

# Efficacy of herbal alternatives in maintaining oral health in cancer patients: A systematic review

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## Abstract

Herbal rinses possess different medicinal properties. Numerous studies have reported the usefulness of various herbal oral rinses. Few studies claimed that herbal rinses are superior to synthetic mouth rinses for certain purposes, but there appears to be a lack of sound scientific evidence to prove the efficacy of herbal rinses in controlling oral plaque in cancer patients. This review analyses the various clinical studies on herbal rinses and aims to find the safety and efficacy of red ginseng mouth rinses over other available mouth rinses in carcinoma patients. A thorough electronic search was conducted in various databases and 10 articles were included in the review based on the inclusion and exclusion criteria. The data extracted were tabulated and analyzed. The risk of bias table was drawn. Meta-analysis was not performed due to the heterogeneity of the included studies. Of the 10 clinical trials included in the review, three studies appeared to have low risk of bias. The mean follow-up period was 14 days, ranging from 7 to 21 days. The sample size in each study was reported to be between 10 and 50, except one study with 240 samples. Seven studies have reported a significant difference between the herbal mouth rinse group and the chlorhexidine group. Of all the herbal rinses, mouth rinses with ginger extracts show more efficacy over other herbal rinses and red ginseng appears to be a more safer herbal rinse. Based on the available evidence, herbal mouth rinses are comparable to synthetic mouth rinses in their anti-bacterial properties. The red ginseng with anti-bacterial, anti-inflammatory and anti-cancerous properties may be an alternative mouth rinse in cancer patients. However, further clinical trials with more samples are required for better evidence.

**Keywords:** Cancer, ginseng, herbal alternatives

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## INTRODUCTION

Ginseng, a short slow-growing plant with fleshy roots, is native to China and Korea.

It is basically a root with stalks resembling a human body with limbs. It has long been used by ancient Chinese as

traditional Chinese medicine. The first documentation of this medicinal herb is dated back to 206 BC.<sup>[1]</sup> Botanically termed as Panax, this herb derives its Chinese name Renshen which means herb resembling human.<sup>[2]</sup> Although known for its Chinese origin, a variant of ginseng has been in use in America during the same ancient period. Marco Polo's reports of medicinal properties of ginseng

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became very popular, but a Jesuit priest named father Jortoux reported its first anti-inflammatory properties.<sup>[3]</sup>

Ginseng has been widely used as an herbal remedy for various disorders. Natural-dried ginseng is known as white ginseng, and red ginseng is prepared by steaming fresh ginseng root before drying on the purpose of enhancing efficacy, safety and preservation.<sup>[4]</sup> The medicinal properties of red ginseng are due to the presence of various compounds in it. The most identified compounds are ginsenosides. Nearly 40 ginsenosides compounds have been reported.<sup>[5]</sup> The compounds of interest with high anti-inflammatory and anti-carcinogenic properties are found in red ginseng. Ginseng is treated by steaming and this process enhances the anti-inflammatory properties of red ginseng.<sup>[6]</sup> The presence of protopanaxadiol further increases the anticarcinogenic activity.<sup>[7]</sup>

The therapeutic property of red ginseng has been used in treating squamous cell carcinoma of several sites in the human body. The anticancer mechanisms include cell cycle arrest, induction of apoptosis and inhibition of angiogenesis.<sup>[8]</sup> The anti-inflammatory property of red ginseng inhibits inflammation and enhances the antioxidant property. The RGE-3 compound of ginsenoside is shown to suppress nitric oxide production and inhibits the expression of proinflammatory mediators and cytokines through necrosis factor-alpha and mitogen-activated protein kinase pathways. This RGE-3 compound with high anti-inflammatory properties is found in higher concentration in Asian red ginseng. Squamous cell carcinoma of the oral cavity exhibits similar pathology and cell destruction as in the other areas of the human body. Hence, the therapeutic properties of red ginseng may be well applied to oral carcinoma as well as for oral inflammatory conditions.<sup>[9]</sup>

Gingivitis is a common inflammatory condition of gingiva. Patients with oral carcinoma often report with poor oral hygiene due to symptoms such as pain and restricted mouth opening. Poor oral hygiene in such patients leads to gingivitis or periodontitis resulting on loss of remaining teeth. The anti-inflammatory property of red ginseng has been used in mouth rinses and significant reduction in oral flora were reported.<sup>[10]</sup>

## SCIENTIFIC RATIONALE

Various studies have been reported in the past claiming the effectiveness of red ginseng as mouth wash in reducing the bacterial count, but there appears to be a lack of scientific evidence to prove this result. This systematic review aims

to collect the available data on ginseng mouth rinses and prove its efficacy in reducing the colony count of oral microbial flora in oral cancer patients.

