



REVIEW ARTICLE

The effect of curcumin as an adjunct in the treatment of chronic periodontitis: A systematic review and meta-analysis



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KEYWORDS

Curcumin;
Curcuma longa;
Turmeric extract;
Gingivitis;
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Abstract *Background:* A large number of trials has been conducted using curcumin as the main ingredient in mouth rinses, topical oral gel, subgingival irrigant, locally delivered gel and locally delivered chips to reduce gingival inflammation and probing pocket depth. However, the results of these trials vary and are debatable.

Objective: To evaluate the effectiveness of oral curcumin products as compared to the routinely used ones in reducing gingival inflammation and probing pocket depth in adults.

Methods: Electronic databases such as Pubmed/Medline and Cochrane Library and hand searching was done for randomised controlled trials (RCTs), which yielded 148 results, of which 27 RCTs compared curcumin products with routinely used ones. Meta-analysis was conducted to check for plaque reduction, gingival inflammation and pocket depth.

Results: 963 participants in the 27 RCT studies were considered for a systematic review. We found that for a long-term evaluation of probing pocket depth in nine studies each with 400 participants, there was a statistically significant difference in the reduction when curcumin topical gel was used as compared with the control [SMD -0.87 , 95% CI: -1.31 to -0.43]. However, in the evaluation of short-term plaque and gingival scores, we found no statistically significant differences in the reduction when curcumin mouth rinse was used [SMD -0.76 , 95% CI: -2.25 to 0.73] and [MD: -0.09 , 95% CI: -0.29 to 0.10].

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Conclusion: Curcumin topical and local delivery gel, mouth rinses and sub-gingival irrigants were found to be equally effective compared to the routinely used agents for reduction of plaque and gingival inflammation. Curcumin local delivery gel had greater reduction in probing pocket depth.

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1. Introduction

Periodontitis is an inflammatory disease of the supporting tissues of teeth (Newman et al., 2006). The prime etiological agent in gingivitis that may later proceed to periodontitis is bacterial plaque (Farjana et al., 2014). Periodontal health is also affected by a multitude of factors among which genetic factors, systemic health and nutrition play a key role (Shariq et al., 2016). During periodontal destruction, there is a complex interplay of this plaque biofilm with host immunoinflammatory reaction and hence there occurs an imbalance between bacteria and the host's defence ability (Kornman, 2008). This imbalance causes injury to tissue manifested as periodontitis.

The goal of periodontal treatment is to restore these injured tissues. Mechanical therapy, chemotherapy and systemic administration of antibiotics include the various treatment modalities. The principle of periodontal therapy is largely built on mechanical debridement of tooth surface and thorough maintenance of oral hygiene thereafter (Shariq et al., 2016). While complete removal of irritants is not possible with mechanical debridement alone, the use of antibiotics and antiseptics in both systemic and local forms have been used (Anuradha et al., 2015).

However, the use of systemic antibiotics requires its administration in a large dosage to obtain a satisfactory concentra-

tion at the site of disease, thereby increasing the possibility of development of bacterial resistance. Local drug delivery (LDD) is an alternative to systemic antibiotics. This type of delivery system has proved to be potent against subgingival microflora (Nagasri et al., 2015). Various LDD use targeted delivery of anti-microbial agents which include fibres, strips and compacts, gels, microparticles, films and nano particles (Anuradha et al., 2015) LDD in the form of chips of varying sizes are also available (such as PerioChip® 2.5 mg). Several chemical agents used as adjuncts to mechanical methods have adverse effects such as allergies and discoloration of teeth, which have been reported (Farjana et al., 2014) There are many natural ways to treat periodontitis that include the use of a number of herbs that help eliminate inflammation and infection associated with periodontitis (Anuradha et al., 2015).

The common herbal products used in dentistry are *Curcuma longa* (turmeric), *Azadirachta indica* (neem), *Aloe barbadensis* Miller (aloe vera), *Syzygium aromaticum* (clove), and *Cinnamomum verum* (cinnamon). *Curcuma longa*, a member of the ginger family, is specific to South East Asia. The rhizome of *Curcuma longa* is turmeric, a yellow-orange spice. Curcumin (diferuloyl methane), demethoxycurcumin and bisdemethoxycurcumin are the main components of turmeric. The anti-inflammatory activity of curcumin is well docu-

mented in the literature (Kohli et al., 2005; Suhag et al., 2007) and is based on its ability to inhibit lipo-oxygenase and cyclo-oxygenase activity in humans. Turmeric as a mouth wash was found to be a potent anti-inflammatory agent by Bhandari and Shankwalker (Farjana et al., 2014).

The use of curcumin as a local applicant in conjugation with SRP have showed improvement in periodontal parameters (Anuradha et al., 2015; Hugar et al., 2016; Nagasri et al., 2015). Also, there is a more favourable outcome regarding periodontal parameters in relation to curcumin when compared with ornidazole gel (Ravishankar et al., 2017) However, Kandwal et al (2015) reported no statistically significant difference between chlorhexidine gel and curcumin gel in relation to plaque index and gingival index.).

