KEY WORDS
Home-based bleaching, Tooth Bleaching, Tooth Bleaching Agents, Bleaching Agents

Cochrane systematic review

HOME-BASED CHEMICALLY-INDUCED WHITENING (BLEACHING) OF TEETH IN ADULTS. A SHORTENED VERSION OF COCHRANE SYSTEMATIC REVIEW

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PURPOSE. To evaluate the effects of home-based tooth whitening products with chemical bleaching action, dispensed by a dentist or over-the counter.

MATERIALS AND METHODS. Several databases were searched till June 2018 with no language, publication year or publication status restrictions. We included in our review randomised controlled trials (RCTs) which involved adults who were 18 years and above and compared dentist-dispensed or over-the-counter tooth whitening (bleaching) products with placebo or other comparable products.
Two review authors independently selected trials. Two pairs of review authors independently extracted data and assessed risk of bias. We estimated risk ratios (RRs) for dichotomous data, and mean differences (MDs) or standardised mean difference (SMD) for continuous data, with 95% confidence intervals (CIs). We assessed the certainty of the evidence using the GRADE approach.

RESULTS. We included 71 trials in the review with 26 studies (1398 participants) comparing a bleaching agent to placebo and 51 studies (2382 participants) comparing a bleaching agent to another bleaching agent. Two studies were at low overall risk of bias; two at high overall risk of bias; and the remaining 67 at unclear overall risk of bias.
The bleaching agents (carbamide peroxide (CP) gel in tray, hydrogen peroxide (HP) gel in tray, HP strips, CP paint-on gel, HP paint on gel, sodium hexametaphosphate (SHMP) chewing gum, sodium tripolyphosphate (STPP) chewing gum, and HP mouthwash) at different concentrations with varying application times whitened teeth compared to placebo over a short time period (from 2 weeks to 6 months), however the certainty of the evidence is low to very low.
In trials comparing one bleaching agent to another, concentrations, application method and application times, and duration of use varied widely. Most of the comparisons were reported in single trials with small sample sizes and event rates and certainty of the evidence was assessed as low to very low. Therefore, the evidence currently available is insufficient to draw reliable conclusions regarding the superiority of home-based bleaching compositions or any particular method of application or concentration or application time or duration of use.

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Tooth sensitivity and oral irritation were the most common side effects which were more prevalent with higher concentrations of active agents though the effects were mild and transient. Tooth whitening did not have any effect on oral health-related quality of life.

CONCLUSIONS We found low to very low-certainty evidence over short time periods to support the effectiveness of home-based chemically induced bleaching methods compared to placebo for all the outcomes tested. When one bleaching agent was compared to another, we were unable to draw any conclusions regarding the superiority of home-based bleaching compositions or any particular method of application or concentration or application time or duration of use, as the overall evidence generated was of very low certainty.

CONFLICT OF INTEREST STATEMENT The authors report no conflicts of interest related to this review

INTRODUCTION

Description of the condition

The importance of aesthetic dentistry lies in the fact that a smile can improve the quality of life[1,2]. The colour of the teeth is an important factor that determines the smile and tooth discolouration is a commonly reported problem[3,4]. Changes in colour or translucency of a tooth may be due to extrinsic or intrinsic staining. Extrinsic staining is due to chromatogenic substances which adhere to the tooth surface and can be removed during routine prophylactic procedures. Common causes for extrinsic staining include smoking, food pigments and metals. Intrinsic stains are integrated into the tooth structure and are difficult to remove[1]. They may be caused due to various reasons like genetic disorders (dentinogenesis imperfecta, amelogenesis imperfecta, thalassaemia, sickle cell anaemia), antibiotics (tetracyclines), high levels of fluoride intake, dental caries, pulpal haemorrhage or necrosis, root fillings or amalgam restorations[5-9]. Ageing also leads to changes in tooth colour as a result of darkening of dentine (due to the formation of secondary dentine) and thinning of enamel. Intrinsic stains can be treated by bleaching agents which penetrate into the tooth structure.

Description of the interventions

Tooth whitening or bleaching is a minimally invasive aesthetic treatment that is gaining popularity, especially among females[2,10]. Bleaching methods can be broadly classified into internal and external. Internal bleaching is performed in-office after endodontic treatment for non-vital teeth. Vital bleaching is an external bleaching method that may be performed in-office (power bleaching) or at home under the supervision of a dentist. Over the counter or consumer purchased products are also available at supermarkets and pharmacies. At home bleaching techniques can be self-administered, require less chairside time, are economical and safe with few adverse effects. However, they require high patient compliance. On the other hand, some patients may use it overzealously which leads to thermal sensitivity[11].

The active ingredient commonly used for external bleaching is Hydrogen peroxide (HP). Carbamide peroxide is also used which breaks down into Hydrogen peroxide and Urea in contact with water. HP in the initial phase diffuses through the inter-prismatic spaces. Thereafter its interaction with organic chromophores is influenced by temperature, pH, light and metal ca-

tions thereby changing the colour due to a chemically altered tooth surface[12]. Inherent lightness potential for a tooth is generally reached in 6 weeks and thereafter there is no improvement in the shade[13,14].

Apart from HP and CP, other chemicals used in external bleaching are Sodium percarbonate (SPC), Sodium hexametaphosphate (SHMP), Sodium tripolyphosphate (STPP) and Calcium peroxide in varying concentrations and using different treatment protocols[11].

Different modes of delivery of these bleaching agents have been described in literature.

Trays. The most common treatment modality is dentist-supervised HP or CP gels in custom trays with or without reservoir[15-17].

Strips. Whitening strips are thin flexible polyethene strips with varying concentrations of HP which can be applied directly to tooth surfaces. Such strips have limitations in that they reach only a finite number of teeth, do not adapt well to malposed teeth and may impinge on gingiva or interfere with speech.

Paint on gels or varnishes. These contain HP or CP and sometimes even SPC in a suspension that may be applied to the tooth surface using a brush. In such a system, the contact time is less and there are issues with the application of the varnish[6,18].

The mode of action of these chemicals when used as gels in trays, strips or paint-on is the chemical degradation on the chromogens by oxidizing the double bonds.

Mouth rinse. Low concentration of HP or SHMP may be used as whitening mouth rinse, but the use is limited to the prevention of new stains.

Chewing gums. Baking soda, SHMP and STPP have been used in whitening chewing gums which have additional benefits of increasing salivary flow and removing food debris and plaque[19-23]. These chemicals act by inhibiting adsorption of salivary proteins thus inhibiting and removing dental stain.

Dentifrices. HP and CP have been added to dentifrices for whitening[24]. Abrasives like alumina, dicalcium phosphate dihydrate and silica are used in dentifrices to remove stains by mechanical action with minimal loss of tooth structure[1]. Casein phosphopeptide - amorphous calcium phosphate is a remineralizing agent commonly used in whitening dentifrices to reduce adverse effects like increased sensitivity[25].

However, we excluded studies evaluating dentifrices from this review as the abrasive action was not under the purview of this review.

This review is an abridged version of an updated systematic review titled "Home-based chemically-induced whitening (bleaching) of teeth in adults" published in the Cochrane Database of Systematic Reviews in the year 2018[26]. This was an update of the previous review which was published in the year 2006[27]. The aim of the review was to evaluate the effects of home-based tooth whitening products with chemical bleaching action, dispensed by a dentist or over the counter.

The aim of this abridged version is to provide a comprehensive overview of the Cochrane systematic review and highlight the key aspects from the main review which may be of interest to the clinical practitioners.

MATERIALS AND METHODS

Criteria for considering studies for this review

Randomised controlled trials (RCT) comparing dentist dispensed or over the counter tooth whitening products with chemical bleaching action with placebo or other comparable products were included for the review. Trials were also restricted to adults aged 18 years and above. Only trials which clearly mentioned that the tooth whitening was applied at home were considered for the review.

The various comparisons that were included in the review were:

- Comparison of different interventions (dentist-supervised vs over the counter product, two different dentist-supervised products, two different over the counter products);
- Intervention *vs* no treatment or placebo;
- Interventions using different concentrations;
- Interventions using different time periods of application.

Search methods for identification of studies

The search was performed by the Cochrane Oral Health's Information Specialist for RCTs. Highly sensitive search strategy designed by Cochrane to identify RCTs was used along with subject search strategy. Search was performed till 12 June 2018 with no language, publication year or publication status restrictions. Search strategies were individually developed for Cochrane Oral Health's Trial register, Cochrane Central Register of Controlled trials, MEDLINE Ovid and Embase Ovid as described in **TABLE 1.** Search for ongoing studies was performed on US National Institutes of Health Ongoing Trials Register and WHO International clinical trials registry.

Study selections and data extraction

Two review authors Eachempati Prashanti (EP) and Salian Kiran (SK) screened the title and abstract for potentially eligible studies. Full text articles of all potentially eligible studies were distributed among two pairs of review authors EP and Ibrahim Ethem (IE) and SK and Puneet Gupta (PG). Characteristics of excluded studies were recorded in "Characteristics of excluded studies table" (**TABLE 2**). Disagreements were resolved by discussion and arbiter Sumanth Kumbargere Nagraj (SKN) was consulted when required. Non-English studies were assessed on the basis of the abstract and when required full-text articles were translated.

Two pairs of review authors (EP and IE, SK and PG) extracted data independently using data extraction form which was designed for this review and entered data in the "Characteristics of Included Studies table". Data from translators was checked and verified using google translate. Data extracted from each study included publication details, demographic details, inclusion and exclusion criteria, sample size, method of randomisation, allocation concealment, blinding, type of trial, method of assessing outcome and dropouts if any.

Risk of bias

We independently assessed the risk of bias in the included trials for seven domains: sequence generation; allocation concealment; performance bias and detection bias; incomplete outcome data; selective outcome reporting; and other biases. For each of these components, we assigned a judgement regarding the risk of bias as either "high", "low" or "unclear", based on guidance in section 8.5.d of the Cochrane Handbook for Systematic Reviews of Interventions[28]. We contacted the trial authors if details were missing in the publications or were unclear. We resolved disagreements through consensus. We recorded our judgements and justifications in "Risk of bias tables" for each included study and generated a "Risk of bias" summary figure.

