.

Hand Search

The following journals was hand searched

- Journal of Conservative dentistry
- Journal of dental research
- World Journal of Dentistry
- Journal of international society of preventive and community dentistry.
- Journal of operative dentistry and endodontics.
- Journal of Islamic dental association of IRAN.
- Journal of oral and maxillofacial pathology.
- Journal of Ayurveda and holistic medicine.

SEARCH

Search was carried out in electronic database (i.e., PUBMEDCENTRAL, COCHRANE, LILAC, SCIENCEDIRECT, and GOOGLE SEARCH) using following search terms alone and in combination by means of PUBMED search builder from January 1990 up to July 2019.

Various "search terms" or "key words" were used to execute the pubmed search. The searched terms were: "Dental decay", "Dental caries", "Human teeth", "enamel caries", "dentinal caries", "proximal caries", "cervical caries", "enamel caries", "acute caries", "mouthwashes and tooth pastes" including various herbal and conventional products such as: "acacia nilotica", "chitosan", "ginger", "baboon", babool", "tulsi", "blood root", "shiitake mushroom", "Punica granatum", "pomegranate", "pomegranate peel extract", "emblica officinalis", "terminalia chebula", "triphala", "licorice", "camellia sinensis", "oolong tea", "black tea", "green tea", "azadiracta Indica", "propolis", "neem", "garlic", "cacao bean extract", "cranberry", "natural products", "herbal", "plant extracts", "conventional products", "0.2% chlorhexidine, "polyvinyl pyrrolidine", "anti-inflammatory", "0.12% chlorhexidine", "analgesic", "benzocaine", "chlorhexidine", "0.2% chlorhexidine", "cetylpyridinium chloride", "triclosan", "betadine", "xylitol", "flouride", "sodium flouride", "0.5% sodium flouride", "antimicrobial", "antibacterial", "anticariogenic", "colony count", "colony forming units", "S.mutans", "Streptococcus mutans", "Streptococcus mutans reduction", "microbial count", "invivo", "clinical trial", "randomised clinical trial", "randomised controlled clinical trial", "clinical study", "invivo study".

Variables of interest (Table I) of the present systematic review were to assess the antimicrobial efficacy and anticariogenic activity of herbal agents against conventional agents on Streptococcus mutans in adult population.

Table I - Variables of Interest.

S.No	Variables of Interest
1	Antibacterial efficacy and anticariogenic activity

Study Selection

The search identified 258 publications out of which 32 duplicates were removed and 200 were excluded after title search. 26 Full text articles were obtained for studies and evaluated. After evaluation, 13 were excluded (Table II) based on inclusion and exclusion criteria. Finally, 6 were included based on the aforesaid criteria. Following hand search, 6 articles were included as it satisfied the inclusion and exclusion criteria. Therefore, a total of 12 publications fulfilled all criteria for inclusion (Chart 1). The above analysis was done by two independent reviewers and incase of disagreement, consensus was reached after discussion with a third reviewer.

Chart 1 - PRISMA Flowchart.