While some authors have reported curcumin, both in the form of chips and mouth rinse, to be better than chlorhexidine, other authors have reported otherwise (Arunachalam et al., 2017; Chatterjee et al., 2017; Elavarasu et al., 2016; Gottumukkala et al., 2014; Mali et al., 2012; Singh et al., 2018; Waghmare et al., 2011) Hence there exists a clinical equipoise regarding the benefits of curcumin gel, chips and mouth rinse when used as an adjunct to scaling and root planing (SRP) in comparison with other commercially available synthetic agents like chlorhexidine, ornidazole or metronidazole.

2. Materials and methods

This systematic review and meta-analysis protocol was registered with PROSPERO (CRD42020168313) and followed the PRISMA reporting guidelines (<http://www.prisma-statement.org/PRISMAStatement/Default.aspx>). The PICO format was used:

- Patients: Adults > 18 years
- Intervention: Curcumin topical gels (CTG), local delivery gels (CLDG), chips (CC), mouth rinses (CMR) and subgingival irrigation (CSGI)
- Comparison: Chlorhexidine (CHX) mouth rinse, CHX chips, CHX gel, saline, ornidazole gel, metronidazole gel
- Outcomes: Reduction in gingival inflammation, plaque scores and periodontal pocket depth

The focussed question for this systematic review and meta-analysis was whether curcumin-based products [gels (topical and local delivery), chips, subgingival irrigation and mouth rinse] are better than other commercially available agents when used as an adjunct in reduction of gingival inflammation, plaque scores and periodontal pocket depth in chronic periodontitis patients.

2.1. Eligibility criteria

Only randomised controlled trials (RCTs) with a parallel arm design on adult participants (18–60 years) of any gender and studies conducted in any country were included for this review. Subjects using curcumin [as gel (topical/local delivery), subgingival irrigants, chips or mouth rinse] were included in the intervention group. Subjects (active controls) using a formulation that was most commonly used commercially available formulations (chlorhexidine, metronidazole and ornidazole) consisted of the control group.

2.2. Outcomes

The intervention arm (CTG and/or CLDG and/or CC and/or CMR and /or CSGI) and the control arm of the studies were assessed for the following outcomes:

- Silness and Loe plaque index or modified Quigley Hein plaque index was measured for mean reduction in plaque score;
- Loe and Silness gingival index for mean reduction of gingival inflammation;
- Mean reduction in probing pocket depth measured in mm.

These outcomes were assessed based on:

- Short-term effects (studies with a 2-weeks follow-up, acceptability range ± 3 days).
- Long-term effects (studies with a 4-weeks follow-up, acceptability range ± 3 days).

Unit of measurement was the site in oral cavity with tooth surface and its associated periodontium.

2.3. Information sources and search

MEDLINE (PubMed), and Cochrane Library were searched using search terms (MeSH) and words. Fig. 1 represents the search strategy employed for MEDLINE database. Additionally, references of retrieved articles were also searched. The search terms included “curcumin” or “curcuma longa” or “turmeric extract” or “curcumin extract” with no language restrictions. Any duplicates, from the results collected, were removed by the two authors (ST and RV) separately. Consequently, the remaining articles were further analysed for the inclusion/exclusion criteria. The inclusion criteria were not met by certain studies and hence those studies were excluded. After titles and abstracts were identified, full text screening was done. The search was done in June 2019 on the aforementioned databases and no time frames were employed for the search.

2.4. Data collection process and data items

Study characteristics were extracted from each study by the two authors (ST and RV) using a Microsoft Excel spreadsheet. Mean and standard deviations (SD) of the study outcomes (PI, GI and PPD) at short-term and long-term end points were chosen for performing meta-analysis. The rationale behind choosing the post-treatment values were because the baseline values of two groups were non-significant. Mean Difference (MD) and Standard Mean Difference (SMD) were used to summarise the treatment effect of each study. Standardized weighted mean differences (SMDs) were calculated when the outcomes were assessed using different indices. Random-effects models (Higgins, 2011) was used for meta-analysis with 95% confidence intervals (CIs). For missing data, the corresponding author was contacted via email. Quantitative synthesis was done using RevMan 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration).