Data synthesis

We analysed the data using Review Manager 5 software[29]. We combined data available from trials with similar comparisons (same concentration and duration of application) and outcomes in the meta-analysis. We used standardised mean differences to combine continuous data as some trials used different scales. We used the random-effects model in the meta-a-

TABLE 1 SEARCH STRATEGIES USED TO IDENTIFY ELIGIBLE TRIALS FOR THIS SYSTEMATIC REVIEW

Cochrane Oral Health's Trial Register	Cochrane Central Register of Controlled Trials (CENTRAL)	MEDLINE Ovid	Embase Ovid	Clinical Trials.gov	WHO International CTRI
1 [([(tooth or teeth or dental) and (whiten* or bleach*)]):ti,ab) AND (INREGISTER) 2 [([(tooth or teeth or dental) and (stain* and remov*)]):ti,ab) AND (INREGISTER) 3 (#1 or #2) AND (INREGISTER) 4 [("tooth whitening system" or "tooth bleaching system"):ti,ab) AND (INREGISTER) 5 [(tray* and (whiten* or bleach* or peroxide)):ti,ab) AND (INREGISTER) 6 [(strip* or dentifrice* or gel* or toothpaste* or paste* or rins* or mouthwash* or mouthrins* or "mouth wash*" or "mouth rins*"):ti,ab) AND (INREGISTER) 7 ("whitening kit*":ti,ab) AND (INREGISTER) 8 (#4 or #5 or #6 or 7) AND (INREGISTER) 9 (#3 and #8) AND (INREGISTER)	#1 [mh "tooth bleaching"] #2 [(tooth or teeth or dental) near/5 (whiten* or bleach* or (stain* near/3 remov*)]):ti,ab #3 #1 or #2 #4 ("tooth whitening system" or "tooth bleaching system"):ti,ab #5 [tray* and (whiten* or bleach* or peroxide)]:ti,ab #6 [mh dentifrices] #7 [(strip* or dentifrice* or gel* or toothpaste* or paste* or rins* or mouthwash* or mouthrins* or "mouth wash*" or "mouth rins*") and (whiten* or bleach* or peroxide)]:ti,ab #8 "whitening kit*":ti,ab #9 {or #4-#8} #10 #3 and #9	1. Tooth bleaching/ 2. [(tooth or teeth or dental) adj5 (whiten$ or bleach$ or (stain$ adj3 remov$)]).ti,ab. 3. 1 or 2 4. ("tooth whitening system" or "tooth bleaching system").ti,ab. 5. (tray$ and (whiten$ or bleach$ or peroxide)).ti,ab. 6. Dentifrices/ 7. [(strip$ or dentifrice$ or gel$ or toothpaste$ or paste$ or rins$ or mouthwash$ or mouthrins$ or "mouth wash$" or "mouth rins$") and (whiten$ or bleach$ or peroxide)].ti,ab. 8. "whitening kit$".ti,ab. 9. or/4-8 10. 3 and 9 This subject search was linked to the Cochrane Highly Sensitive Search Strategy (CHSSS) for identifying randomised trials in MEDLINE: sensitivity- maximising version (2008 revision) as referenced in Chapter 6.4.11.1 and detailed in box 6.4.c of theCochrane Handbook for Systematic Reviews of Interventions, Version 5.1.0 (updated March 2011) (Lefebvre 2011). 1. randomised controlled trial.pt. 2. controlled clinical trial.pt. 3. randomized.ab. 4. placebo.ab. 5. drug therapy.fs. 6. randomly.ab. 7. trial.ab. 8. groups.ab. 9. or/1-8 10. exp animals/ not humans.sh. 11. 9 not 10	1. tooth discoloration/ 2. [(tooth or teeth or dental) adj5 (whiten$ or bleach$ or (stain$ adj3 remov$)]).ti,ab. 3. 1 or 2 4. tooth bleaching agent/ 5. ("tooth whitening system" or "tooth bleaching system").ti,ab. 6. (tray$ and (whiten$ or bleach$ or peroxide)).ti,ab. 7. toothpaste/ 8. (strip$ or dentifrice$ or gel$ or toothpaste$ or paste$ or rins$ or mouthwash$ or mouthrins$ or "mouth wash$" or "mouth rins$").ti,ab. 9. "whitening kit$".ti,ab. 10. or/4-9 11. 3 and 10 This subject search was linked to an adapted version of the Cochrane Embase Project filter for identifying randomised controlled trials in Embase Ovid (see http://www.cochranelibrary.com/help/central-creation-details.html for information). 1. Randomized controlled trial/ 2. Controlled clinical study/ 3. Random$.ti,ab. 4. randomization/ 5. intermethod comparison/ 6. placebo.ti,ab. 7. (compare or compared or comparison).ti. 8. ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab. 9. (open adj label).ti,ab. 10. ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab. 11. double blind procedure/ 12. parallel group$1.ti,ab. 13. (crossover or cross over).ti,ab. 14. ((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant $1)).ti,ab. 15. (assigned or allocated).ti,ab. 16. (controlled adj7 (study or design or trial)).ti,ab. 17. (volunteer or volunteers).ti,ab. 18. trial.ti. 19. or/1-18 20. (exp animal/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans).ti.) 21. 19 not 20	whiten and teeth bleach and teeth tooth and stain and removal	whiten and tooth or whiten and teeth bleach and tooth or bleach and teeth tooth and stain and removal

TABLE 2 CHARACTERISTICS OF EXCLUDED STUDIES

Reason for exclusion	Trial ID*
In-office bleaching: Six trials	Burgio 2001; Matis 2005; Zantner 2006; Martin 2015; NCT02603354; NCT02682329
Children or adolescents in as participants: Nine trials	Tam 1999; Donly 2002; Donly 2002a; Loyola-Rodriguez 2003; Gerlach 2004d; Cardoso 2010; Corby 2014; Pinto 2014; Pinto 2017
Mechanical method of stain removal like toothbrushing, and whitening dentifrices: Five trials	Simon 2001; Gerlach 2002c; Gerlach 2003a; Karpinia 2003; Gerlach 2004a
Home bleaching agent was applied by a professional: One trial	Farrell 2006
Non-whitening chewing gum without an active ingredient: One trial	Yankell 1997
Effects of whitening agents on pulp	Schulte 1994; Fugaro 2004; Fugaro 2005
Dilution kinetics of whitening agents	Matis 1999; Matis 2002; Gerlach 2004c; Marques 2012
Outcome reported plaque retention post-bleaching: Two trials	Schiff 1994; Gursoy 2008
Outcome reported effect of bleaching on oral microflora: One trial	Alkmin 2005
Outcome reported effect of a desensitising agent: One trial	Leonard 2004
Outcome reported effect of coffee exposure on bleaching	Rezende 201
Outcome reported effect of bleaching on orthodontic brackets: One trial	Jadad 2011
Outcome reported effect of two different tray designs used during bleaching: One trial	Matis 2002a
Outcome reported efficacy of using a chromameter to assess bleaching: One trial	Gerlach 2002e
Abstracts of conference presentations: 22 trials	Andreana 2000; Dickinson 2000; Browning 2001; Donly 2001; Godson 2001; Sagel 2001; Smith 2001; Swift 2001; Gerlach 2002d; Lee 2003; Amini 2009; Auschill 2009; Lisante 2009; Anastasia 2010; Archila 2010; Amini 2011; Majeed 2011; Simon 2011; Walter 2011; Garcia-Godoy 2012; Mazur 2013; Perdigao 2013

**For the full text citation of the studies, refer the main review*

nalysis. If data were presented as adjusted mean and SE, we calculated SD from SE and considered the adjusted mean for analysis. If data were described in the form of ordinal outcomes, we converted the scale into dichotomous data by combining relevant adjacent categories and analysed using risk ratios and 95% CI. When data were presented as odds ratios, log (odds ratio) was calculated based on the odds ratios and 95% CI given in the trial and the generic inverse variance method was applied. We calculated mean difference and standard error in split-mouth and cross-over trials and analysed the data using the generic inverse variance method.

We assessed heterogeneity by examining the forest plot to check for overlapping CIs, using the Chi^2 test for heterogeneity with a 10% level of significance to detect inconsistency in study results that were not due to random error (chance), and the I^2 statistic to denote the percentage of inconsistency in results due to inter-trial variability that exceeded chance. We used the guidance given by the Cochrane Handbook for Systematic Reviews of Interventions to interpret the I^2 statistic[28].

To identify the reasons for clinical or methodological heterogeneity in meta-analyses, we carried out subgroup analyses based on different concentrations, varying application times and duration of treatment.

We tested for publication bias using funnel plots and a formal test investigation of the degree of asymmetry using the method proposed by Egger et al.[30] wherever possible.

RESULTS

Characteristics of trial settings and investigators

Of the 169 potentially eligible trials 68 trials were excluded (**TABLE 2**), 22 trials were classified as awaiting and one was an ongoing trial (**TABLE 3**). We included 71 trials in the review (78 reports) (details in PRISMA diagram) (**FIG. 1**).

Among the included trials, majority were from USA[13,31-71]. Seven trials were split mouth[13,37,58,59,72-74] and three had a crossover design[22,32,75]. All the remaining 61 trials were parallel-design trials. Twelve of the included trials had more than two groups for comparison[33,42,55,56,58,76-82]. Out of the 71 trials, 54 provided grant information and out of these one was government funded[83]. Other 53 trials were funded by pharmaceutical companies[13,20,22,31,32,35-51,53-56,58-65,67-71,74,75,78,79,81,82,84-91]. All included trials were conducted at single center.

Characteristics of participants

Forty-seven trials included both genders while the remaining 24 trials did not report on distribution of gender[15,22,33-35,39-41,51-53,57,59-61,63,70,73,77,79,83,85,89,92]. The minimum age included in the studies was 18 years and the maximum age was 79 years[66]. The minimum sample size was six[15] and the maximum sample size was 117[86] with a median value of 58.