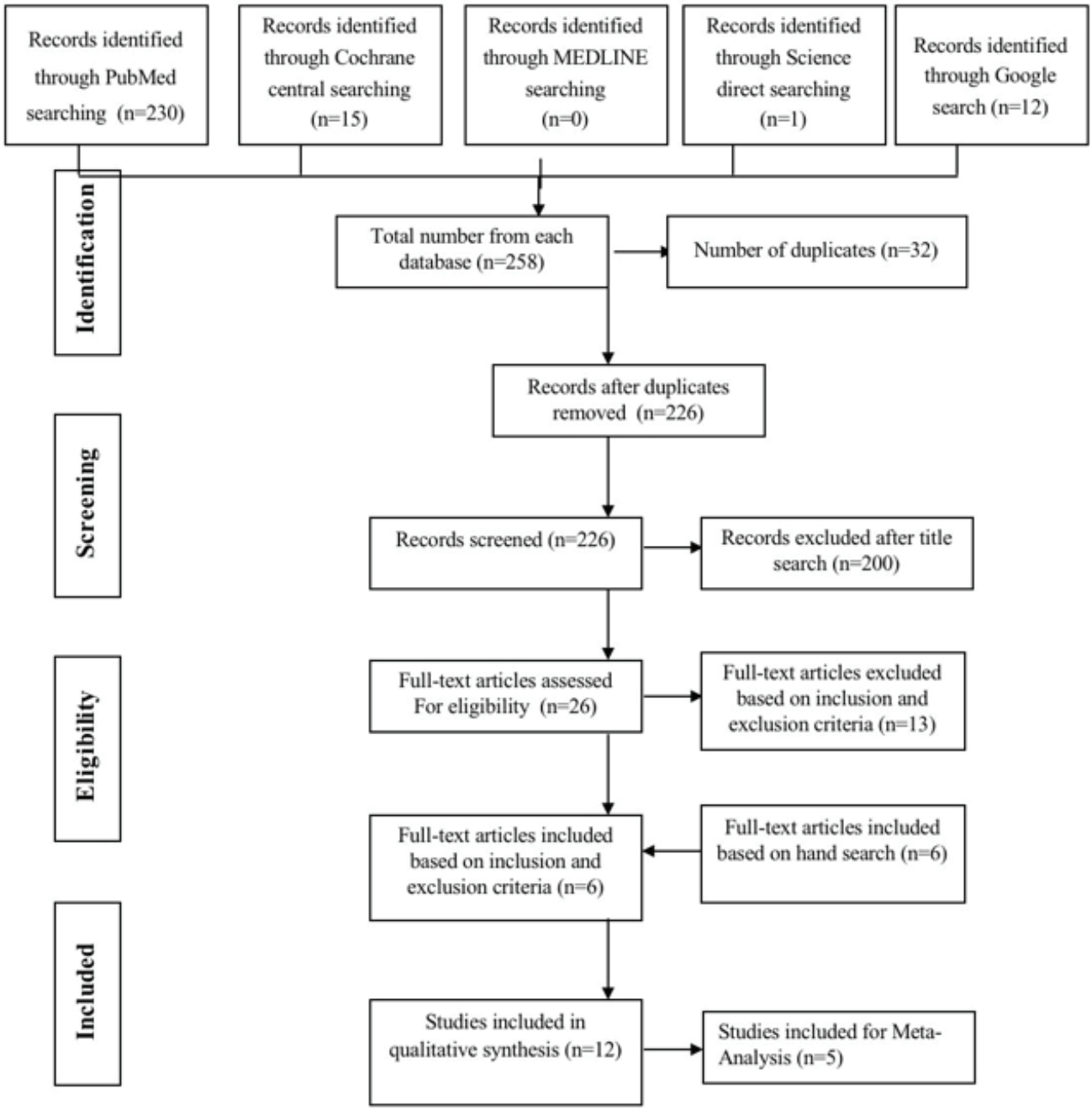


Table II - Charecteristics of Excluded Articles.

S.No	AUTHOR	YEAR	REASON FOR EXCLUSION
1	Mohankumar KP et al. [15]	2013	In vitro study
2	Chatterjee A et al. [16]	2017	Irrelevant
3	Namiranian H et al. [17]	2012	Irrelevant
4	Megalaa N et al. [18]	2018	Irrelevant
5	Nayak SS et al. [19]	2012	Irrelevant
6	Agarwal P et al. [20]	2011	Irrelevant
7	Hegde RJ et al. [21]	2017	Irrelevant
8	Yoshihara A et al. [22]	2001	Irrelevant
9	Malhotra N et al. [23]	2001	In vitro study
10	Kulkarni VV et al. [24]	2003	Irrelevant
11	Jauhari D et al. [25]	2015	Irrelevant
12	Waly NG [26]	1995	Irrelevant
13	Ullsfoss BN et al. [27]	1994	Irrelevant
2	Chatterjee A et al. [16]	2017	Irrelevant

Data Collection Process and Data Items

The quality assessment of included trails was undertaken independently as a part of data extraction process, where assessment was based on four main quality criteria, which included: method of randomization, allocation concealment, outcome assessor blinding and completeness of follow up. Other methodological criteria included presence or absence of sample size calculation, comparability of groups at the start, clear inclusion and exclusion criteria.

Risk of Bias of Individual Studies

Risks of bias of included studies were assessed using Cochrane Risk of Bias assessment tool based on major and minor assessment criteria's. No risk of bias across the studies included in the present systematic review.

Synthesis of Results & Additional Analysis

Among the 12 included studies, [7,28-38] only five [7,30,32,36,37] were considered for meta-analysis. Only studies, which provided baseline and post-analysis data (Mean & S.D), were only considered. Meta-analysis was not possible for the studies [28,29,31,33,34,35,38] interpreted the Streptococcus mutans count in terms of percentage reduction.

Risk of Bias in Included Studies

The assessments for the four main methodological quality items are shown in table. The study was assessed to have a "High risk" of bias if it did not record a "Yes" in three or more of the four main categories, "Moderate" if two out of four categories did not record a "Yes", and "Low" if randomization assessor blinding and completeness of follow – up were considered adequate.

RESULTS

Study Selection

The purpose of this review is to evaluate the antibacterial efficacy of natural products versus conventional products against Streptococcus mutans (Table I).

The search identified 258 publications out of which 32 duplicates were removed and 200 were excluded after title search. 26 Full text articles were obtained for studies and evaluated. After evaluation, 13 were excluded (Table II) based on inclusion and exclusion criteria. Finally, 6 were included based on the aforesaid criteria. Following hand search, 6 articles were included as it satisfied the inclusion and exclusion criteria. Therefore, a total of 12 publications fulfilled all criteria for inclusion (Chart 1).

In the present systematic review, all 12 articles included were randomized controlled trials which compared the antibacterial efficacy of natural and conventional products by quantitative analysis using microbial culture method (Colony forming units) (Table III), (Table IV), (Table V).

Table III - General Information of Selected Articles.