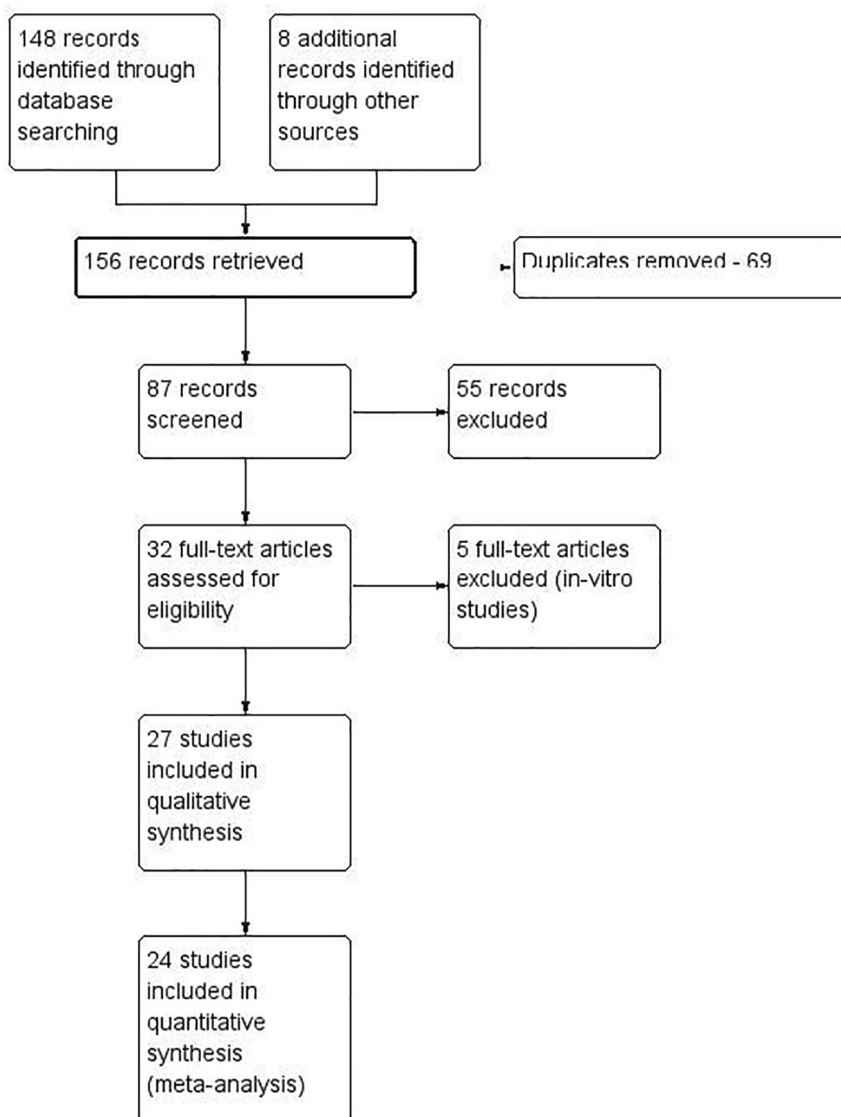


Fig. 1 Search strategy.

2.5. Assessment of risk of bias

The risk of bias assessment was done using the Cochrane Collaboration's tool (Higgins et al., 2011). All included studies were first assessed independently and then in duplicate by the two authors (ST and RV). A third reviewer (MS) resolved disagreement if any. Risk of bias assessment within and across studies was performed.

2.6. Synthesis of results

Heterogeneity of the data was evaluated using the Cochran's Q statistic, with the threshold p-value of less than 0.10 (Huedo-Medina et al., 2006) and I^2 statistic (Higgins and Thompson, 2002). Forest plots were generated for visual interpretation.

3. Results

3.1. Study selection

A total of 156 articles were retrieved using electronic search (Fig. 1). Among them, 69 were duplicates and thus excluded. Out of the remaining 87 records, 55 were excluded after title and abstract screening. The remaining 32 articles with full text were screened, of which five were excluded because the studies were animal and in-vitro studies. Thus, 27 articles were included for the review.

3.2. Study description

A total of 27 RCTs comprising of 963 sites (250 mouth rinse, 215 chips, 73 subgingival irrigation, 160 topical gel and 265

local delivery gel) were included. **Table 1** shows the characteristics of the included studies. There were three subgingival irrigation, six mouth rinse, three chips, four topical gel and 11 local delivery gel trials in each study group that used commercially available subgingival irrigant, chips, mouth rinses and gels as the control arm.

There was clinical heterogeneity in the composition of CC, CMR, CTG and CLDG used. For gels, eight studies used Cur-enext oral gel (Anuradha et al., 2015; Dave et al., 2018; Ganai et al., 2019; Kandwal et al., 2015; Nagasri et al., 2015; Ravishankar et al., 2017; Sharma and Kalsi, 2016; Varghese et al., 2014), four studies used 2% turmeric gel (Behal et al., 2011; Hugar et al., 2016; Jaswal et al., 2014; Nasra et al., 2017), one study each with 1 mg/ml of turmeric extract (Bhatia et al., 2014) and 250 g in 95 ml glycerol (Anitha et al., 2015 prepared by the respective investigator).

For mouth rinses, two studies used 10 mg in 100 ml (Arunachalam et al., 2017; Waghmare et al., 2011) while one study with 20% curcumin (Muglikar et al., 2013) and two studies with 0.1% turmeric (Chatterjee et al., 2017; Divya, 2017).