## MATERIALS AND METHODS

This systematic review was conducted according to the preferred reporting items for systematic reviews and meta-analyses guidelines. The population, intervention, comparison, outcomes and study (PICOS) framework was used as a strategy for this review. P-patients with oral squamous cell carcinoma

I-intervention using red ginseng mouth wash, C-Colony count before and after the intervention with herbal mouth wash, O-reduction in bacterial colonial count, S-randomized trials and observational studies. Using the above PICOS strategy, the following structured question was framed.

1. What is the efficacy of red ginseng mouthwashes in reducing microbial load in oral cavity?
2. Can red ginseng mouthwashes be recommended for patients with oral carcinoma? Can the anti-cancerous property of red ginseng be effective in oral squamous cell carcinoma cases too?
3. What is the safety profile of red ginseng mouthwash? Are there any significant adverse reactions?

To obtain evidence for the PICOS question, the inclusion and exclusion criteria were as follows:

### Inclusion criteria

1. Clinical trials reporting on the efficacy of ginseng mouthwashes in reducing microbial load in the oral cavity
2. Case reports on the efficacy of ginseng mouthwashes in cancer therapy
3. Clinical trials and case reports on the anti-inflammatory properties of red ginseng mouthwashes
4. Articles that reported on antioxidant properties of ginseng mouthwashes
5. Articles reported on anti-microbial properties of red ginseng mouthwashes
6. Articles reported on various ginseng compounds (Asian and American ginseng).

### Exclusion criteria

1. Articles proving medicinal benefits of ginseng for other systemic conditions.

The parameter that was evaluated was reduction in the microbial load after the use of red ginseng mouth wash in oral cancer patients. A detailed electronic search (Boolean

search) was performed in all the main databases such as PubMed, Embase, Elsevier and Ebsco using the MESH terms. The search was narrowed down using the inclusion and exclusion criteria. Articles were excluded if the abstracts did not meet the inclusion criteria. Full-text articles were obtained for the included studies, and data were extracted. Two authors performed the search related to this review. Any disagreement on including the article was resolved using discussion between the authors and the final decision to include the article was done using kappa statistics and was at 0.8 percent agreement. Finally, 10 articles met the inclusion criteria and were included for the review. The randomized trials in this review were qualitatively analyzed using the CONSORT guidelines. The case reports were analyzed using the CARE guidelines and check list by Garg *et al.*<sup>[11]</sup> All the observational studies were qualitatively analyzed using the new castle Ottawa guidelines.<sup>[12]</sup> The risk of bias was assessed using the guidelines by Higgins and green.<sup>[13]</sup> The data referred from the articles were tabulated for further discussion.

## RESULTS

The initial search resulted in 1962 articles, of which 1291 were filtered as they did not meet the inclusion criteria. The 671 articles were screened, and based on authors' agreement, 22 were selected for full-text reading, and finally, 10 articles were included in the study Figure 1.

Out of the ten clinical trials, only two authors reported about red ginseng, and two authors about turmeric mouthwashes, two authors compared marigold mouthwashes and two authors reported on neem. One article discussed about homeopathic mouth wash and Ayurvedic mouth wash, respectively. All the 10 articles evaluated the gingival and plaque indices. Five articles evaluated the bacterial count.