S.No	Author	Year	Study Design	Sample Size	Techniques Used	Method of Evaluation
1	Khairnar MR et al. [7]	2015	In Vivo study	N=50 Group 1 (n=25) – Chlorhexidine Group 2 (n=25) – Cranberry	Quantitative analysis using microbial culture method (Colony forming units)	Paired t-test for intra-group comparison for evaluation of *Streptococcus mutans* CFU count, unpaired t-test for intergroup comparison for difference in reduction
2	Botelho MA et al. [28]	2009	In vivo study	N=55 Group 1 (n=27) – Essential oil Group 2(n=28) – 0.12% chlorhexidine	Quantitative analysis using microbial culture method (Colony forming units)	Fisher's exact test and Mann-Whitney U-test, Wilcoxon test
3	Srinagesh J et al. [29]	2011	In vivo study	N=57 Group 1 (n=18) – 6% triphala Group 2(n=19) – 0.2% chlorhexidine Group 3 (n=20) – Plain water	Quantitative analysis using microbial culture method (Colony forming units)	ANOVA, post hoc test
4	Srinagesh J et al. [30]	2012	In vivo study	N=60 Group 1 (n=20) – 6% triphala Group 2(n=20) – 0.2% chlorhexidine Group 3 (n=20) – Plain water	Quantitative analysis using microbial culture method (Colony forming units)	ANOVA, post hoc test
5	Velmurugan A et al. [31]	2013	In Vivo study	N=45 Group 1 (n=15) - 20% aqueous extract of T. chebula Group 2 (n=15) - 20% aqueous extract of E. officinalis Group 3 (n=15) – 0.2% Chlorhexidine	Quantitative analysis using microbial culture method (Colony forming units)	One way ANOVA, Post-hoc Tukey test.
6	Sam JE et al. [32]	2016	In vivo study	N=100 Group 1 (n=25)- fluoride tooth paste and mouth wash Group 2 (n=25)- chlorhexidine tooth paste and mouth wash Group 3 (n=25)- herbal tooth paste and mouthwash(false black, pepper, Indian gum Arabic, neem,pomegranate,triphala) (Himalya complete care) Group 4 (n=25)- xylitol tooth paste and mouthwash	Quantative analysis using commercial caries risk test (CRT)	Post-hoc with a bonferroni test
7	Yadav M et al. [33]	2017	In vivo study	N=45 Group 1 (n=15) – 2% Green coffee bean extract Group 2 (n=15) – 0.2% Chlorhexidine Group 3 (N=15) – Sterile water	Quantitative analysis using microbial culture method (Colony forming units)	One-way ANOVA, Paired t-test for intra-group comparison, Post-hoc test.
8	Usha C et al. [34]	2017	In vivo study	N=46 Group 1 (n=23) – 0.12% chlorhexidine Group 2 (n=23) – Stevia mouthwash	Quantitative analysis using microbial culture method (Colony forming units)	Wilcoxon matched--pairs signed-rank test for intergroup comparison, Mann-Whitney test for intragroup comparison.
9	Biria M et al. [35]	2017	In vivo study	N=60 Group 1 (n=30)- masdent tooth paste (pistacia lentiscus extract) Group 2 (n=30)- Crest complete tooth paste (Fluoride tooth paste)	Quantitative analysis using microbial culture method (Colony forming units)	Mann Whitney U test and Wilcoxon test
10	Vinod KS et al. [36]	2018	In vivo study	N=200 Group1(n=100)- 0.12% chlorhexidine Group 2 (n=100)- Formulated herbal mouthwash (tulsi,-neem,triphala,turmeric)	Quantitative analysis using microbial culture method (Colony forming units)	Paired t test, ANOVA, followed by Tukey's post hoc test
11	Jeddy N et al. [37]	2018	In vivo study	N=60 Group 1(n=15)- Dr.Dental care liquid (red ginseng extract, sweterica japonica, camellia sinensis, licorice) Group 2 (n=15)- colgate plax mouth wash (cetylpyridium chloride and sodium fluoride) Group 3 (n=15)- Listerine mouth wash Group 4 (n=15)- Rexidine mouth wash (0.2% w/v chlorhexidine)	Quantitative analysis using microbial culture method (Colony forming units)	Wilcoxon sign-rank test
12	Aparna M et al. [38]	2018	Invivo study	Group 1 (n=25)- Licorice mouth wash) Group 2 (n=25)- triphala mouth wash Group 3 (n=25)- chlorhexidine mouthwash	Quantitative analysis using microbial culture method (Colony forming units)	Anova test

Table IV - general information of variables of interest and interpretation.

S.No	Author & Year	Study Type	Study Design	Outcome Variables	Time of Assessment	Statistical Test	Intervention	Overall Interpretation
1	Khairnar MR et al. 2015 [7]	In Vivo study	50 patients, 18-20 years	Antibacterial efficacy of 0.2% chlorhexidine mouthwash and 0.6% cranberry mouthwash against Streptococcus mutans.	At baseline and after 14 days	Paired t-test, unpaired t-test	Group 1- 0.2% chlorhexidine mouthwash Group 2- 0.6% cranberry mouthwash	No statistically significant difference between group 1 and group2
2	Botelho MA et al. 2009 [28]	In Vivo study	55 patients, 18-69 years	Antibacterial effect of Essential oil mouthwash and 0.12% chlorhexidine mouthwash against Streptococcus mutans	At baseline, after 7 days and 30 days	Fisher's exact test and Mann-Whitney U-test, Wilcoxon test	Group 1-Essential oil mouthwash, Group 2- 0.12% chlorhexidine mouthwash,	There was no difference in the baseline colony count between the 2 groups. Both the groups showed similar effectiveness in decreasing the salivary Streptococcus mutans levels.
3	Srinagesh J et al. 2011 [29]	In Vivo study	57 patients, 18-25 years	Antibacterial effect of 6% triphala mouthwash and 0.2% chlorhexidine mouthwash against oral Streptococcus mutans	At baseline, after 15 days and 45 days	ANOVA, post hoc test	Group 1- 6% triphala mouthwash, Group 2- 0.2% chlorhexidine, Gorup 3- No mouthwash	There was no difference in the baseline colony count between the 3 groups; difference at 15 days and 45 days was statistically significant. The difference in the decrease in colony count between group 1 and group 2 was not statistically significant. The difference between group 1 and group 3, group 2 and group 3 was highly significant.
4	Srinagesh J et al. 2012 [30]	In Vivo study	60 patients, 18-25 years	Antibacterial effect of 6% triphala mouthwash and 0.2% chlorhexidine mouthwash against oral Streptococcus mutans	At baseline, After 48 hours and 7 days	ANOVA, post hoc test	Group 1- 6% triphala mouthwash, Group 2- 0.2% chlorhexidine, Gorup 3- plain water	Reduction in colony count was statistically significant between group 1 and group 3 as well as group 2 and group 3. No significant difference between group 1 and group 2 at 48 hours or 7 days.
5	Velmurugan A et al. 2013 [31]	In Vivo study	45 patients	Antimicrobial efficacy of 20% aqueous extract of Terminalia chebula, Emblica officinalis and chlorhexidine mouthwash against *Streptococcus mutans* and Lactobacilli.	At baseline, 10, 30, 60 and 90 minutes	One way ANOVA, Post-hoc Tukey test.	Group 1 – 20% aqueous extract of T. chebula mouthwash Group 2 – 20% aqueous extract of E. officinalis mouthwash Group 3 – 0.2% chlorhexidine mouthwash	Group 2 showed highly significant antimicrobial activity compared with group 3 and group 1 against *Streptococcus mutans*. Group 3 showed least antimicrobial activity against Streptococcus mutans when compared with group1 and group 2.
6	Sam JE et al. 2016 [32]	In vivo study	100 patients, 18-22 years	Antibacterial efficacy of fluoride, chlorhexidine, herbal and xylitol mouth washes and pastes against *Streptococcus mutans*	At baseline, 1 month, 3 months and 6 months.	Post-hoc with a bonferroni test	Group 1- fluoride tooth paste and mouth wash Group 2- chlorhexidine tooth paste and mouth wash Group 3- herbal tooth paste and mouthwash(false black, pepper, Indian gum Arabic, neem,pomegranate,triphala) (Himalya complete care) Group 4- xylitol tooth paste and mouthwash	Group 1 showed a statistical significant difference on S.mutans when compared to the other 3 groups at all time intervals. Intergroup comparison showed a significant reduction in group 2 followed by group 1, 3 and 4.