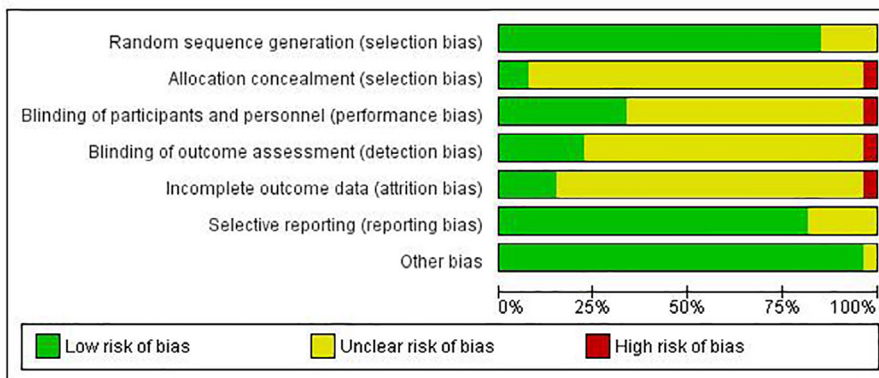
For chips, out of the three studies that used curcumin, one study used 5% (Singh et al., 2018), one study with 50 mg/sq.cm (Gottumukkala et al., 2014) and one study with 0.20% (Elavarasu et al., 2016) Two of these studies used chlorhexidine as control (Gottumukkala et al., 2014; Singh et al., 2018) while Elavarasu et al. (2016) used only SRP as the control arm

All six mouth rinse studies used CHX as the control arm (Arunachalam et al., 2017; Chatterjee et al., 2017; Divya, 2017; Mali et al., 2012; Muglikar et al., 2013; Waghmare et al., 2011) and all three subgingival irrigation studies also used CHX as the control arm (Gottumukkala et al., 2013; Nandini et al., 2012; Suhag et al., 2007). Six gel studies used CHX as the control arm (Anitha et al., 2015; Dave et al., 2018; Hugar et al., 2016; Jaswal et al., 2014; Kandwal et al., 2015; Singh et al., 2015.), two gel studies used ornidazole as the control (Ganai et al., 2019; Ravishankar et al., 2017), one gel study with metronidazole (Varghese et al., 2014) and six gel studies with SRP only (Anuradha et al., 2015; Behal et al., 2011; Bhatia et al., 2014; Nagasri et al., 2015; Nasra et al., 2017; Sharma and Kalsi, 2016).

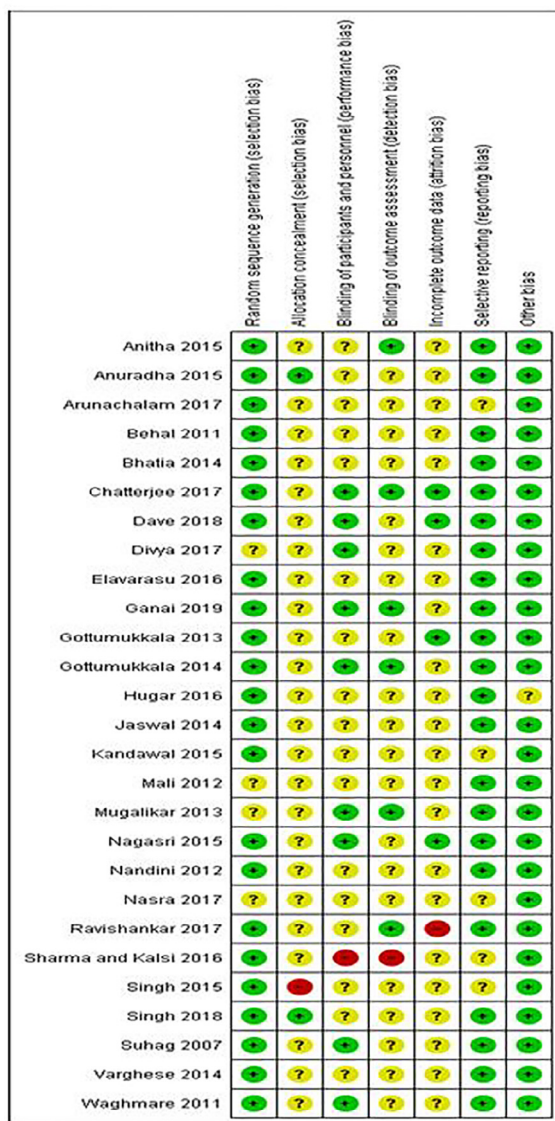
Table 1 Summary of Characteristics of Included Studies.