Two trials compared the effects of bleaching agent on participants with tetracycline stains[53,58]. One trial discussed the effect of dietary habits of participants on tooth whitening[93]. One trial compared the effect of tooth whitening between smokers and non-smokers[75].

Outcomes and outcome measures reported

Primary outcomes

There were two primary outcomes of interest in this review.

1. Tooth whitening - assessed by the dentist using any relevant tool

Sixty-nine trials reported this outcome in the included studies which used two main methods to measure tooth color:

a. Value-oriented shade guides (subjective measurement) using ordinal scales (for e.g., 1 representing the lightest shade and 16 representing the darker shade) and

TABLE 3 CHARACTERISTICS OF TRIALS AWAITING CLASSIFICATION AND ONGOING TRIALS

Reason for classifying as awaiting	Trial ID*
Incomplete or missing data: 12 trials	Gegauff 1993; Reinhardt 1993; Rosenstiel 1996; Barnes 1998; Pohjola 2002; Ozcan 2003; Browning 2004; Ferrari 2004; Gambarini 2004; Braun 2007; Shin 2010; Simon 2014
Trials with no access to full texts: Eight trials	Heymann 1998; Sielski 2003; Gerlach 2004b; Guerrero 2007; Bizhang 2017; Kim 2018; Maran 2018; Rossi 2018
Registered protocol of completed studies with no access to full text: Two trials	NCT02151058; NCT03217994
Ongoing trial:	NCT03026725

**For the full text citation of the studies, refer to the main review*

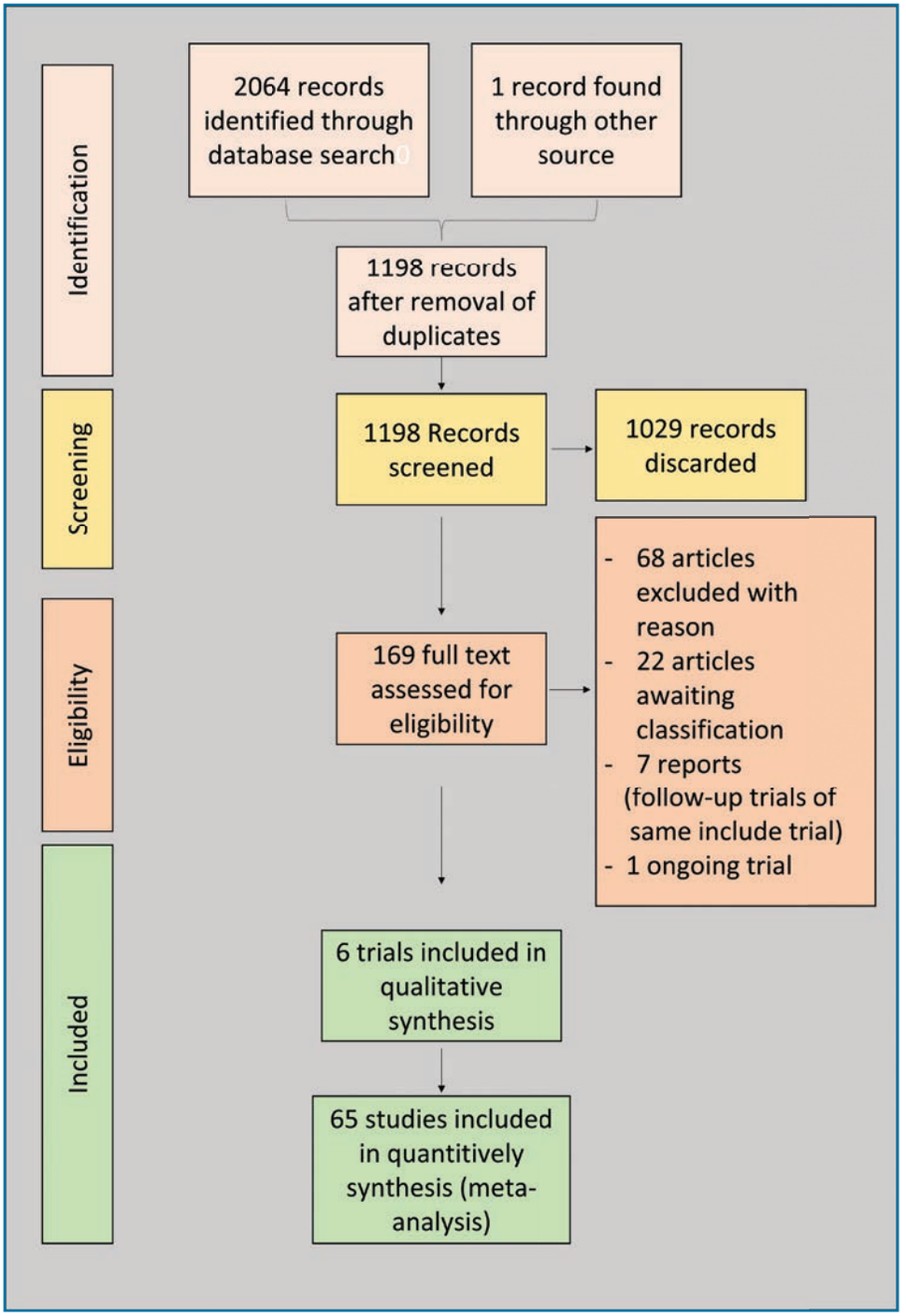

FIG. 1: *PRISMA flow diagram.*

b. Electronic devices/color measurement devices (objective measurement) using spectrophotometers, colorimeters and imaging systems which allow computation of CIE XYZ or CIEL*a*b* values described by commission internationale de l'éclariage (CIE 1978) an international standard for three-dimensional color space. In our review we considered the composite score represented by W* or E* (composite color change irrespective of the direction of change) wherever provided. In the absence of both, the value of L* (degree of lightness) is considered as it indicates a positive change towards increased lightness.

2. Tooth whitening - reported by the patient using any relevant tool

11 trials reported improvement in tooth whitening based on patient's satisfaction levels using visual analogue scale (VAS) as the outcome measure[34,37,52,58,76,80,81,88,93-95].

Secondary outcomes

There were three secondary outcomes of interest: Patient satisfaction or acceptability of the tooth whitening procedure (patient comfort) were reported in eight trials[37,53,70,81,84,90,91,93]. Adverse effects (any side effects reported due to the bleaching procedure) were reported in all except 14 studies[20,22,32,35,41,49,62,63,66,70,75,86,93,96]. Oral health-related quality of life was reported in three studies[34,81,93]. We described all the secondary outcomes reported in included studies qualitatively.

Characteristics at baseline

Inclusion and exclusion criteria

The included studies had patients who were adults above the age of 18 in good general health, having permanent dentition and who were available for multiple follow ups.

Authors excluded patients with hypersensitivity, previous history of bleaching, caries or restoration on the teeth, presence of prosthesis, periodontal pathology, or ongoing orthodontic treatment.

Thirty-one trials reported the baseline shade. A2 shade was the baseline in 12 trials[36,40,41,50,54,64,65,81,88-91], A3 shade in 14 trials[33,38,48,51,55,56,61-63,70,73,84,85,96], C1 shade in three trials[58,92,93] and two studies used Trubyte shade guide with B85[59] and B65[39] as the baseline shades.

Characteristics of interventions in included studies

Included trials were divided into two main groups as discussed below:

I. Bleaching agent* versus *placebo

26 trials were included in this group and had comparisons as shown below for the outcome of tooth whitening reported by the dentist (**TABLE 4**). Patient reported tooth whitening was presented in comparisons 1 and 3. Four comparisons discussed at least one secondary outcome (Comparisons 1, 3, 4, 5).

1. Six trials compared carbamide peroxide (CP) gel in tray *versus* placebo[33,57,66,76,79,94].
2. Two trials compared hydrogen peroxide (HP) gel in tray *versus* placebo[60,96].
3. Ten trials compared HP strips *versus* placebo[34,40,43,44,54,65,68,69,78,81].
4. One trial compared CP paint-on gel *versus* placebo[70].
5. Two trials compared HP paint-on gel *versus* placebo[82,86].
6. Three trials compared sodium hexametaphosphate (SHMP) chewing gum *versus* placebo[22,32,75].
7. One trial compared sodium tripolyphosphate (STPP) chewing gum *versus* placebo[20].
8. One trial compared HP mouthwash *versus* placebo[49].

TABLE 4 BLEACHING AGENT *VERSUS* PLACEBO: CHARACTERISTICS OF INTERVENTIONS

Comparisons	Study	Intervention used for analysis	Duration
CP gel in tray *vs* placebo	Hyland 2015 (Multi-arm)	5% carbamide peroxide gel 10% carbamide peroxide gel	2 hours per day for 2 weeks
	Browning 2008 (Multi-arm)	10% carbamide peroxide, 0.5% potassium nitrate, 0.25% sodium fluoride	11 weeks
	Aka 2017 (Multi-arm)	10% carbamide peroxide gel	8 to 10 hours daily for 14 days
	Russel 1996 and Matis 1998	10% carbamide peroxide	2 weeks (follow-up was done for 6 months)
	Mederios 2008	10% carbamide peroxide	Overnight for 3 Weeks
HP gel in tray *vs* placebo	Mohan 2008	6% hydrogen peroxide	Twice daily for 2 weeks
	Meyers 2003	3% hydrogen peroxide Nightguard	2 weeks
HP Strip *vs* placebo	Gerlach 2004e	10% hydrogen peroxide whitening strips	30 min for 1 week
	Bizhang 2007	6% hydrogen peroxide whitening strips	Twice daily for 2 weeks
	Kugel 2000	5.3% hydrogen peroxide	Twice daily for 30 min for 2 weeks
	Swift 2009	6% hydrogen peroxide	Twice daily for 2 weeks and 6 weeks
	Wong 2004 (Multi-arm)	6% hydrogen peroxide	Twice daily for 30 min for 2 weeks
	Papas 2009	10 % hydrogen peroxide	Twice daily for 30 min for 1 week and 2 weeks
	Swift 2004	14% hydrogen peroxide	Twice daily for 30 min for 3 weeks
	Garcia-Godoy 2004	14% hydrogen peroxide	Twice daily for 30 min for 6 weeks
	Gerlach 2002	5.3% hydrogen peroxide	Twice daily for 30 min for 2 weeks and follow up for 6 months
	Bruhn 2012	14% hydrogen peroxide	Twice daily for 3 weeks (Patient reported improvement in shade)
CP paint on gel *vs* placebo	Nathoo 2002	18% carbamide peroxide gel	30 sec after brushing and before rinsing for 3 weeks
HP paint on gel *vs* placebo	Xu 2007	6% hydrogen peroxide gel	Twice daily for 2 weeks
	Collins 2004	5.9% hydrogen peroxide gel	Twice daily for 2 weeks (Evaluation was also done at end of 1 week)
SHMP chewing gum *vs* placebo	Biesbrock 2004- (Crossover)	7.5% SHMP chewing gum	For 5 minutes daily for 2 days followed by 60 seconds rinse with tea. This was repeated approximately 8 times a day
	Porciani 2006 (Crossover)	4% SHMP on 54 subjects each in placebo and experimental groups.	The subjects chewed chewing gum 4 times a day for 12 weeks
	Walters 2004	5.6% SHMP on 54 subjects each in placebo and experimental groups.	3-day cross-over trial separated by a 10-day wash out period including
STPP chewing gum *vs* placebo	Porciani 2010	sodium tripolyphosphate	3 times a day for 10 minutes for 6 weeks
HP mouth wash *vs* placebo	Hasturk 2004	1.5% fluoridated hydrogen peroxide-based mouth wash	Twice daily for 30 sec for 6 months