S.No	Author & Year	Study Type	Study Design	Outcome Variables	Time of Assessment	Statistical Test	Intervention	Overall Interpretation
7	Yadav M et al. 2017 [33]	In Vivo study	45 patients, 18-22 years	Antibacterial efficacy of green coffee bean extract and chlorhexidine mouthwash against *Streptococcus mutans*	At baseline and after 14 days	ANOVA and Post-Hoc Tukey	Group 1- Green coffee bean extract Group 2- 0.2% Chlorhexidine	No statistically significant difference between group 1 and group 2.At baseline, no statistically significant difference for all 3 groups. Statistically significant difference was observed for all 3 groups after 14 days.
8	Usha C et al. 2017 [34]	In vivo study	46 subject, 18-25 yesrs	Antibacterial effect of 0.12% chlorhexidine mouthwash and 0.5% Stevia mouthwash against *Streptococcus mutans*	At baseline, after 7 days	Wilcoxon matched--pairs signed-rank test for intergroup comparison, Mann-Whitney test for intragroup comparison.	Group 1– 0.12% chlorhexidine Group 2–0.5% Stevia mouthwash	100% reduction in microbial colony count in group 1 and group 2 after 8th day.
9	Biria M et al. 2017 [35]	In vivo study	60 patients, 18-20 years	Antibacterial effect of pistacia lentiscus extract tooth paste and fluoride tooth paste on *Streptococcus mutans*	Base line and after a month	Mann Whitney U test and Wilcoxon test	Group 1 (n=30)- masdent tooth paste (pistacia lentiscus extract) Group 2 (n=30)- Crest complete tooth paste (Fluoride tooth paste)	No statistical significant difference in colony forming units at base line and 1 month revaluation also revealed a significant reduction in colony forming units, but the reduction was not statistically significant.
10	Vinod KS et al. 2018 [36]	In vivo study	200 patients, 18-22 years	Antibacterial effect of 0.12% chlorhexidine and Formulated herbal mouthwash (tulsi,neem,triphala,turmeric) on *Streptococcus mutans* colony forming units.	Baseline and after a month	Paired t test, ANOVA, followed by Tukey's post hoc test	Group1(n=100)- 0.12% chlorhexidine Group 2 (n=100)- Formulated herbal mouthwash (tulsi,neem,triphala,turmeric)	There was a reduction in colony forming units from baseline to day 7 which was not statistically significant in both the groups and at 14 day there was a significant reduction in CFU counts, which was higher in herbal group.
11	Jeddy N et al. 2018 [37]	Invivo study	60 patients, 18-24 years	Antibacterial effect of Dr.Dental care liquid (red ginseng extract, sweterica japonica, camellia sinensis, licorice), colgate plax mouth wash (cetylpyridium chloride and sodium fluoride), Listerine mouth wash, Rexidine mouth wash (0.2% w/v chlorhexidine) on *Streptococcus mutans*	Baseline and after 5 days	Wilcoxon sign-rank test	Group 1(n=15)- Dr. Dental care liquid (red ginseng extract, sweterica japonica, camellia sinensis, licorice) Group 2 (n=15)- colgate plax mouth wash (cetylpyridium chloride and sodium fluoride) Group 3 (n=15)- Listerine mouth wash Group 4 (n=15)- Rexidine mouth wash (0.2% w/v chlorhexidine)	There was a statistical significant reduction in the colony forming units at 5 days as compared with baseline. At 5 day follow up, group I had maximal reduction followed by group II, III and IV.
12	Aparna M et al. 2018 [38]	Invivo study	75 patients, 18-30 years	Antibacterial effect of Licorice mouth wash), triphala mouth wash and chlorhexidine mouthwash	Base line and after 1 week	Anova test	Group 1 (n=25)- Licorice mouth wash) Group 2 (n=25)- triphala mouth wash Group 3 (n=25)- chlorhexidine mouthwash	Compared to the baseline, there was a statistical significant reduction in colony forming units at 1 week time interval. There was no statistical significant difference noted in all the three groups at 1 week interval.

Table V - Results.