Study ID	Country	Control	Intervention	Index used		
				PS	GS	PPD
<i>Gel (Local delivery)</i>						
(Anitha et al., 2015)	INDIA	SRP + CHX GEL	SRP + CUR GEL	TG	LS	mm
(Anuradha et al., 2015)	INDIA	SRP	SRP + CUR GEL	TG	LS	mm
(Behal et al., 2011)	INDIA	SRP	SRP + CUR GEL	TG	LS	mm
(Bhatia et al., 2014)	INDIA	SRP	SRP + CUR GEL	SL		mm
(Hugar et al., 2016)	INDIA	SRP + CHX GEL	SRP + CUR GEL	SL	LS	mm
(Ganai et al., 2019)	INDIA	SRP + ORN GEL	SRP + CUR GEL	SL		mm
(Nasra et al., 2017)	CAIRO	SRP	SRP + CUR GEL	SL		mm
(Varghese et al., 2014)	INDIA	SRP + MTZ GEL	SRP + CUR GEL		LS	mm
(Nagasri et al., 2015)	INDIA	SRP	SRP + CUR GEL	SL	LS	mm
(Ravishankar et al., 2017)	INDIA	ORN GEL	CUR GEL	SL		mm
(Jaswal et al., 2014)	INDIA	SRP + CHX GEL	SRP + CUR GEL	SL	LS	mm
<i>Gel (topical use)</i>						
(Dave et al., 2018)	INDIA	SRP	SRP + CUR GEL	SL		mm
(Kandwal et al., 2015)	INDIA	CHX GEL	CUR GEL	SL	LS	
(Singh et al., 2015.)	INDIA	SRP + CHX GEL	SRP + CUR GEL	SL	LS	
(Sharma and Kalsi, 2016)	INDIA	SRP	SRP + CUR GEL	(M) QH	(M) LS	
<i>Mouth Rinse</i>						
(Mali et al., 2012)	INDIA	CHX MR	CUR MR	TG	LS	
(Arunachalam et al., 2017)	INDIA	CHX MR	CUR MR	SL	LS	
(Chatterjee et al., 2017)	INDIA	CHX MR	CUR MR	SL	LS	
(Muglikar et al., 2013)	INDIA	SRP + CHX MR	SRP + CUR MR	SL	LS	
(Divya, 2017)	INDIA	CHX MR	CUR MR	SL	LS	
(Waghmare et al., 2011)	INDIA	CHX MR	CUR MR	TG	LS	
<i>Subgingival irrigation</i>						
(Suhag et al., 2007)	INDIA	SRP + CHX SBGI	SRP + CUR SBGI			mm
(Nandini et al., 2012)	INDIA	SRP + CHX SBGI	SRP + CUR SBGI	TG	LS	mm
(Gottumukkala et al., 2013)	INDIA	SRP + CHX SBGI	SRP + CUR SBGI	SL		mm
<i>Chips</i>						
(Singh et al., 2018)	INDIA	SRP + CHX CHIPS	SRP + CUR CHIPS	SL		mm
(Gottumukkala et al., 2014)	INDIA	SRP + CHX CHIPS	SRP + CUR CHIPS	SL	LS	mm
(Elavarasu et al., 2016)	INDIA	SRP	SRP + CUR CHIPS	SL		

SRP: scaling and root planing; SL: Silness and Loe Plaque index; LS: Loe and Silness Gingival index; mm: millimetre; CUR: curcumin; TG: Turkey Gilmore plaque index; (M)QH: Modification of Quigley Hein and Eliot Index; (M)LS–Lobene et al. modification of Loe and Silness index.