II. Bleaching agent* versus *bleaching agent

Fifty-one trials were included in this group and had comparisons as shown below (**TABLE 5**). All the comparisons had tooth whitening assessed by dentist as an outcome. Five comparisons included patient reported tooth whitening (comparisons 1, 2, 3, 7, 8). Almost all comparisons discussed at least one secondary outcome (except comparison 11).

1. Eighteen trials compared CP tray *versus* CP tray[13,33,35,39,48,51,52,58,61,63,74,79,80,83,89,92,93,95].
2. Seven trials compared CP tray *versus* HP tray[15,38,59,72,76,77,91].
3. Ten trials compared HP strips *versus* CP tray[37,42,46,47,50,53,56,87,88,97].
4. Two trials compared HP strips *versus* HP tray[44,84].
5. Two trials compared HP strips *versus* HP strips[64,67].
6. One trial compared HP strip *versus* HP mouthwash[45].
7. Two trials compared CP paint-on *versus* HP strip[36,81].
8. Two trials compared HP paint-on *versus* HP strip[73,82].
9. One trial compared SPC paint-on *versus* HP strip[78].
10. Two trials compared CP paint-on *versus* CP paint-on[55,85].
11. One trial compared CP paint-on *versus* HP paint-on[62].
12. One trial compared HP paint-on *versus* HP paint-on[90].
13. One trial compared sodium percarbonate (SPC) paint-on *versus* CP paint-on[31].
14. One trial compared SPC paint-on *versus* HP paint-on[41].

Risk of bias in included studies

The overall risk of bias was low for two studies[48,56], and high for two studies[76,92]. The remaining 67 studies were assessed as unclear. The summary and details of the risk of bias assessment is given in **FIG. 2** and **TABLE 6**.

Description of effect of interventions

Bleaching agent versus *placebo*

For the outcome of tooth whitening as reported by the dentist, the bleaching agents CP gel in tray, HP gel in tray, HP strips, CP paint-on gel, HP paint-on gel, SHMP chewing gum, STPP chewing gum, and HP mouthwash at different concentrations with varying application times whitened teeth compared to placebo over a short time period (from 2 weeks to 6 months) (**FIG. 3**). However, SHMP chewing gum did not show any difference in tooth whitening at 12 weeks compared to placebo (MD -0.14, 95% CI,-0.38 to 0.10; 1 trial, 54 participants)[75].

For outcome of tooth whitening as reported by the patients, patients in the CP tray group were more satisfied by the bleaching effect compared to placebo[76,94]. Similarly patient satisfaction of whitening effect was highest for the HP strip group compared to the placebo[34,81].

Patient comfort was reported in one trial[70] and participants reported ease of application of the paint-on gel.

Most common adverse effects were gingival sensitivity, tooth sensitivity, tongue and throat sensitivity, gastrointestinal sensitivity which were more in intervention group compared to placebo group. However, the effects were transient and mild.

Bleaching agent versus *bleaching agent*

In trials comparing one bleaching agent to another, concentrations, application method and application times, and duration of use varied widely. For this shortened version of the Cochrane review, we chose to discuss a few comparisons which are commonly prescribed and available over-the counter. Rest of the comparisons are presented in the **TABLE 7**.

FIG. 2: *Risk of bias in included studies.*

TABLE 5 BLEACHING AGENT *VERSUS* BLEACHING AGENT: CHARACTERISTICS OF INTERVENTION

Comparisons	Study	Intervention used for analysis	Duration
CP tray *vs* CP tray	Nathoo 2001	10% carbamide peroxide 5% carbamide peroxide	6 to 8 hours daily for 1 week
	Hyland 2015	10% carbamide peroxide 5% carbamide peroxide	2 hours daily for 2 weeks
	Kowitz 1994	10% carbamide peroxide of two different brands	3 hours or more for 2 weeks
	Nathoo 1994	10% carbamide peroxide of two different brands	Twice daily for 2 hours for 2 weeks
	Cibirka 1999	10% carbamide peroxide of two different brands	Overnight for 2 weeks
	Tsubura 2005	10% carbamide peroxide of two different brands	Overnight for 2 weeks
	Turkan 2010	10% carbamide peroxide 28% carbamide peroxide	8 hours overnight and 20 minutes per day for 2 weeks
	Meireles 2010	10% carbamide peroxide 16% carbamide peroxide	2 hours per day for 2 weeks. Follow-up done after 1&2 year
CP tray *vs* CP tray	Gallo 2009	30% carbamide peroxide 30% carbamide peroxide + potassium nitrate	1 hour per day for 10 days
	Kose 2011	16% carbamide peroxide 16% carbamide peroxide + potassium nitrate	6 hours for 2 weeks
	Giniger 2005	16% carbamide peroxide 16% carbamide peroxide + amorphous calcium phosphate	3 hours per day for two weeks. Follow-up done up to 5 years
	Matis 2006 (Split-mouth)	10% carbamide peroxide 15% carbamide peroxide	For 6 months
	Krause 2008	10% carbamide peroxide 17% carbamide peroxide	2 hours per day for 2 weeks
	Matis 2006 Kihn 2000	10% carbamide peroxide 16% carbamide peroxide	Overnight for 2 weeks
	Navarra 2014 Browning 2008	10% carbamide peroxide 10% carbamide peroxide + potassium nitrate + sodium fluoride	Overnight for 2 weeks
CP tray *vs* CP tray	Tam 2001	10% carbamide peroxide 10% carbamide peroxide + potassium nitrate	Overnight for 2 weeks
CP tray *vs* HP tray	Ziebolz 2007	20% carbamide peroxide 7.5% hydrogen peroxide	CP: 4 hours per day for 2 weeks HP: 30 minutes per day for 2 weeks
	Mokhlis 2000	20% carbamide peroxide 7.5% hydrogen peroxide	1 hour twice daily for 12 weeks
	Alonso 2014 (Multi arm)	10% carbamide peroxide 7.5% hydrogen peroxide	1 hour per day for 2 weeks
	Delgado 2007	20% carbamide peroxide 9% hydrogen peroxide	30 minutes per day for 2 weeks
	Aka 2017 (Multi-arm)	10% carbamide peroxide 9% hydrogen peroxide	8-10 hours per day for 2 week
	Berga-Caballero 2006	10% carbamide peroxide 3.5% hydrogen peroxide	CP: 3 hours per day for 24 days HP: 2 hours per day for 28 days
	Alonso 2006	10% carbamide peroxide 3.5% hydrogen peroxide + 5% potassium nitrate	3 hours per day for 4 weeks

(continues)