S.No	Author &Year	Materials used		Method of Evaluation	Mean values	Outcome
		Conventional product	Herbal product			
1	Khairnar MR et al. 2015[7]	Group 1: Chlorhexidine	Group 2: Cranberry	Quantitative analysis using microbial culture method (Colony forming units	Group 1: 69% Group 2: 68%	No statistically significant difference between group 1 and group2
2	Botelho MA et al. 2009 [28]	Group 2: Chlorhexidine	Group 1: L.sidoides	Quantitative analysis using microbial culture method (Colony forming units	Group 1: 58% Group 2: 58%	No significant difference between the two groups.
3	Srinagesh J et al. 2011 [29]	Group 2: Chlorhexidine	Group 1: 6% triphala Group 3: Passive control group	Quantitative analysis using microbial culture method (Colony forming units	At 15 days Group 1: 83% Group 2: 80% Group 3: 3% At 45 days Group 1: 67% Group 2: 65% Group 3: -7%	Group 1 and 2 differed significantly from control. No significant difference between group 1 and group 2.
4	Srinagesh J et al. 2012 [30]	Group 2: Chlorhexidine	Group 1: 6% triphala Group 3: Passive control group	Quantitative analysis using microbial culture method (Colony forming units	At 48 h Group 1: 17% Group 2: 14% Group 3: -6% At 7 days Group 1: 44% Group 2: 45% Group 3: -2%	Group 1 and 2 differed significantly from control. No significant difference between group 1 and group 2.
5	Velmurugan A et al. 2013 [31]	Group 3: Chlorhexidine	Group 1: 20% aqueous extract of T. chebula Group 2: 20% aqueous extract of E. officinalis	Quantitative analysis using microbial culture method (Colony forming units	Group 1: 68% Group 2: 78% Group 3: 65%	Group 2 is significantly better than group 1 and group 3. Group 2 is significantly better than group 1 and group 3.
6	Sam JE et al. 2016 [32]	NÖ100 Group 1 (n=25)- fluoride tooth paste and mouth wash Group 2 (n=25)- chlorhexidine tooth paste and mouth wash Group 4 (n=25)- xylitol tooth paste and mouthwash	Group 3 (n=25)- herbal tooth paste and mouthwash(false black, pepper, Indian gum Arabic, neem,pomegranate,triphala) (Himalya complete care)	Quantitative analysis using microbial culture method (Colony forming units)	Group 1: At 1 month - 12% At 3 months - 24% At 6 months-33.3% Group 2: At 1 month -18.6% At 3 months - 28% At 6 months - 33% Group 3: At 1 month - 6.8% At 3 months-11.36% At 6 months 20.45% Group 4: At 1 month - 9.5% At 3 months 16.6% At 6 months 23.8%	Statistical significant difference was seen in group 1 and 2 at three different time intervals. There was no significant difference noted in group 3 and 4 at 3 different time intervals.
7	Yadav M et al. 2017 [33]	Group 2: 0.2% chlorhexidine	Group 1: 2% Green Coffee bean extract Group 3: Sterile water	Quantitative analysis using microbial culture method (Colony forming units)	Group 1: 51±57 Group 2: 55±27 Group 3: 7±16	No significant difference between two groups but both the groups were significantly better than group 3

S.No	Author & Year	Materials used		Method of Evaluation	Mean values	Outcome
		Conventional product	Herbal product			
8	Usha C et al. 2017 [34]	Group 1: Chlorhexidine	Group 2: 0.5%Stevia mouthwash	Quantitative analysis using microbial culture method (Colony forming units	Group 1: 100% Group 2: 100%	No statistically significant difference between group 1 and group2
9	Biria M et al. 2017 [35]	Group 2 (n=30)- Crest complete tooth paste (Fluoride tooth paste)	Group 1 (n=30)- masdent tooth paste (pistacia lentiscus extract)	Quantitative analysis using microbial culture method (Colony forming units)	Group 1: 61.7% Group2: 80.415%	No statistical significant difference between the two groups.
10	Vinod KS et al. 2018 [36]	Group1(n=100)- 0.12% chlorhexidine	Group 2 (n=100)- Formulated herbal mouthwash (tulsi,-neem,triphala,turmeric)	Quantitative analysis using microbial culture method (Colony forming units)	Group 1: At day 7 - 20.9% At day 14- 60.74% Group 2: At day 7- 28.94% At day 14- 40.64	Compared to baseline values, statistical significant difference was seen in group 2 as compared to group 1.
11	Jeddy N et al. 2018 [37]	Group 2 (n=15)- colgate plax mouth wash (cetylpyridium chloride and sodium fluoride) Group 3 (n=15)- Listerine mouth wash Group 4 (n=15)- Rexidine mouth wash (0.2% w/v chlorhexidine)	Group 1(n=15)- Dr. Dental care liquid (red ginseng extract, sweterica japonica, camellia sinensis, licorice)	Quantitative analysis using microbial culture method (Colony forming units)	Group 1: 69.94% Group 2: 85.23% Group 3: 70.2% Group 4: 76.9%	Compared to baseline values, group 2 showed statistical significant reduction as compared to other three groups.
12	Aparna M et al. 2018 [38]	Group 3 (n=25)- chlorhexidine mouthwash	Group 1 (n=25)- Licorice mouth wash) Group 2 (n=25)- triphala mouth wash	Quantitative analysis using microbial culture method (Colony forming units)	At 7th day Group 1: 44.91% Group 2: 45.85% Group 3: 40.62%	No statistical significant difference in all the three groups.

Study Characteristics & Results of Individual Studies

Botelho MA et al. [28] evaluated and compared the antibacterial efficacy of an essential oil mouthwash comprising of L.sidoides with that of chlorhexidine. It was clearly shown that both the groups exerted a 58% reduction in Streptococcus mutans count at the end of 7 days.

Two studies established the effect of Triphala on Streptococcus mutans by comparing its antibacterial efficacy with chlorhexidine. In a study conducted by Srinagesh J et al. (2011) [29], there was a significant reduction in the colony forming units of Streptococcus mutans in both Triphala (83% and 67%) and chlorhexidine (80% and 65%) at 15 and 45 days respectively in a sample of 57 people. In another study done by Srinagesh J et al. (2012) [30], a CFU reduction of 17% and 44% was found at 48 hours and 7 days respectively in Triphala group while a reduction of 16% and 45% was seen in chlorhexidine group in a total sample size of 60 subjects.

Velmurugan A et al. [31] have compared the antibacterial efficacy of Emblica officinalis, Terminalia chebula with chlorhexidine. The results projected a marked decrease in Streptococcus mutans in all the three groups i.e; 78.1% in E.officinalis group followed by 67.8% in T.Chebula group, and 65.0% in chlorhexidine group post 90 minutes of usage in a total sample size of 45 subjects.