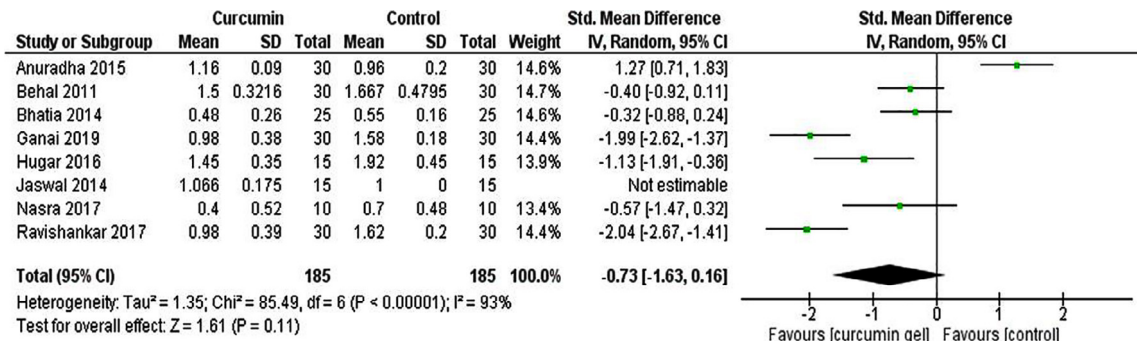


Risk of bias across studies

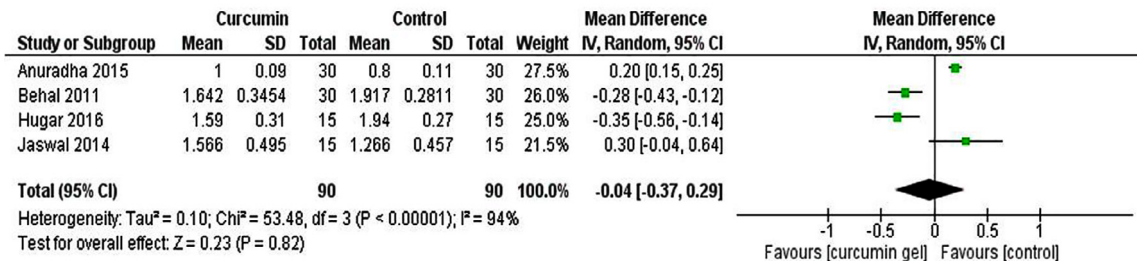


Risk of bias within studies

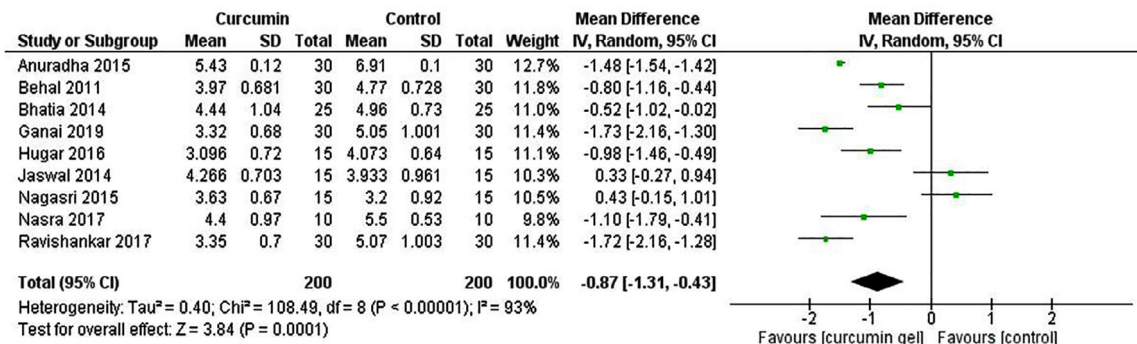
Fig. 2 Risk of Bias.



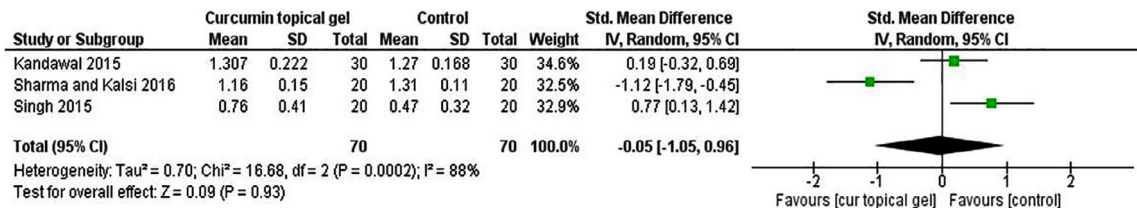
Curcumin gel (local delivery) - Plaque index (long-term)



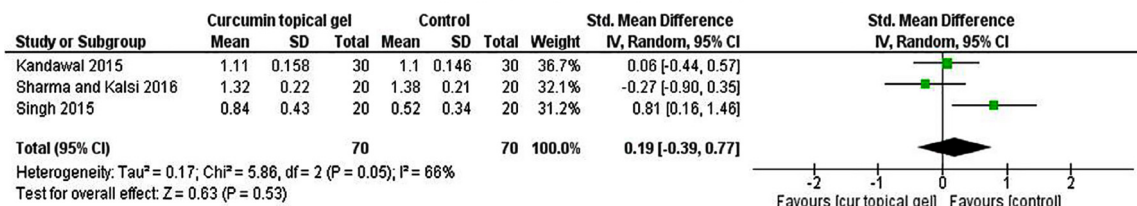
Curcumin gel (local delivery) - Gingival index (long-term)



Curcumin gel (local delivery) - Probing pocket depth (long-term)



Curcumin gel (topical) - Plaque index (short-term)



Curcumin gel (topical) - Gingival index (short-term)

Fig. 3 Comparison of curcumin gel vs control.