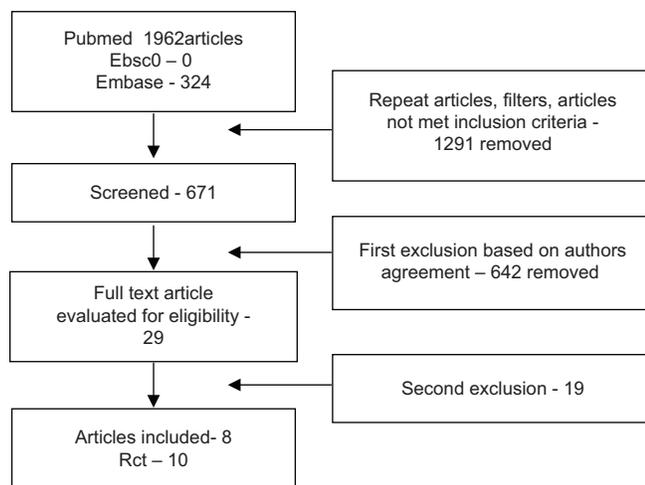


Figure 1: Flow chart

The average follow-up period in all the included studies was 21 days, except one study that had follow-up of 5 days. The sample size of the included studies was between 10 and 50, but one study by Faria *et al.* comparing marigold mouth wash tested 240 samples. The trials were conducted on healthy individuals in nine studies, but one trial was conducted on postsurgical patients who underwent third molar extraction. The data extracted are summarized and presented in Table 1. All the included studies are clinical trials, and the risk of bias is assessed and presented in Table 2.

## DISCUSSION

Natural products are known to be safe than synthetically manufactured ones, and mouth rinses are no exceptions. Each herbal mouth rinses discussed in the table possess anti-inflammatory, antibacterial property and other benefits. Synthetic mouthwashes became popular during the past few decades. The long-term side effects such as discoloration, have made the natural mouth rinses gain popularity again. Neem is native to India, and the medicinal benefits of neem are known since ancient days. Neem when used as a mouth wash has been reported to have antibacterial and anti-inflammatory properties. The study included in this review reports that neem can be effective such as chlorhexidine mouth wash, but no significant difference or superiority of neem over the synthetic mouthwashes are reported. Due to its bitterness, Neem mouthwashes are manufactured using artificial flavors and sweeteners to enhance patient compliance.<sup>[17]</sup> These additions to the original neem extract could reduce the actual antimicrobial property, thereby making neem comparable to chlorhexidine, but not significantly better than the synthetic chlorhexidine. Turmeric from another Indian-origin medicinal plant has been used as a mouth wash.<sup>[19]</sup> Turmeric is known for its anti-inflammatory properties and this can be attributed to the reduced gingival and plaque index. The efficacy of turmeric in reducing the bacterial count is comparable to chlorhexidine.<sup>[20]</sup> It is recommended as an adjuvant to routine mechanical hygiene procedures. The homeopathic mouth rinse prepared with all the essential oils has been reported to show significantly effective as mouthwash, but more studies are needed to understand the properties of the new mouth rinse.<sup>[16]</sup> Triphala (ginger extract) mouthwash was found to be effective in reducing the bacterial count and improving hygiene.<sup>[23]</sup>

Freshol (homeopathic rinse) is a combination of essential oils, unlike turmeric and neem not a single composition product, and hence, more studies are required to study