Sam JE et al. [32], have compared both the combined effect of both tooth pastes and mouthwashes together. The antibacterial efficacy of fluoride, chlorhexidine, (false black, pepper, Indian gum Arabic, neem, pomegranate, triphala) and xylitol. Fluoride group showed 12%, 24%, 33.3% reduction at 1, 3 and 6 months intervals. Chlorhexidine group showed 18.6%, 28%, 33% reduction at 1, 3 and 6 months. Herbal group showed 6.8%, 11.36%, 20.45% reduction at 1, 3, 6 months. Xylitol group showed 9.5%, 16.6%, 23.8% reduction at 1, 3, 6 months, for a total sample of 100 subjects.

Usha C et al. [34], compared the anti-cariogenicity of Stevia rebaudiana with chlorhexidine and found 100% Streptococcus mutans reduction in both the groups post 8 days of administration in a total sample of 46.

In a clinical trial by Khairnar MA et al. [7], chlorhexidine was compared with cranberry and it was found that there were a 69% CFU reduction in chlorhexidine group and 68% CFU reduction in cranberry group after 2 weeks in sample of 50 patients.

Yadav M et al. [33], compared green coffee bean extract with chlorhexidine and found 51.5 % Streptococcus mutans reduction in coffee group and 55.60% reduction in chlorhexidine group after 2 weeks in a sample of 45 subjects.

Biria M et al. [35], study compared pistacia lentiscus extract tooth paste with fluoride tooth paste. Fluoride group showed 80.415% reduction in streptococcus mutans levels at1month interval and pistacia group showed only 61.7% reduction at 1 month interval, in a sample of 60.

Vinod KS et al. [36], study compared chlorhexidine with formulated herbal mouthwash (tulsi, neem, triphala, turmeric). chlorhexidine showed 20.94%, 60.74% at 7th and 14th day, herbal group showed 28.94%, 40.64% at 7th and 14th days, in a sample of 100.

Jeddy N et al. [37], study compared herbal mouth wash with combination of (red glistening extract, sweterica japonica, camellia sinensis, licorice), cetyl pyridium chloride and fluoride containing mouth wash, Listerine mouth wash and 0.2% chlorhexidine mouth wash. Herbal mouthwash showed 69.94% reduction of Streptococcus mutans at 5 days, cetylpyridium combined fluoride combination showed 85.23% reduction, Listerine showed 70.2% reduction and 0.2% chlorhexidine showed 76.9% reduction.

Aparna M et al. [38], study compared licorice, triphala and chlorhexidine mouthwashes. Licorice mouthwash showed 44.91%, triphala showed 45.85%, chlorhexidine showed 40.62% reduction in Streptococcus mutans at 7th day.

When all the included studies were evaluated only two studies compared the effectiveness of herbal tooth pastes on Streptococcus mutans reduction [32,35]. Study by Biria M et al. [35], is the only study in literature search, which has evaluated the effectives of tooth paste alone without any adjunctive aid.

In all the studies compared, the reduction of Streptococcus mutans was almost insignificant or nearly approachable to conventional products (Table V, Table VI).

Table VI - Summation Tables for Individual Parameters.

Author	Year	Evaluation period	Outcome
Khairnar MR et al. [7]	2015	Before treatment and after 14 days	No significant difference between two groups
Botelho MA et al. [28]	2009	Before treatment and after 7 days	No significant difference between two groups
Srinagesh J et al. [29]	2011	Before treatment, at 15 days and at 45 days	No significant difference between two groups
Srinagesh J et al. [30]	2012	Before treatment, after 48 hours and after 7 days	No significant difference between two groups
Velmurugan A et al. [31]	2013	Before treatment and after treatment	Group 2 significantly better than group1 and group 3
Sam JE et al. [32]	2016	Before treatment, after 3 and 6 months	Statistical significant difference was seen in group 1 and 2 at three different time intervals. There was no significant difference noted in group 3 and 4 at 3 different time intervals.
Yadav M et al. [33]	2017	Before treatment and after 14 days	No significant difference between two groups but both the groups were significantly better than group 3
Usha C et al. [34]	2017	Before treatment and 7 days	No statistically significant difference between group 1 and group2
Biria M et al. [35]	2017	Before treatment and after a month	No statistical significant difference between the two groups.
Vinod KS et al. [36]	2018	Before treatment, at 7th day and at 14th day	Compared to baseline values, statistical significant difference was seen in group 2 as compared to group 1.
Jeddy N et al. [37]	2018	Before treatment and after 5 days.	Compared to baseline values, group 2 showed statistical significant reduction as compared to other three groups.
Aparna M et al. [38]	2018	Before treatment and after 7 days	No statistical significant difference in all the three groups.

Table VII - Evidence Level of Selected Articles.

S.N.O	Author	Year	Study Design	Level of Evidence
1	Khairnar MR et al. [7]	2015	Randomized clinical trial	Level 2
2	Botelho MA et al. [28]	2009	Randomized clinical trial	Level 2
3	Srinagesh J et al. [29]	2011	Randomized clinical trial	Level 2
4	Srinagesh J et al. [30]	2012	Randomized clinical trial	Level 2
5	Velmurugan A et al. [31]	2013	Randomized clinical trial	Level 2
6	Sam JE et al. [32]	2016	Randomized clinical trial	Level 2
7	Usha C et al. [33]	2017	Randomized clinical trial	Level 2
8	Yadav M et al. [34]	2017	Randomized clinical trial	Level 2
9	Biria M et al. [35]	2017	Randomized clinical trial	Level 2
10	Vinod KS et al. [36]	2018	Randomized clinical trial	Level 2
11	Jeddy N et al. [37]	2018	Randomized clinical trial	Level 2
12	Aparna M et al. [38]	2018	Randomized clinical trial	Level 2

Risk of Bias Within and Across the Studies

The risk of bias for all the studies included in the present systematic review was assessed using Cochrane criteria (Table VIII), (Table IX). Four parameters were evaluated to assess the risk of bias on individual studies. Five out of twelve studies showed low risk of bias [7,28,29,30,31] and the remaining four showed moderate risk of bias [33,34,35,36]. Finally three included studies, showed high risk of bias [32,37,38].