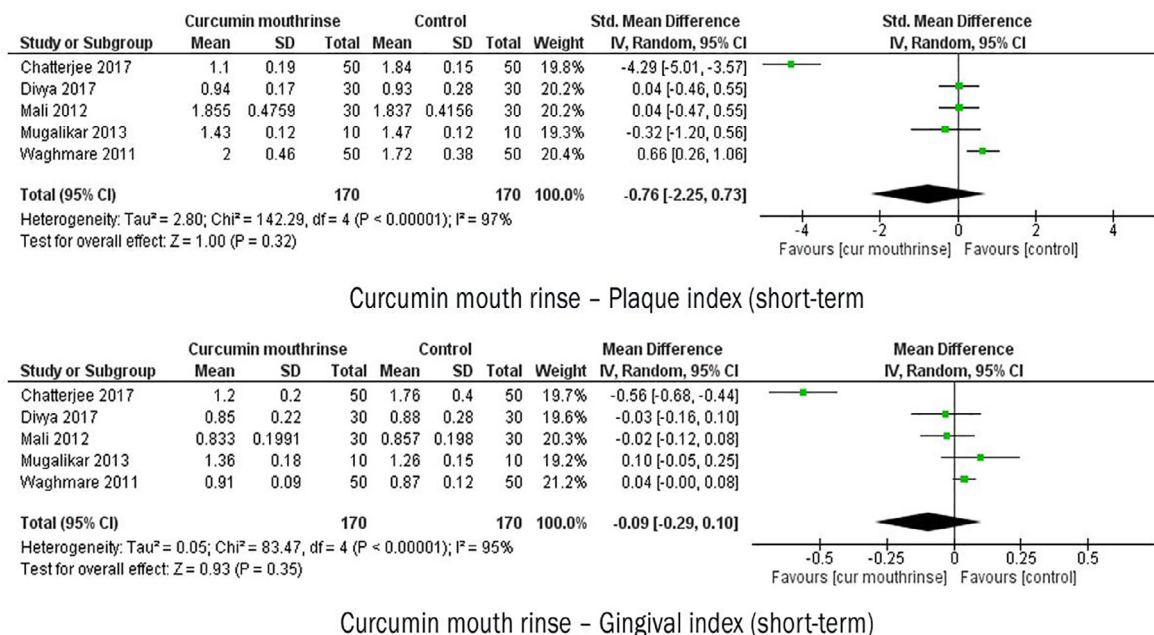


Fig. 4 Comparison of curcumin mouth rinse vs control.

Gingival inflammation was assessed by Silness and Loe gingival index in all studies in all studies except one in topical gel (Sharma and Kalsi, 2016) that used Lobene et al. modification of Silness and Loe.

Three studies in CC (Elavarasu et al., 2016; Gottumukkala et al., 2014; Singh et al., 2018), three in CTG (Dave et al., 2018; Kandwal et al., 2015; Singh et al., 2015), seven in CLDG studies (Bhatia et al., 2014; Ganai et al., 2019; Hugar et al., 2016; Jaswal et al., 2014; Nagasri et al., 2015; Nasra et al., 2017; Ravishankar et al., 2017), four in CMR (Arunachalam et al., 2017; Chatterjee et al., 2017; Divya, 2017; Mugalikar et al., 2013) and one in CSGI (Suhag et al., 2007) assessed the reduction in dental plaque using Loe and Silness plaque index while three CLDG studies (Anitha et al., 2015; Anuradha et al., 2015; Behal et al., 2011), one CTG study (Sharma and Kalsi, 2016), one CSGI study (Nandini et al., 2012) and two studies in CMR (Mali et al., 2012; Waghmare et al., 2011) assessed reduction in dental plaque using the Turesky Gilmore modification of Quinley–Hein plaque index.

Short-term gingival score outcome in curcumin subgingival irrigation group and long-term evaluation of gingival score, plaque score and probing pocket depth under curcumin chips have not been included in the meta-analysis due to insufficient studies for comparison.

3.3. Risk of bias

Fig. 2 depicts the risk of bias graph. It was observed that allocation concealment and blinding of participants had higher proportions of bias across the studies. Risk of bias within individual studies are also given in Fig. 2.

3.4. Synthesis of results

3.4.1. Curcumin local delivery gel

In eight studies involving 370 participants we found no statistically significant difference in the long-term plaque scores

[SMD -0.73 , 95% CI: -1.63 to 0.16] of curcumin gel when locally delivered as compared to that of control (Fig. 3). Statistical heterogeneity was found to be high (93%).

Also, in case of long-term gingival index in four studies involving 180 participants, there was no statistically significant difference in the gingival inflammation [MD -0.04 , 95% CI: -0.37 to 0.29] using curcumin gel compared to the control (Fig. 3). Statistical heterogeneity was found to be high (94%).

For the long-term evaluation of probing pocket depth in nine studies involving 400 participants, statistically significant difference was found in the reduction in pocket depth [MD -0.87 , 95% CI: -1.31 to -0.43] using curcumin gel as compared to the control (Fig. 3). Statistical heterogeneity was found to be high (93%).

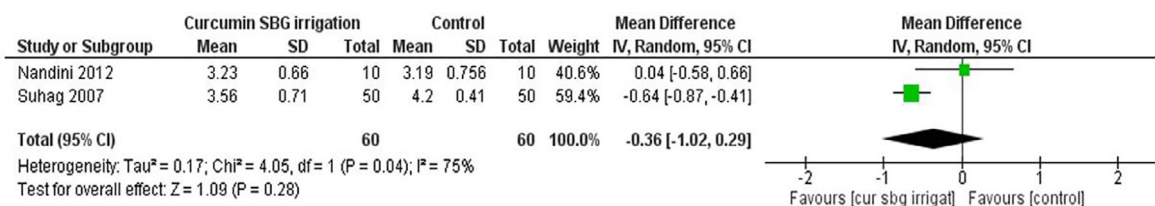
3.4.2. Curcumin topical gel

For the short-term evaluation of plaque score and gingival score in three studies each with 140 participants, we found no statistically significant difference in the reduction of scores when curcumin topical gel was compared with control [SMD -0.05 , 95% CI: -1.05 to 0.96] and [SMD 0.19 , 95% CI: -0.39 to 0.77] respectively (Fig. 3). Statistical heterogeneity was high for plaque index (88%) while it was moderate for gingival index studies (66%).