Comparisons	Study	Intervention used for analysis	Duration
HP strip *vs* CP Tray	Gerlach 2002b	5% carbamide peroxide gel+ 5% potassium nitrate 3.5% hydrogen peroxide strip	30 min per day for 1 weeks
	Gerlach 2000	10% carbamide peroxide gel 5.3% hydrogen peroxide strip	Gel: 2 hours a day for 2 weeks Strip:30 minutes twice daily for 2 weeks
	Gerlach 2002a	10% carbamide peroxide gel 5.3% hydrogen peroxide strip	Gel: 2 hours per day for 2 weeks Strip: twice daily for 1 hours for 2 weeks
	Hannig 2007	10% carbamide peroxide gel 5.3% hydrogen peroxide strip	Gel: 1 hours a day for 2 weeks Strip:30 minutes twice daily for 2 weeks
	Karpinia 2002	10% carbamide peroxide gel 5.3% hydrogen peroxide strip	Gel: 2 hours a day for 2 weeks Strip:30 minutes twice daily for 2 weeks
	Costa 2012 (Split mouth)	35% carbamide peroxide gel 14% hydrogen peroxide strip	30 minutes twice daily for 2 weeks. Each application separated by 30 minutes
	Ferrari 2007 Kugel 2002	10% carbamide peroxide gel 6% hydrogen peroxide strip	Gel: 2 hours a day for 2 weeks Strip:30 minutes twice daily for 2 weeks
	Botelho 2017	16% carbamide peroxide gel 6.5% hydrogen peroxide strip	Gel: 2 hours or overnight for 2 months Strip: on labial surface for 30 min for 3 months
	Li 2003	16% carbamide peroxide gel 7.5% hydrogen peroxide strip 7.5% hydrogen peroxide strip	Gel: Overnight for 21 days Strip: 30 minutes twice daily for 21 days
HP strip *vs* HP tray	Gerlach 2004	9.5% hydrogen peroxide gel 14% hydrogen peroxide strip	Gel: 30 minutes for 9 days Strip: 30 minutes for 21 days
	Auschill 2012	9.5% hydrogen peroxide gel 14% hydrogen peroxide strip	30 minutes twice daily for 2 weeks
HP strip *vs* HP tray	Oliveira 2013	9.5% high adhesion hydrogen peroxide strip 10% hydrogen peroxide strip (Control strip)	2 hours daily for 8 days and control strip for 30 minutes once daily for 8 days
	Shahidi 2005	6% hydrogen peroxide strip (thin strip: 0.12mm) 10% hydrogen peroxide strip (regular strip: 0.2mm)	30 minutes twice daily for 2 weeks
HP strip *vs* HP mouth wash	Gerlach 2005	2% hydrogen peroxide mouth wash 10% hydrogen peroxide strip	Mouth wash: 15 ml for 60 seconds for before brushing for 1 week Strip: 30 minutes twice daily for 1 week
CP paint on gel *vs* HP strip	Cronin 2005	2% hydrogen peroxide strip 18% carbamide peroxide paint on gel	Strip: twice daily for 2 weeks Gel: 30 min for 2 weeks
	Wong 2004	2% hydrogen peroxide strip 18% carbamide peroxide paint on gel	Strip: twice daily for 2 weeks Gel: 15 min for 2 weeks
HP paint on gel *vs* HP strip	Auschill 2007	5.9% hydrogen peroxide strip 5.9% hydrogen peroxide paint on gel	Strip: 30 minutes twice daily for 1 week Gel: 15 minutes twice daily for 1 week
	Xu 2007	6% hydrogen peroxide strip 5.9% hydrogen peroxide paint on gel	Strip: 30 minutes twice daily for 1 week Gel: 15 minutes twice daily for 1 week
SPC paint on gel *vs* HP strip	Bizhang 2007	19% sodium per carbonate paint on gel 6% hydrogen peroxide strip	30 minutes twice daily for 2 weeks
CP paint on *vs* CP paint on	Li 2004	18% carbamide peroxide paint on gel with different application protocol	2x: twice daily, no air drying and 15 minutes without eating/drinking 3x: 3 times daily, 30-second air drying and 30 minutes without eating/drinking 4x: 4 times daily, 30-second air drying and 30 minutes without eating/drinking
	Brunton 2004	18% carbamide peroxide paint on gel 16.4% carbamide peroxide paint on gel	30 seconds twice daily for 2 weeks

(continues)

Comparisons	Study	Intervention used for analysis	Duration
CP paint on *vs* HP paint on	Nathoo 2003	25% carbamide peroxide paint on gel 8.7% hydrogen peroxide paint on gel	15 min two times a day for 2 weeks
HP paint on *vs* HP paint on	Ziebolz 2008	6% hydrogen peroxide paint on gel + potassium flouride 6% hydrogen peroxide paint on gel	10 minutes twice daily for 1 week
SPC paint on *vs* CP paint on	Barlow 2003	18% carbamide peroxide paint on gel 19% sodium per carbonate paint on gel	Twice a day for 2 weeks
SPC paint on *vs* HP paint on	Gerlach 2003	8.7% hydrogen peroxide paint on gel 19% sodium per carbonate paint on gel	Overnight for 2 weeks

TABLE 6 SUMMARY OF RISK OF BIAS IN INCLUDED STUDIES

Characteristic	Judgement of risk	Included studies	Reason for Judgement
Random sequence generation	Low	Russell 1996; Cibirka 1999; Kihn 2000; Mokhlis 2000; Karpinia 2002; Kugel 2002; Li 2003; Myers 2003; Hasturk 2004; Giniger 2005; Delgado 2007; Krause 2008; Mederios 2008; Meireles 2010; Porciani 2010; Kose 2011; Auschill 2012; Alonso 2014; Aka 2017; Botelho 2017	Reported the method of sequence generation. For e.g., Quote: "The patients were randomly assigned to one of the two treatment groups and a control group using a randomisation table"
	Unclear	All remaining included trials	Only word 'randomly' is mentioned in the articles, but the method of sequence generation is not included For e.g., Quote:"...subjects were randomly assigned to one of two groups." However, method is not reported
	High	Nil	-
Allocation (selection bias)	Low	Kowitz 1994; Nathoo 1994; Mokhlis 2000; Li 2003; Myers 2003; Hasturk 2004; Giniger 2005; Navarra 2014	Reported concealment of allocation For e.g., Quote: "allocated groups were recorded on cards contained in sequentially numbered, sealed envelopes that were blindly assigned"
	Unclear	All remaining included trials	Method of allocation concealment is not explained
	High	Nil	-
Blinding (performance and detection bias)	Low	31 remaining trials (other than those below)	Satisfactory blinding of participants and personnel reported. For e.g., Quote: "Participants were supplied with blinded study kit boxes"
	Unclear	Nathoo 1994; Gerlach 2000; Kihn 2000; Matis 2000; Mokhlis 2000; Gerlach 2002b; Myers 2003; Nathoo 2003; Biesbrock 2004; Brunton 2004; Collins 2004a; Garcia-Godoy 2004; Li 2004; Swift 2004; Walters 2004; Cronin 2005; Gerlach 2005; Tsubura 2005; Alonso 2006; Berga-Caballero 2006; Matis 2006; Porciani 2006; Auschill 2007; Delgado 2007; Hannig 2007; Ziebolz 2007; Browning 2008; Mohan 2008; Ziebolz 2008; Gallo 2009; Auschill 2012; Bruhn 2012; Costa 2012; Oliveira 2013; Alonso 2014; Navarra 2014; Hyland 2015; Aka 2017; Botelho 2017	Studies have reported that blinding was done. However, details are not provided. For e.g., Quote: "double-blinded, randomised, controlled, parallel-group clinical trial." But method of blinding is not reported

(continues)

Characteristic	Judgement of risk	Included studies	Reason for Judgement
	High	Turkun 2010	In this study one group had a custom-made tray while the other used a prefabricated tray. There is a high risk that participants get to know the difference
Blinding of assessors	Low	Matis 1998; Kugel 2000; Nathoo 2001; Kugel 2002; Li 2003; Hasturk 2004; Giniger 2005; Porciani 2006; Bizhang 2007; Krause 2008; Porciani 2010; Turkun 2010; Auschill 2012; Bruhn 2012	Blinding of assessors was clearly explained in the studies. For e.g., Quote: "A dental assistant was responsible for group balancing, so that the evaluators could continue to be blind to which treatment group each patient was assigned"
	Unclear	Kowitz 1994; Nathoo 1994; Russell 1996; Cibirka 1999; Gerlach 2000; Kihn 2000; Matis 2000; Mokhlis 2000; Tam 2001; Gerlach 2002; Gerlach 2002a; Gerlach 2002b; Karpinia 2002; Nathoo 2002; Barlow 2003; Gerlach 2003; Myers 2003; Nathoo 2003; Biesbrock 2004; Brunton 2004; Collins 2004a; Garcia-Godoy 2004; Gerlach 2004; Gerlach 2004e; Li 2004; Swift 2004; Walters 2004; Wong 2004; Cronin 2005; Gerlach 2005; Shahidi 2005; Tsubura 2005; Alonso 2006; Berga-Caballero 2006; Matis 2006; Auschill 2007; Delgado 2007; Hannig 2007; Ferrari 2007; Xu 2007; Ziebolz 2007; Browning 2008; Mederios 2008; Mohan 2008; Ziebolz 2008; Gallo 2009; Papas 2009; Swift 2009; Meireles 2010; Kose 2011; Costa 2012; Oliveira 2013; Alonso 2014; Navarra 2014; Hyland 2015; Botelho 2017.	Authors described their studies as 'double-blinded', but no details of assessor blinding were given, or were single-blinded studies.
	High	Aka 2017	Due to lack of clarity of how teeth were selected for outcome assessment.
Incomplete outcome data (attrition bias)	Low	65 remaining trials	Either the studies had no dropouts or it was reported. For e.g., Quote: "2 patients from 6% HP/Go groups with 6 light shades of teeth did not attend the 6 months visit" [Comment: Plausible effect size (difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size]
	Unclear	Cibirka 1999; Tam 2001; Hasturk 2004; Shahidi 2005; Delgado 2007; Bruhn 2012	Trials did not mention any details about dropouts and there was a mismatch between the number randomised and number analysed.
	High	Nil	-
Selective reporting (reporting bias)	Low	All 71 trials	All outcomes described were reported. Conclusions are in accordance with the results
	Unclear	Nil	
	High	Nil	
Other potential sources of bias	Low	All 71 trials	None of the studies had any other relevant sources of bias
	Unclear	Nil	
	High	Nil	

TABLE 7 EFFECTS OF INTERVENTION FOR THE REMAINING COMPARISONS

Comparisons	Included studies	Outcome reported	Effect of intervention
HP strip *versus* HP mouthwash (10% HP whitening strips *versus* 2% HP rinse)	Gerlach 2005	Tooth whitening – reported by dentist	7-day use of resulted in significant tooth colour improvement in strip group relative to 2% HP rinse group (MD -1.10, 95% CI -1.49 to -0.71; 1 trial, 28 participants)
		Adverse events	Tooth sensitivity and oral irritation was more common in the strip group. All adverse events were mild in severity and no subjects discontinued treatment because of these events.
SPC paint-on *versus* HP strip (6% HP strips *versus* 19% sodium percarbonate (SPC) paint-on film)	Bizhang 2007	Tooth whitening – reported by dentist	HP strips group was favoured compared to SPS paint-on film (MD 0.93, 95% CI 0.59 to 1.27; 1 trial, 47 participants).
		Adverse events	Tooth sensitivity and oral irritation as the most common adverse events, with strip use. These adverse events were typically symptomatic only and confined to the treatment period.
CP paint-on *versus* HP paint-on (25% CP and 8.7% HP paint-on gels)	Nathoo 2003	Tooth whitening – reported by dentist	No evidence of difference was found between, the groups (MD -0.16, 95% CI -1.39 to 1.07; 1 trial, 59 participants)
HP paint-on *versus* HP paint-on. (6% hydrogen peroxide + potassium fluoride *versus* 6% hydrogen peroxide paint on gel)	Ziebolz 2008	Tooth whitening – reported by dentist	No evidence of a difference was found between the groups (MD -0.10, 95% CI -0.56 to 0.36; 1 trial, 67 participants)
		Patient comfort	In both groups similar proportion of the subjects reported lack of comfort.
		Adverse events	Tooth sensitivity in both groups with no evidence of a difference.
Sodium percarbonate (SPC) paint-on *versus* CP paint-on (19% sodium percarbonate *versus* 18% CP paint-on)	Barlow 2003	Tooth whitening – reported by dentist	sodium percarbonate group showed improved shade when used overnight compared to 18% CP used twice daily for 7 days and 14 days (14 days: MD -0.58, 95% CI -0.95 to -0.21; 1 trial, 38 participants)
		Adverse events	Gum irritation and lip irritation were reported in both groups. All events were mild and only one subject in the 18% CP group discontinued the treatment.
SPC paint-on *versus* HP paint-on (8.7% HP and 19% SPC paint-on)	Gerlach 2003	Tooth whitening – reported by dentist	Greater improvement in composite colour for the 19% SPC group (MD -0.36, 95% CI -0.71 to -0.01; 1 trial, 56 participants).
		Adverse events	Tooth sensitivity was reported in one subject from both groups. One subject in the 19% SPC film group reported oral sensitivity. All adverse events were symptomatic and mild in severity.