Low risk of bias was shown in the study conducted by Srinagesh J et al. 2011[32] as randomization, assessor blinding and dropouts or withdrawals if any, were well explained. Randomization and assessor blinding were done and well described in the trials reported by Khairnar MA et al. 2015,[7] Botelho MA et al. 2009,[28] Srinagesh J et al. 2012,[30] and Velmurugan A et al. 2013[31] also, there were no incidence of dropouts or withdrawals in the aforesaid clinical trials as well. Therefore, the five studies discussed above have low risk of bias.

Table VIII - Risk of BIAS - Major Criteria.

S.No	Study	Randomization	Allocation Concealed	Assessor Blinding	Dropouts Described	Risk Of Bias
1	Khairnar MR et al. 2015 [7]	Yes	No	Yes	None	Low risk
2	Botelho MA et al. 2009 [28]	Yes	No	Yes	None	Low risk
3	Srinagesh J et al. 2011 [29]	Yes	Unclear	Yes	Yes	Low risk
4	Srinagesh J et al. 2012 [30]	Yes	No	Yes	None	Low risk
5	Velmurugan A et al. 2013 [31]	Yes	No	Yes	None	Low risk
6	Sam JE et al. 2015 [32]	Yes	Unclear	Unclear	None	High risk
7	Usha C et al. 2017 [33]	Yes	No	No	None	Moderate risk
8	Yadav M et al. 2017 [34]	Yes	No	Unclear	None	Moderate risk
9	Biria M et al. 2017 [35]	Yes	No	No	None	Moderate risk
10	Vinod KS et al. 2018 [36]	Yes	No	Unclear	None	Moderate risk
11	Jeddy N et al. 2018 [37]	Unclear	No	No	None	High risk
12	Aparna M et al. 2018 [38]	Unclear	Unclear	No	None	High risk

Table IX - Risk of Bias – Minor Criteria.

S.No	Study	Sample Justified	Baseline Comparison	I/E Criteria	Method Error
1	Khairnar MR et al. 2015 [7]	Yes	Yes	Yes	No
2	Botelho MA et al. 2009 [28]	Yes	Yes	Yes	No
3	Srinagesh J et al. 2011 [29]	Yes	Yes	Yes	No
4	Srinagesh J et al. 2012 [30]	No	Yes	Yes	No
5	Velmurugan A et al. 2013 [31]	No	Yes	Yes	No
6	Sam JE et al. 2016 [32]	No	Yes	Yes	No
7	Usha C et al. 2017 [33]	No	Yes	Yes	No
8	Yadav M et al. 2017 [34]	Yes	Yes	Yes	No
9	Biria M et al. 2017 [35]	Yes	Yes	Yes	No
10	Vinod KS et al. 2018 [36]	Yes	Yes	Yes	No
11	Jeddy N et al. 2018 [37]	No	Yes	Yes	No
12	Aparna M et al. 2018 [38]	No	Yes	Yes	No

Srinagesh J et al. 2011[29] described the limitations of their study emphasizing that only short-term effect of triphala was assessed against oral streptococci. Therefore more trials are required to explore long term antibacterial efficacy of triphala against various oral microorganisms. Yadav M et al. 2016[34] explained the limitations pertaining to small sample size and that more samples have to be incorporated in order to further validate the results.

Moderate risk of bias was seen in the studies conducted by Usha C et al. 2017,[33] Yadav M et al. 2016,[34] Biria M et al. 2017,[35] Vinod KS et al. 2018[36] as allocation concealment and assessor blinding was not done.

High risk of bias was shown in Sam JE et al. 2016,[32] Jeddy N et al. 2018,[37] Aparna M et al. 2018,[38] studies as most of the things assessed were unclear.

Risk of bias of 5 studies- (Khairnar MR et al. 2015[7], Botelho MA et al. 2009,[28] Srinagesh J et al. 2011,[29] Srinagesh J et al. 2012,[30] Velmurugan A et al. 2013,[31]) had a low risk of bias, studies (Yadav M et al. 2016,[34] Usha C et al. 2017,[33] Biria M et al. 2017,[35] Vinod KS et al. 2018[36]) had a moderate risk of bias.

Sam JE et al. 2016, Aparna M et al. 2018, Jeddy N et al. 2018 studies had high risk of bias.

Synthesis of Results & Additional Analysis

Meta-analysis was done for only five included studies [7,30,32,36,37]. Studies which provided the baseline & post-analysis data (Mean & S.D) were considered for Meta-analysis. Other seven studies [28,29,31,33,34,35,38] which analyzed the Streptococcus mutans count in terms of percentage reduction were considered for qualitative assessment.

DISCUSSION

Summary of evidence

The purpose of this review is to evaluate the antibacterial efficacy of natural products versus conventional products against Streptococcus mutans (Table I).

Literature has shown substantial evidence that; higher dental caries incidence was associated with infrequent tooth brushing than the counterpart [39]. Although brushing seems to be beneficial, it has no additional role in antibacterial activity or added beneficial anticariogenic activity, except for transient localized delivery of fluoride ions [40].

Hence, mouthwashes seemed to have an additional benefit in reducing the cariogenic plaque load, thereby enhancing the anticariogenic activity. Although, when mouthwashes are compared, most of the studies in the literature were concentrated on usage of chlorhexidine at different concentrations and it's considered to be a gold standard [41].

In the present systematic review too, most of the studies compared only the chlorhexidine at different concentrations ranging from 0.2 to 0.12 as a conventional product (Table IV, Table V).

As mentioned earlier, due to increasing threat of using antimicrobial agents leading to development of resistant microorganisms. The herbal trend is increased and various studies using animal and human tests, evaluated, these herbal compounds exhibiting antibacterial activity against various pathogens, anti-adhesive and inhibitory activity against the extracellular polysaccharide [42].

Among the various compounds evaluated, the polyphenolic compounds claimed to have maximal beneficial effect.