3.4.3. Curcumin mouth rinse

In the five studies done for the evaluation of short-term plaque scores involving 340 participants, no statistically significant difference in the reduction of dental plaque [SMD -0.76 , 95% CI: -2.25 to 0.73] was observed when curcumin mouth rinse was compared to control (Fig. 4). High statistical heterogeneity was observed (97%).

Short-term evaluation of gingival scores also did not show a significant reduction in the five studies involving 340 participants [MD -0.09 , 95% CI: -0.29 to 0.10] when curcumin mouth rinse was compared to control (Fig. 4). High statistical heterogeneity was observed (95%).



Curcumin subgingival irrigation – Probing pocket depth (short-term)

Fig. 5 Comparison of Curcumin sub gingival irrigation vs control.

3.4.4. Curcumin subgingival irrigation

For the short-term evaluation of probing pocket depth, no statistically significant reduction in the scores was found [MD -0.36 , 95% CI: -1.02 to 0.29] between curcumin subgingival irrigation and control in two studies involving 120 participants (Fig. 5). High statistical heterogeneity was observed (75%).

4. Discussion

We assessed if curcumin could be used as an alternative to the commercially available adjunct like chips, gels, mouth rinses and subgingival irrigation.

The primary objective of periodontal treatment is to decrease the microbial load hence improving the clinical parameters of plaque index, gingival index, and pocket depth. SRP remains the gold standard of periodontal treatment with the use of various other adjuncts (Bhatia et al., 2014). Curcumin known for its anti-inflammatory, antioxidant, antibacterial and wound healing properties (Bhatia et al., 2014) is also used as an adjunct therapeutic modality.

The role of dental plaque as a risk factor for periodontal disease is very well established. Curcumin gel (topical) is found effective in reducing plaque for a short term (up to 14 days) though statistically not significant, which could be attributed to the antiplaque properties of curcumin as described in previous literature (Singh et al., 2015). The anti-microbial property exhibited by curcumin could more likely be due to its ability to inhibit bacterial lipopolysaccharide-induced cytokine expansion and bacterial quorum sensing systems (Kandwal et al., 2015). The reduction in the plaque scores could also possibly be attributed to curcumin's antibiofilm activity as curcumin inhibits production of biofilm and disperses the biofilm made by micro-organisms (Dave et al., 2018).

The short-term reduction in gingival inflammation of curcumin topical gel when compared to the control (CHX/SRP alone) may be attributed to curcumin's anti-inflammatory property (Singh et al., 2015). They evaluated the anti-inflammatory effect on gingiva and stated a possible mechanism of action due to the inhibition of inflammatory mediators. It selectively inhibits the synthesis of prostaglandin E2 and thromboxane and not the synthesis of prostacyclin. However, the difference was not statistically significant.

Long-term probing pocket depth scores showed a significant reduction in the curcumin local drug delivery group. Considering probing pocket depth as one of the key periodontal outcome indicators, this observation is of clinical significance. However, no significant difference were noted in short term PPD for subgingival irrigation though the reduction was more in curcumin group. It could possibly be due to curcumin's anti-inflammatory and wound healing properties (Dave et al.,

2018). Curcumin helps accelerating wound healing by increasing fibronectin and promoting epithelial cell migration to the wound site (Bhatia et al., 2014).

No difference was observed between curcumin mouth rinse and the control group for decrease in gingival inflammation. All trials had used CHX as control. Mouth rinses require substantivity to maintain its efficacy. CHX has been proven to have this substantivity for 12 h and is highly effective whereas the substantivity of curcumin mouth rinse is not known. Based on the gingival or plaque score reduction results, there is not enough evidence to suggest curcumin mouth rinse is superior to CHX. Therefore, we did not find curcumin mouth rinse better for the treatment of specific oral conditions (gingivitis or periodontitis) unlike CHX. However, with regard to the concerns of adverse effects of long-term use of CHX, curcumin mouth rinse may be suggested as an alternative.

Studies conducted by Merlin et al. (2014, cited in Varghese et al., 2014) and Sukumari et al. (2016, cited in Elavarasu et al., 2016) was not included for meta-analysis due to missing data. In addition, a study done (Gottumukkala et al., 2013) comparing the curcumin subgingival irrigation with CHX was not included as the technique followed for the subgingival irrigation was different than the standard.

The results of this review should be interpreted with caution due to the following limitations. Clinical heterogeneity was observed with regard to concentrations and forms of curcumin used in the included studies. Few studies had small sample sizes which could probably be the reason for the high statistical heterogeneity. Also, the sample size in the studies stated above are small with participants ranging from 20 to 60 subjects and only two studies with subjects of 100 and 150. Due to this variation, this systematic review and meta-analysis of studies would have provide better estimates of clinical outcomes compared to individual study results.

5. Conclusion

Curcumin topical and local delivery gel, mouth rinses and sub-gingival irrigants were found to be equally effective compared to the routinely used agents for reduction of plaque and gingival inflammation. Curcumin local delivery gel had greater reduction in probing pocket depth. Therefore, our findings suggest that curcumin can be used as an alternative to latter although not better.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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