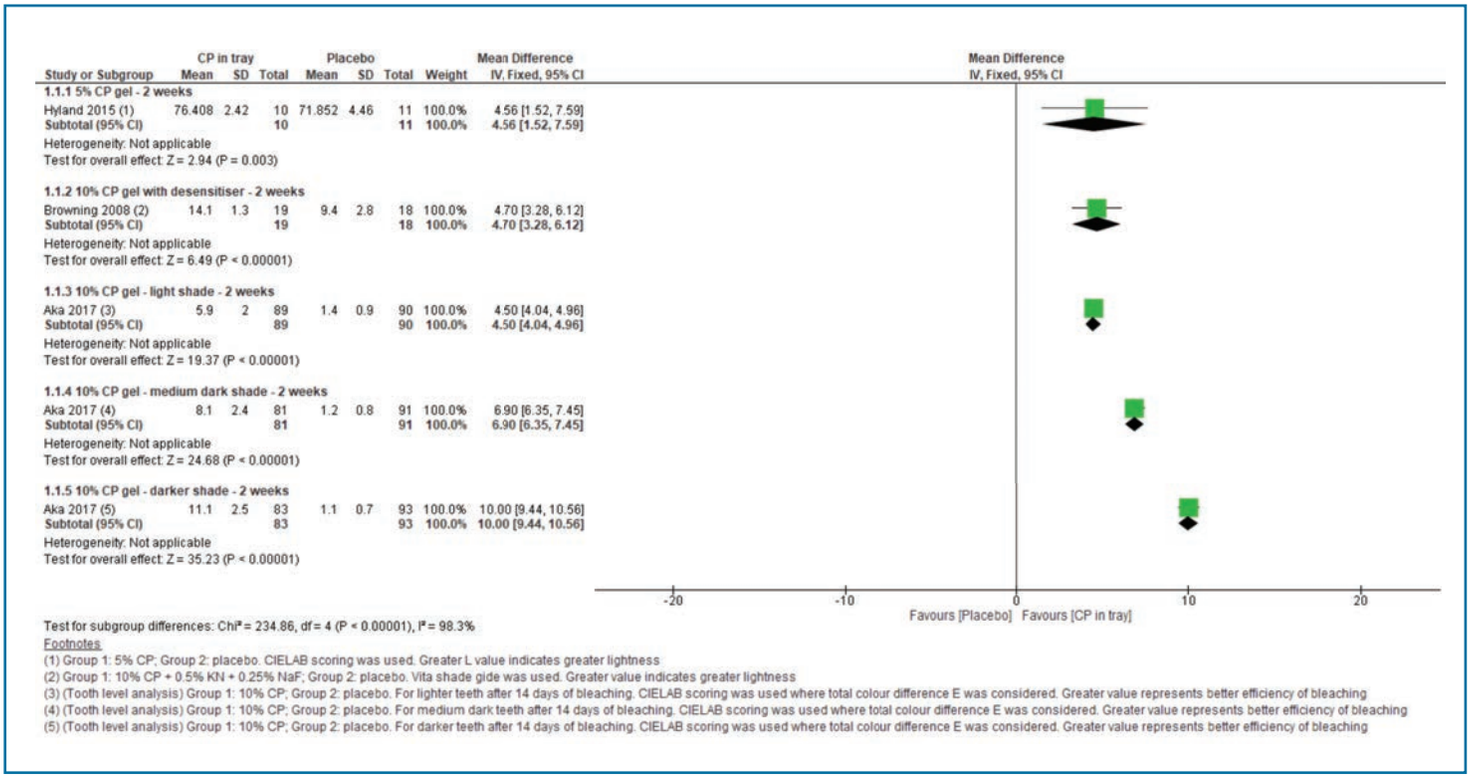

FIG. 3: *CP tray* versus *placebo - Forest plot.*

a. CP tray *versus* CP tray

Tooth whitening - reported by dentist

In most of the studies comparing different concentrations of CP in tray (**TABLE 5**), there was no evidence of difference between the groups[33,35,39,58,61,79,83,89,92,93] (**FIG. 4**).

Colgate Platinum (CLP) *versus* Rembrandt Lighten (RL)[52,63] (both 10% CP formulations) and Polanight (PN) *versus* Opalescence (OP)[74] (both 10% CP formulations) showed significantly higher L* values for CLP (MD -1.92, 95% CI -2.80 to -1.03; 2 trials, 88 participants) and PN (MD 1.46, 95% CI 0.13 to 2.79; 1 trial, 116 participants) respectively.

Compared to 10% CP, 16% CP with amorphous calcium phosphate (ACP)[48] (MD 0.78, 95% CI 0.37 to 1.19; 1 trial, 27 participants) and 15% CP13[51], had better whitening effect. (Kihn et al.[51]: MD 1.65, 95% CI 0.22 to 3.08; 1 trial, 52 participants); (Matis et al.[13]: MD 2.22, 95% CI 1.29 to 3.15; 1 trial, 25 participants).

Tooth whitening - reported by the patient

In none of the studies with different concentrations of CP, there was evidence of difference between the groups for this outcome[58,80,93,95].

Patient comfort

CP 10% group reported less interference with the tray when talking and less discomfort after application compared to the CP 16% group[93].

Adverse effects

Higher concentrations of CP had more sensitivity compared to lower concentrations[58,61,80,93].

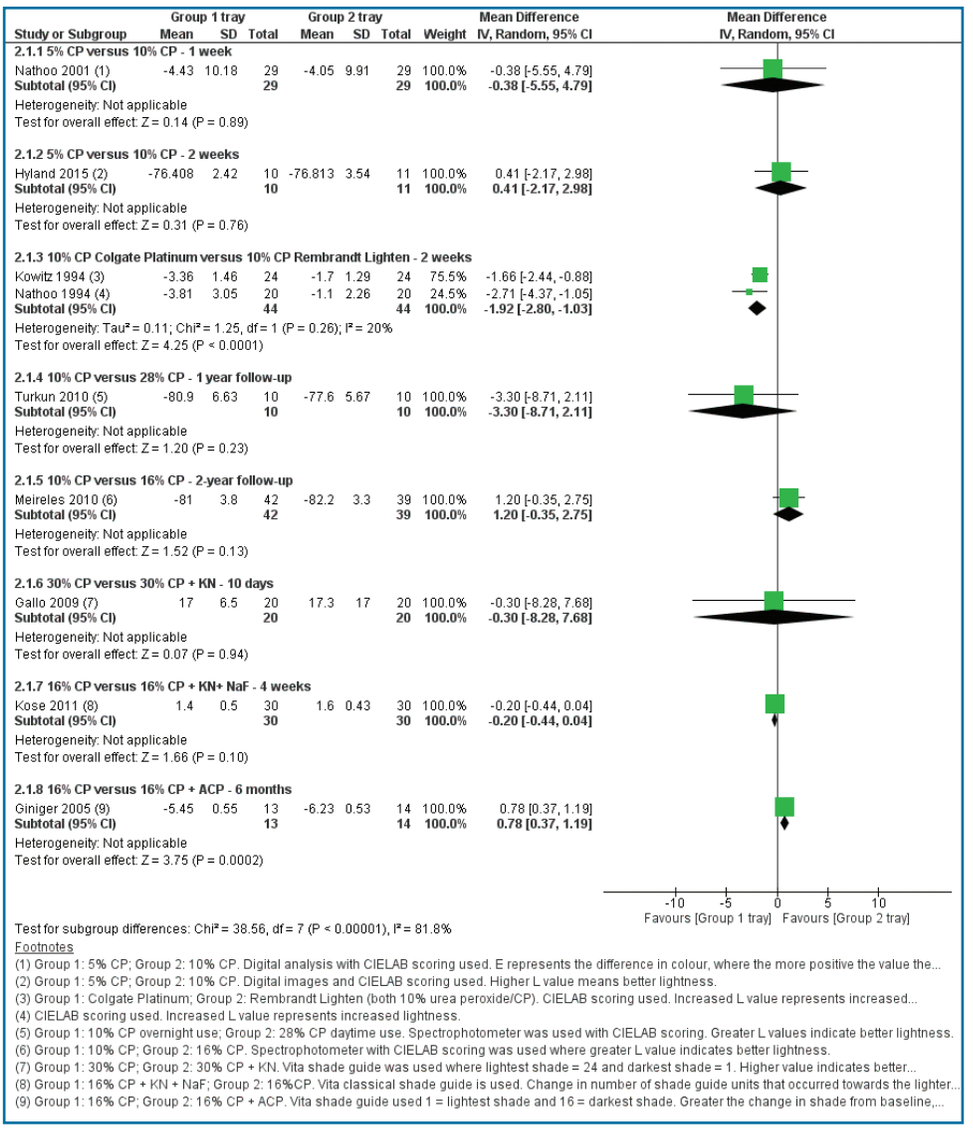

FIG. 4: *CP tray* versus *CP tray - Forest plot.*

Navarra et al.[83] and Browning et al.[33] reported bleaching agents with desensitiser with significantly lower sensitivity than the bleaching product that did not contain desensitising agents.