The natural products used in the studies compared were Essential oil, Triphala, Terminalia chebula, Emblica officinalis, Stevia rebaudiana, Cranberry, Green coffee bean, falseblack pepper, Indian gum arabic, neem, pomegranate, pistacia lentiscus extract, tulsi, turmeric,red glistening extract, sweterica japonica, camellia sinensis, and licorice (Table III, Table V).

Report on Quality of Evidence Looked Upon

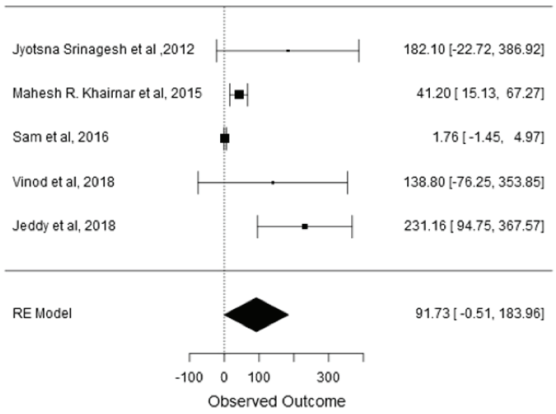
Twelve trials were included in this review. All 12 studies included in this review have a level of evidence 2 (Table VII). Thus the level of evidence is high.

META-ANALYSIS

Only five [7,30,32,36,37] included studies were considered for meta-analysis. Meta-analysis was not possible for the studies interpreted the Streptococcus mutans reduction in terms of percentage reduction. A random-effects model was used for interpreting the data. The assessment for baseline and follow-up showed a significant reduction of Streptococcus mutans levels were seen at follow-up for both Herbal (I^2 (%) = 95.688, H^2= 23.191, z= 1.9492, p=0.051), (Figure 1) and conventional products (I^2 (%) = 94.315, H^2= 17.591, z= 2.0196, p=0.043), (Figure 2). The overall estimated data indicated that, there was no difference in the herbal and conventional products on Streptococcus mutans reduction (I^2 (%) = 7.0128, H^2= 1.0754, z= 0.7921, p=0.428), (Figure 3).

Figure 1 - Herbal baseline vs follow-up.

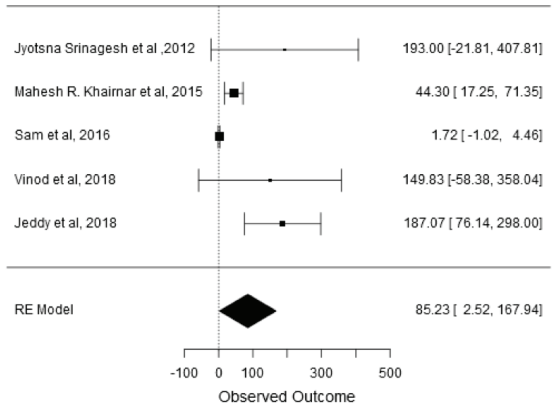
Forest plot



(I^2 (%) = 95.688, p=0.051)

Figure 2 - Conventional baseline vs follow up.

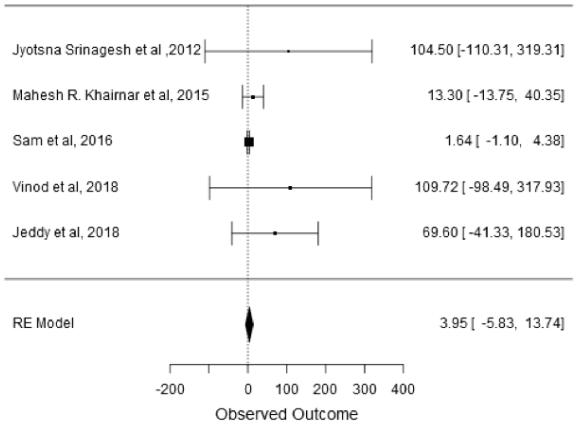
Forest plot



(I^2 (%) = 94.315, p=0.043)

Figure 3 - Herbal vs conventional.

Forest plot



(I^2 (%) = 7.0128, p=0.428)

Inference

From this systematic review it can be concluded that natural products can be used as an alternative to conventional products and proved to have a beneficial activity against Streptococcus mutans.

Limitations

Although, meta-analysis showed no significant difference between the conventional and herbal products on Streptococcus mutans reduction, the included studies were very less and most of them were of high risk. Most of the studies with high quality were not included for meta-analysis, as the data was provided in terms of percentage reduction. Studies included assessed only one pathogen and concentration was on antimicrobial reduction. But when dental caries is considered, it's multifactorial and various factors come into play to create a caries susceptible environment. None of the studies included concentrated on the caries index and susceptibility. The assessment was only based on the baseline microbial count. When critically appraised, studies concentrated mostly on different chlorhexidine for mutations and to a little extent of flouride combinations. Although, many other conventional agents proved to have a beneficial role, the dearth of studies concentrating on this aspect is low or almost nil. The assessments periods and follow up periods were also less to come to a specific conclusive remark.

Future implications

When the present review was considered, most of the research was concentrated on usage of mouth washes and the literature was scarce on comparing herbal versus conventional tooth pastes. When mouthwashes alone are considered, most of the studies compared and evaluated to chlorhexidine as a conventional product. None of the studies included a comparison on fluoride mouthwashes with the herbal products on re-mineralizing effect. It is a known fact that several herbal plant extracts have an additional re-mineralizing effect. So, it would be beneficial if future studies concentrate more on re-mineralizing mouthwashes. As a known fact, it

is not always possible to achieve beneficial effect, with a single constituent. To combat the future antimicrobial agents, its better if future studies concentrate on the combination of plant extracts in obtaining the beneficial effect.

CONCLUSION

Herbal products were equally effective as conventional products in reducing Streptococcus mutans levels in adult population.

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Implications of Key Findings: The review revealed a unique perspective about the herbal agents which proved to be equally efficacious against Streptococcus mutans as conventional agents. This review highlighted the importance of herbal agents to combat the present antimicrobial resistance especially in relevance to oral pathogens.

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