**Table 1: Summary of data of included studies**

Journal year/ authors	Level of evidence randomization	Sample size/sample groups	Comparison	Follow-up time	Outcome
Journal of pharmaceutical sciences and research 2019 <sup>[10]</sup> / Subramaniam S <i>et al.</i>	1 a not mentioned	N - 10 each Three groups (red ginseng, chlorhexidine, and placebo) Chronic periodontitis patients	Baseline and postintervention comparison of probing depth Full mouth plaque scores Full mouth bleeding scores Gingival index clinical attachment level	Baseline, 21 days	Statistically significant difference found between the groups. Red ginseng groups baseline and postintervention score revealed sharp reduction in fmbms scores. Intragroup comparison also revealed red ginseng was effective compared to other groups
Journal of oral and maxillofacial pathology 2018 <sup>[14]</sup> / Jeddy <i>et al.</i>	1a not mentioned	N - 15 each four groups (red ginseng, Listerine, colgate plax, and rexidine)	Baseline and postintervention bacterial count from saliva samples	Baseline, 5 days/twice daily	Red ginseng group showed statistically significant decrease in the bacterial count postintervention
Journal of Indian association of public health dentistry 2020 <sup>[15]</sup> /Khobragade VR <i>et al.</i>	1a block randomization technique	N - 15 each 2 groups Chlorhexidine, indigenous herbal liquid (triphala ginger extracts)	Baseline and postintervention gingival and plaque index were evaluated	Baseline, 7 <sup>th</sup> , 14 <sup>th</sup> , 21 days	Indigenous mouth wash with ginger extracts showed significant. Improvement in gingival health
Journal of international society of preventive dentistry 2013 <sup>[16]</sup> / Mehta S <i>et al.</i>	1 a cross over trial Randomization not mentioned	N - 35 N - 20 Homoepathic mouthwash containing chamomile extracts chlorhexidine mouthwash	Plaque index Bleeding index <i>Streptococcus mutans</i> count from saliva	Baseline, 10 days/ twice daily	Significant difference in reduction of streptococcus mutans count in saliva in the experimental group
Journal of Indian society of periodontology 2011 <sup>[17]</sup> /Chatterjee A <i>et al.</i>	1a not mentioned	N - 15 3 groups (neem, chlorhexidine, and saline)	Plaque index, bleeding index, and gingival index	Baseline, 7, 14, 21days/ twice daily	No statistically significant difference between the groups Equally effective
Journal of Indian association of public health dentistry 2011 <sup>[18]</sup> /Sabyasachi saha <i>et al.</i>	1a not mentioned	N - 30 Three groups (neem, chlorhexidine, and distilled water)	Bacterial count for caries and periodontitis	Baseline, 7, 15 days	Neem mouthwash equally effective as chlorhexidine mouth rinses
Journal of Indian society of periodontology 2012 <sup>[19]</sup> /Mali AM <i>et al.</i>	Not mentioned	N - 30 2 groups (turmeric, chlorhexidine)	Plaque index and gingival index	Baseline, 14, 21 days	No significant difference between the groups
Journal of contemporary dental practice 2011 <sup>[20]</sup> /Waghmare <i>et al.</i>	Not mentioned	N - 50 Two groups (chlorhexidine, turmeric)	Plaque index and gingival index	Baseline, 14, 21	No significant difference between the groups
Journal of Indian society of periodontology 2013 <sup>[21]</sup> /Khairnar <i>et al.</i>	Randomization by nonoperator	N - 240 Two groups (marigold, placebo)	Plaque index, gingival index	Baseline, 3 months, months	Statistically significant difference between marigold and placebo group, marigold group revealed better plaque control and improved oral hygiene
Journal of applied oral sciences <sup>[22]</sup> / Faria <i>et al.</i>	Not mentioned	N - 18, three groups, (marigold, tea extract, and chlorhexidine)	Bacterial count	Baseline, 7 <sup>th</sup> postoperative day	Chlorhexidine was effective compared to marigold and tea tree extract mouth washes

and reveal the properties of each ingredient.<sup>[16]</sup> One study compared the marigold (*Calendula officinalis*) and tea tree extract (*Camellia sinensis* Kuntze) with chlorhexidine and reported a reduction in bacterial count in all three groups, but the efficacy of chlorhexidine was reported to be superior compared to marigold and tea tree extract mouthwashes.<sup>[22]</sup> However, statistically significant differences in plaque and gingival indices were observed when marigold was tested against a placebo group.<sup>[21]</sup> Reduction in bacterial and oral microbial count leads to improved healthy gingival which

is reflected as reduced plaque and gingival indices. Hence, reduced plaque and gingival index is a gold standard method to test the efficacy of mouthwashes, all the trials have used this method. The risk of bias is given in Table 2. Only two studies have reported the method of randomization. The risk of bias appears to be low in all the studies. The method of randomization is unclear in eight of the included studies. From the evidence available, herbal mouth rinses can be compared to synthetic mouth rinses in reducing the bacterial count and improving oral hygiene

**Table 2: Risk of bias in the included studies**

Author year	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Sangeetha <i>et al.</i>	?	?	?	+	+	+	+
Jeddy <i>et al.</i>	?	?	?	+	+	+	+
Vrushali <i>et al.</i>	+	+	Blinding of participants alone	+	+	+	+
Shivika <i>et al.</i>	?	+	+	+	+	+	+
Anirban <i>et al.</i>	?	+	+	+	+	+	+
Sabyasachi saha <i>et al.</i>	?	+	+	+	+	+	+
Amita <i>et al.</i>	?	?	/	+	+	+	+
Waghmare <i>et al.</i>	?	?	?	+	+	+	+
Khairner <i>et al.</i>	+	+	-	+	+	+	+
Faria <i>et al.</i>	?	-	-	+	+	+	+