Oral health-related quality of life

In one trial[93], 16% CP group showed greater bleaching effect than 10% CP, however, OHRQoL was similar for both groups.

b. CP tray *versus* HP tray

Tooth whitening - reported by dentist

In most of the studies comparing different concentrations of CP and HP in tray, there was no evidence of difference between the groups[15,38,72,77,91].

Irrespective of the original shade, 10% CP bleaching groups in Aka 2017[76] multi-arm trial showed

significantly higher E values compared to 6% HP: medium dark and light shade: MD -2.22, 95% CI - 2.63 to -1.81; 2 trials, 349 teeth; darker shade: MD -4.30, 95% CI -5.02 to -3.58; 1 trial, 164 teeth). Similar concentrations of HP were used in another trial[59] and were compared to 20% CP. 20% CP group showed better lightness in the first 14 days. But at the end of the study there was no evidence of a difference between the two groups (12 weeks: MD 0.25, 95% CI 0.10 to 0.40; 1 trial, 24 participants).

Tooth whitening - reported by the patient
Aka et al.[76] reported that patients in the 10% CP (Opalescence PF) group were more satisfied with the bleaching effect than those in the 6% HP groups.

Patient comfort and adverse effects
No difference was found between the CP and HP groups for patient comfort[59,76,91] and adverse events[15,38,72,77].

c. HP strips *versus* CP tray
Tooth whitening -reported by dentist
In most of the studies comparing different concentrations of CP in tray and HP strips, there was no evidence of difference between the groups (**FIG. 5**)[37,42,46,50,87,88,97].
Four studies with similar concentrations (5.4-6.5%) of HP strips and 10% CP in tray[42,46,50,88] were combined in meta-analysis. However, there was no evidence of difference between the groups (MD -0.42, 95% CI -0.92 to 0.09; 4 trials, 149 participants).
In two studies[20,26], HP strip groups revealed greater composite colour change compared to CP tray groups (Gerlach et al.[47]: MD -0.71, 95% CI -1.35 to -0.07; 1 trial, 32 participants); (Kugel et al.[53]: 2 months: MD -2.63, 95% CI -4.45 to -0.81; 1 trial, 33 participants). In contrast, Li et al.[56] who used 6.5% HP strips and higher concentrations of CP in tray (16%) favoured the CP tray group (MD 2.10, 95% CI 1.16 to 3.04; 1 trial, 55 participants).

Tooth whitening - reported by the patient
In a trial by Costa et al.[37] although 75% of participants could not see the difference in tooth whitening between the tray and strips, 255 of the patients felt the side that was whitened by the tray was whiter. Hannig et al.[88] reported subjective colour score as reported by the patients and found no difference between the groups. (MD -0.41, 95% CI -2.05 to 1.23; 1 trial, 43 participants).

Patient comfort
In a split mouth trial[37], 83% of participants preferred the tray treatment to the strips. Kugel et al.[53] reported that two patients in the 10% CP tray group dropped out from the study after 1 month due to inconvenient regimen which included wearing the custom tray for two hours daily.

Adverse effects
Most of the trials did not show any difference in adverse events between groups[37,43,47,53,56,87,88]. Gerlach et al.[45] reported sensitivity was more common with the 20% CP tray. In one trial[50] tooth sensitivity was more common in the HP strip group and oral irritation was common in the CP tray group.

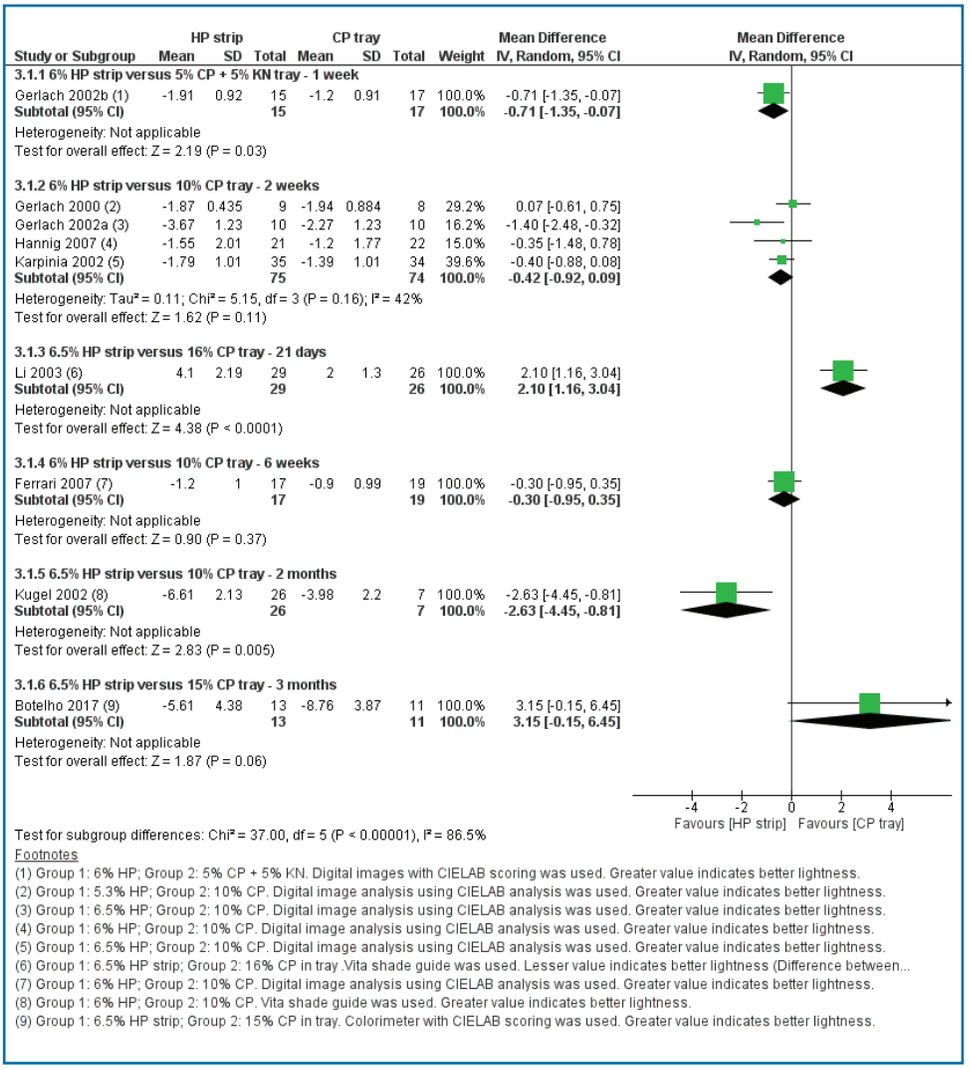

FIG. 5: *HP strip* versus *CP tray - Forest plot.*

d. HP strips *versus* HP tray

Tooth whitening - assessed by the dentist

Gerlach et al.[44] compared 14% HP strips and 9.5% HP in tray and reported a superior 2-fold increase in lightness in the strip group at the end of treatment (22 days) compared to the tray group (MD -1.40, 95% CI -2.35 to -0.45; 1 trial, 29 participants).

Comparison of 5% HP strips to 5.3% HP gel in tray in Auschill et al.[84] showed no difference in whitening between the groups at 7 days, 2 weeks and 18 months intervals (18 months: MD -0.06, 95% CI -2.24 to 2.36; 1 trial, 28 participants).

Patient comfort

Auschill et al.[84] reported that patients in the tray group were more comfortable than the strip group (MD 1.27, 95% CI 0.13 to 2.41; 1 study, 28 participants).

Adverse effects

Tooth sensitivity and oral irritation were mild and transient and did not differ between the groups[44,84].

e. HP strip *versus* HP strip

Tooth whitening - assessed by the dentist

In Oliveira et al.[64], 2-hour 9.5% HP high adhesion strips group demonstrated significant lightness improvement (L*) than the 30 minutes 10% HP group on 3, 5 and 9 days (9 days: MD -1.50, 95% CI -2.33 to -0.67; 1 trial, 29 participants).

Shahidi et al.[67] concluded that twice daily use of the very thin 10% HP gel strips were better than lower concentration strips (6% HP strips) (MD 0.68, 95% CI 0.16 to 1.20; 1 trial, 35 participants).

Adverse effects

Oliveira et al.[64] reported that nearly all adverse events were classified as mild in severity. Very thin gel group exhibited lower occurrence of oral irritation and higher tooth sensitivity compared to the 6% group[67].

f. CP paint-on gel *versus* HP strips

Tooth whitening - assessed by the dentist

6% HP strips were found to be more effective in tooth whitening compared to 18% CP paint-on gel for[36,81] (SMD 1.50, 95% CI 1.06 to 1.94; 2 trials, 102 participants; **FIG. 6**).

Tooth whitening - assessed by the patient

One trial[81] reported patient satisfaction, rated using a product satisfaction questionnaire. Satisfaction regarding the whitening effect of the product was highest for the strip group (91%) compared to the paint-on group (33%).

g. HP paint-on gel *versus* HP strips

Tooth whitening - assessed by the dentist

Two trials, Auschill et al.[73] and Xu et al.[82] showed that HP strips provided superior whitening compared to the paint-on gel group (Xu et al.[82] : MD 1.28, 95% CI 0.77 to 1.79; 1 trial, 33 participants); (Auschill et al.[73]: MD 2.70, 95% CI 2.08 to 3.32; 1 trial, 40 participants).

Tooth whitening - reported by the patient

One trial[73] reported no difference in patient satisfaction score between the HP strip and paint-on groups (MD -0.25, 95% CI -1.88 to 1.38; 1 trial, 40 participants).

Adverse effects

Auschill et al.[73] found a slightly higher tooth hypersensitivity and gingival irritation in the strip group, although there was no difference between the groups.

Publication bias

We found publication bias in different concentrations and application period in the comparison CP tray *versus* CP tray (**FIG. 7**).

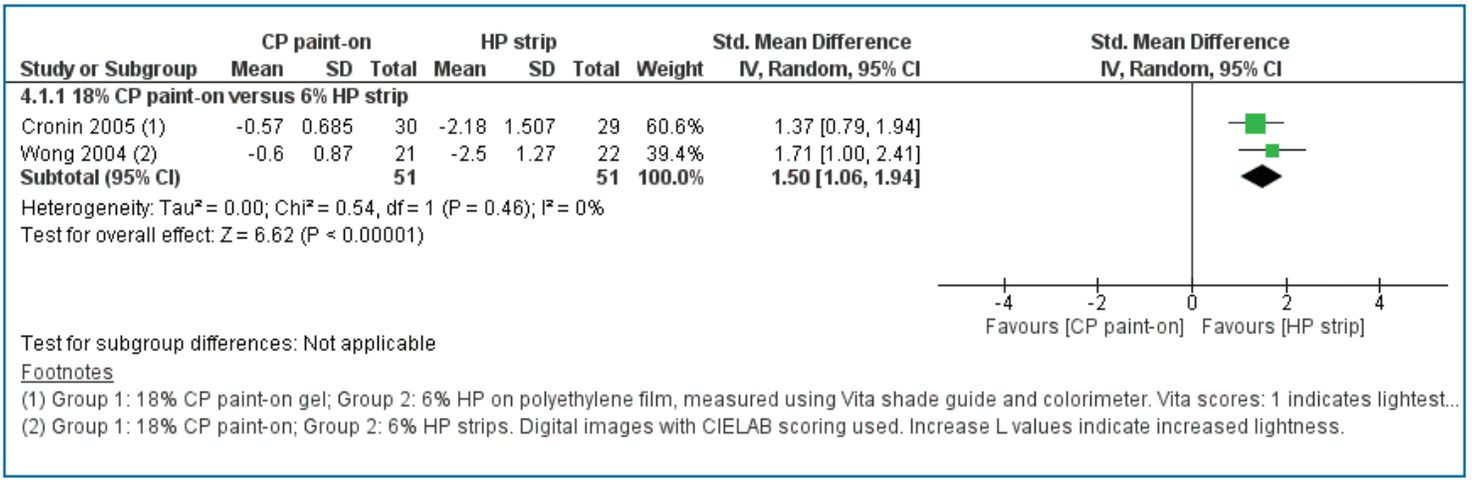

FIG. 6: *CP paint-on* versus *HP strip - Forest plot.*

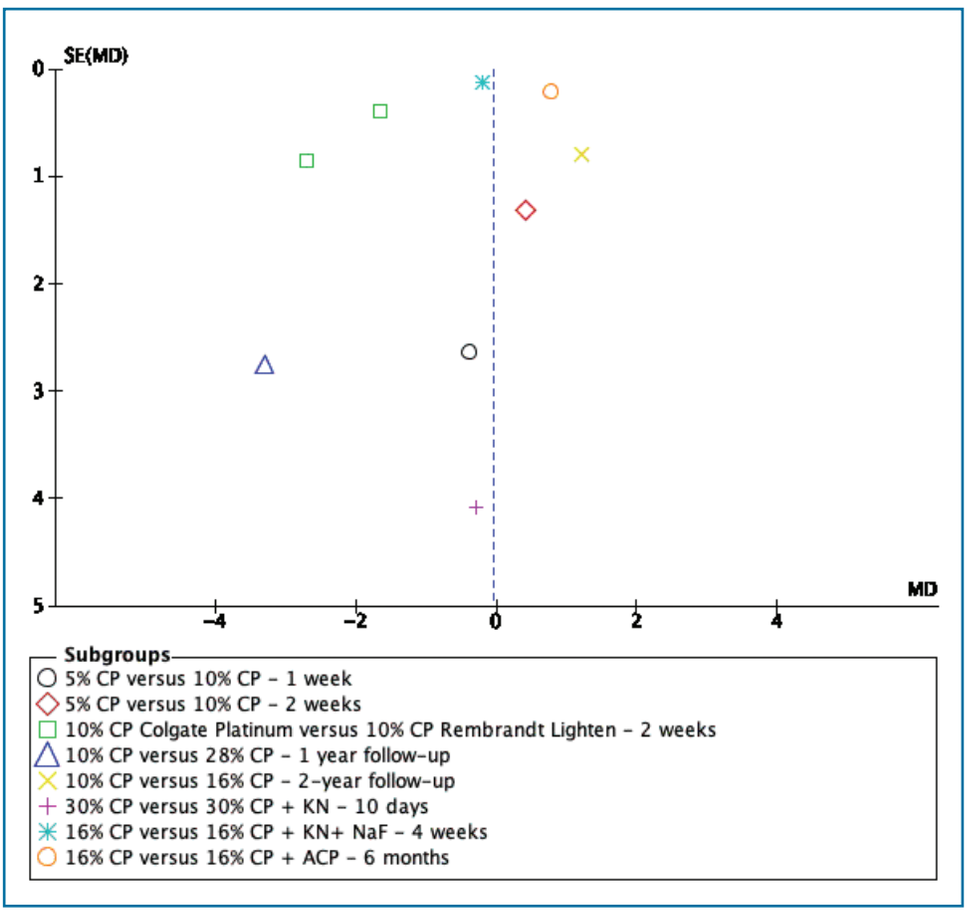

FIG. 7: *Funnel plot for CP tray* versus *CP tray.*

Summary of findings

We used the GRADE approach to interpret findings[98]. The overall certainty of the evidence was low to very low for all comparisons. When a bleaching agent was compared to placebo for the first outcome looking into improvement of shade as measured by the dentist, except for 6% HP strips compared to placebo, for which evidence was of low certainty, all the other comparisons had very low-certainty evidence. In the bleaching agent *versus* bleaching agent comparisons, the evidence for 16% CP in tray compared to 6.5% HP strip and 16% CP with amorphous calcium phosphate compared to 16% CP was graded as low certainty. The evidence from all remaining studies was graded as very low certainty. Three studies on patient contentment or satisfaction related to whitening treatment, which were included in the meta-analysis were graded as of very low-certainty evidence.

DISCUSSION

We included 71 trials (78 reports) in the review with 26 studies (1398 participants) comparing a bleaching agent to placebo and 51 studies (2382 participants) comparing a bleaching agent to another bleaching agent. Most of the comparisons were single trials and could not be combined in meta-analyses due to varying methods of application, concentrations, application times, and duration of use.

Majority of the trials report on short-term improvement of shade (ranging from 1 day to 1 month) using home bleaching methods. As follow-up has not been reported in most trials, the results cannot reflect the retention period for the whitening effect. We also noticed that the use of higher concentration bleaching methods and longer duration resulted in more whiter shades of teeth although the level of evidence is low to very low.

The common adverse effects reported were tooth sensitivity and oral/gingival irritation. These adverse effects were more commonly seen in groups who had used either higher concentration bleaching agents or had longer time of application. Participants using thick gel or strips reported these adverse effects compared to using thin gel or trays.

Out of 71 trials, 67 of them were assessed to have unclear risk of bias. In addition to this, several comparisons were from single trials with limited number of participants and low event rates. Few trials that were combined in meta-analysis had high heterogeneity. In view of these issues, we downgraded the quality of evidence as very low quality to low quality.

In this systematic review, we did not exclude any trials due to missing data. Wherever the data was presented only as median values, we qualitatively described the results and contacted trial authors for additional data. We searched in the mentioned databases, conference proceedings and trial registries. We checked all cross-references of the included studies and other systematic reviews on this topic. In addition to this, we included non-English language reports. Nevertheless, there could be unpublished data or grey literature which we could not trace.

Our review had a broader focus as we included all types of bleaching agents, different concentrations, and application methods. However, other systematic reviews on home-based bleaching products were either limited to one type of product or application method. The previous version of this Cochrane review[27] had included quasi-randomised trials and whitening dentifrices which we have excluded.

Further research should be undertaken to know the effectiveness of home-based bleaching methods by conducting well-planned RCTs with more clarity and uniformity in the variables. In designing such clinical trials, the following needs to be considered.

Evidence**.** The present evidence was insufficient to conclude that any of the comparisons of home-based bleaching methods are effective. Trials should focus on testing similar concen-

trations with similar methods of application. Trials should focus on both short-term and long-term benefits of treatment. Studies should also focus on patient-related outcomes and cost effectiveness. Furthermore, reports on clinical trials would be improved by following CONSORT recommendations.

Population**.** Inclusion criteria for clinical trials should be well defined. Trials should include both genders in equal distribution.

Intervention**:** Intervention should focus on similar concentrations used in earlier studies and similar application times with a longer follow-up. This will add on to the existing evidence pool allowing us to make robust conclusions.

Comparison**.** Various comparisons have been reported, but we found only single trials in most of the comparisons due to which the quality of evidence is very low. Hence, RCTs need to be conducted keeping in mind already published studies so that the number of trials for a particular comparison increase.

Outcome**.** Patient-reported outcomes were not considered in most of the trials. Cost effectiveness also needs to be added in the RCTs, which is of most interest to consumers.

CONCLUSIONS

We found low to very low-certainty evidence over short time periods to support the effectiveness of home-based chemically induced bleaching methods compared to placebo for the primary outcome of the review i.e., tooth whitening as reported by the dentist or patient using any relevant measurement tool. Patient comfort was better in tray group compared to application group. There were no differences in the oral health-related quality of life between intervention groups. Majority of the trials reporting adverse effects were related to tooth sensitivity and oral/gingival irritation. We were unable to draw any conclusions regarding the superiority of home-based bleaching compositions or any method of application or concentration or application time or duration of use, as the overall evidence generated was of very low certainty. Well-planned randomised controlled trials (RCTs) need to be conducted by standardising methods of application, concentrations, application times, and duration of treatment.

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