Higgins and green risk assessment. ?: Unclear risk of bias, +: Low risk of bias, -: High risk of bias

in healthy individuals. Of all the herbal mouth rinses, mouth rinses containing ginger extracts (red ginseng and triphala) appear to be superior to other herbal mouth rinses. However, further studies are required for this evidence.

Looking for evidence to our second structured question, red ginseng appears to be more promising herbal rinse compared to other available herbal rinses. Red ginseng has been reported to have anti-inflammatory, anti-oxidant, anti-bacterial and anti-cancer property.<sup>[5,7]</sup> The various ginsenoside compound in red ginseng exhibits several properties that make it a superior herbal rinse. Two clinical trials included in the study evaluated the efficacy in terms of anti-inflammatory and anti-bacterial properties. The clinical trial by Subramaniam S *et al.* showed that red ginseng has a comparable anti-inflammatory effects as chlorhexidine with no reported side effects. However, the sample size included in this trial is low and more studies with increased sample size could provide better evidence. The red ginseng is consumed as a dietary supplement in western countries as it is known to reduce the risk of cancer.<sup>[6]</sup> Extracts of red ginseng have been reported to be used for cancer chemotherapy.<sup>[24]</sup> It has been recommended as an adjuvant to chemotherapy to reduce the symptoms of carcinoma, to enhance the efficacy of chemotherapeutic agents and to reduce the risk of recurrence in such patients. The disease progress of carcinoma in any site of the body follows the same histological pattern, and hence, the red ginseng could be recommended for oral carcinoma. When used as a mouth rinse, significant changes have been observed in a week, hence long-term use of red ginseng could prevent oral carcinoma, especially in patients with premalignant conditions and this can be attributed to the high antioxidant property unlike in other herbal mouth rinses. Aich *et al.* reported the antioxidant property of combination of herbal mouth rinse containing triphala, turmeric, and honey in the treatment of oral submucous fibrosis. The anti-oxidant property of these mouth rinses improved the mouth opening in submucous fibrosis patients.<sup>[25]</sup> This

antioxidant and anti-inflammatory properties could reduce the symptoms of oral carcinoma, prevent recurrence in such patients at the same time providing anti-microbial effect in reducing the oral bacterial count.

Red ginseng with high antioxidant property can be beneficial in oral squamous cell carcinoma in reducing the bacterial count as well as prevent the progress of carcinoma. Saponin compound is found in very high concentrations in red ginseng. This saponin content was very effective in the treatment of cancer in other sites of the body.<sup>[26]</sup> The anticancer property of red ginseng can be increased by the steaming process. Ginsenosides and ginseng polysaccharides are the main compounds responsible for antioxidant and anticancerous properties of the red ginseng.<sup>[24]</sup> The major anticancer properties of red ginseng include cell cycle arrest, induction of apoptosis and inhibition of angiogenesis. Red ginseng was effective in all the above histopathological stages. A meta-analysis conducted to find the incidence of cancer in population who consumed red ginseng regularly revealed that the relative risk of cancer occurrence is low.<sup>[27]</sup> However, the chemical compounds of red ginseng from Asian origin have been included in the meta-analysis.

Unlike other synthetic compounds, red ginseng has been proved to be nontoxic and showed no side effects on long-term use.<sup>[28]</sup> Although the anticancerous property of red ginseng in the oral cavity could be cautiously claimed, future clinical trials can add evidence to this claim.

Although all the studies included under this review are clinical trials, the sample size, follow-up duration and randomization techniques of the included articles could be stated as the limitations of this review.

## CONCLUSION

Evidence suggest that anti-inflammatory and antibacterial property of red ginseng has made this a safer herbal mouth

rinse. Owing to its antioxidant property, this could be recommended for patients with oral carcinoma, but further studies on this aspect are required for lasting evidence.

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### Conflicts of interest

There are no conflicts of interest.

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