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EFFECTIVENESS OF BLUE COVARINE IN WHITENING OF TEETH: A SYSTEMATIC REVIEW

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ABSTRACT:

BACKGROUND:

Blue covarine is a new and emerging pigment used in whitening toothpaste. On its use, a thin coat of semi-transparent film is deposited on the surface of the teeth. This layer modifies the interaction of the incident light on the surface of the tooth, causing a shift in the yellow-blue colour axis leading to decreased yellowness and increased blueness, making the teeth look perceptibly whiter.

OBJECTIVE:

The objective of this systematic review is to prove the effectiveness of blue covarine in the whitening of teeth.

SEARCH METHODS:

In this systematic review, seven databases(Google Scholar, PubMed, Ovid, Science Direct, Lilacs, Wiley, Cochrane) were searched with the relevant search words for articles pertaining to the aim of the systematic review and to answer the review question. The databases were searched without a focused time limit(from the inception of the database up to July 2021). After a thorough evaluation, a total of fifteen randomized control trials(RCT) were selected to be included in this systematic review.

SELECTION CRITERIA:

The RCTs included in this study have been selected based on the inclusion and exclusion criteria. The included studies all pertain to the comparison of blue covarine to either other test groups or a control group, and they are all related to the aim of this systematic review. The RCTs that did not meet the criteria have been excluded.

DATA COLLECTION AND ANALYSIS:

The whiteness of the specimen have been calculated using various parameters such as Vita Classical (ΔSGU), the difference in luminescence (ΔL*), the shift in the red-green (Δa*) and blue-yellow (Δb*) axis, the tooth whitening index (WIO), calculated using the CIELAB colour system obtained with the chromameter Minolta CR241 or using digital photographs analysed in Adobe Photoshop or the Vita EasyShade reflectance spectrophotometer. Other subjective means of assessment were using a vita shade guide by a panel of assessors, patient's opinion and evaluation.

MAIN RESULT:

Thirteen of the fifteen RCTs supported the claim that blue covarine is effective in increasing the whiteness of the teeth, while three of the RCTs refuted the claim. It has also been seen that blue covarine had a dose-dependent effect as well as a synergistic effect when combined with 40% H2O2 bleaching gel.

AUTHOR'S CONCLUSION:

Overall there is adequate evidence to conclude that blue covarine is effective in increasing the whiteness of the teeth. The adverse effects of blue covarine have not been studied, but it does help in overcoming the adverse effects caused by hydrogen peroxide and carbamide peroxide bleaching and other over-the-counter abrasive whitening agents. Blue covarine is a new and emerging whitening agent that has shown promising results in the whitening of teeth, as concluded from this systematic review.

1.0 INTRODUCTION:

Toothbrushes and dentifrices have been in use for a long time. The usage of toothbrushes and toothpaste has become an integral part of our daily oral hygiene routine[1]. The role of a dentifrice is to clean the teeth thoroughly[2] and to provide other additional benefits such as management of malodour[3], external stain removal[4] etc.

According to the Smithsonian museum, the early toothbrushes were made out of carved ivory or bone with bristles made out of pig's hair, while dentifrices; a collective term given to any form of tooth cleaning concoction such as a toothpaste, tooth soap, tooth powder or a tooth-cleaning liquid; contained ingredients such as orris root, baking soda(sodium bicarbonate), powdered cuttlebone, chalk (calcium carbonate), charcoal, phenol(37.15%), peppermint oil for flavouring and many more[5]. Before the enactment of the new drug and

cosmetic regulations, there was not as much awareness of the ill effects of the ingredients used in these dentifrices. There was an article that was published in 1931 in the journal of the American dental association on the dangers of certain ingredients in the dentifrices used in the market[6].

The practice of whitening teeth was present from 4000 years ago but, modern teeth whitening treatments were in practice only in the 19th century. In 1960, dentist William Klusimer invented different peroxide-based whitening agents; and it was widely used until carbamide peroxide was introduced in 1989, which had comparatively fewer adverse effects.

Since then, with the advancement of new research and technology, the number of teeth whitening agents have increased. One such agent recently introduced into the market is Blue covarine; it works on the basis of creating an optical effect; after brushing, a thin layer of blue covarine is deposited on the surface of the tooth, which shifts the observable colour perception from yellow to blue and this has shown to increase the perception of whiteness of the teeth[7][8].

A systematic review and a meta-analysis comparing conventional toothpaste and whitening toothpaste done by Soeteman et al. in 2018 showed that the whitening toothpaste was superior to conventional toothpastes with regards to increasing the whiteness of the teeth[9] but, neither has there been any emphasis made on the effectiveness of individual components in whitening of teeth nor was there any mention of the use of blue covarine.

The effectiveness of various agents in whitening of the tooth has been discussed in a literature review on over-the-counter whitening agents[10]; however, the agents containing blue covarine has been excluded in this review. Another literature review written by joiner A in 2010[7] discussed the possibility of the use of blue covarine in whitening teeth.

There is a wide range of products that are available in the market containing for whitening teeth, which are approved by ADA. These products, however, mainly contain abrasives and enzymes, which have been proved to be effective in removing external stains[11][12]. But these abrasive dentifrices cause wearing away of the enamel surface[13]. Hence blue covarine is a better alternative to all the whitening toothpaste that depend on their Abrasivity to cause whitening.

Although numerous articles have been published proving the effectiveness of blue covarine on the whitening of teeth through randomized clinical trials on both human and animal teeth, there has never been a systematic review published to indisputably prove that blue covarine alone has the ability to whiten the teeth. Therefore the purpose of this systematic review is to compare

and contrast the effectiveness of blue covarine or blue covarine containing agents in the whitening of teeth using variously available and suitable parameters.

2.0 MATERIALS AND METHODS:

2.1 QUESTION TO BE REVIEWED:

Is blue covarine effective in the whitening of teeth?

2.2 SEARCH STRATEGY:

In this systematic review, seven databases(Google Scholar, PubMed, Ovid, Science Direct, Lilacs, Wiley, Cochrane) were searched with the relevant search words for articles pertaining to the aim of the systematic review and to answer the review question. The databases were searched without a focused time limit(from the inception of the database up to July 2021).

Table 1 :

S. NO.	DATABASES	SEARCH WORDS	NUMBER OF ARTICLES
1.	GOOGLE SCHOLAR	blue covarine AND whitening AND bleaching AND toothpaste AND teeth AND efficacy	200
2.	PUBMED	blue covarine AND whitening	23
3.	OVID	blue covarine AND whitening (in advanced search under keyword)	10
4.	SCIENCE DIRECT	blue covarine AND whitening	21
5.	LILACS	blue covarine AND whitening (searched under title abstract subject)	5
6.	WILEY	blue covarine AND whitening	20
7.	COCHRANE	blue covarine AND whitening	8

2.3 SCREENING FOR ELIGIBILITY:

Eligibility criteria for the selection of the articles were initially decided under inclusion and exclusion criteria which encompassed the type of studies, type of participants, type of interventions and type of outcome measures.

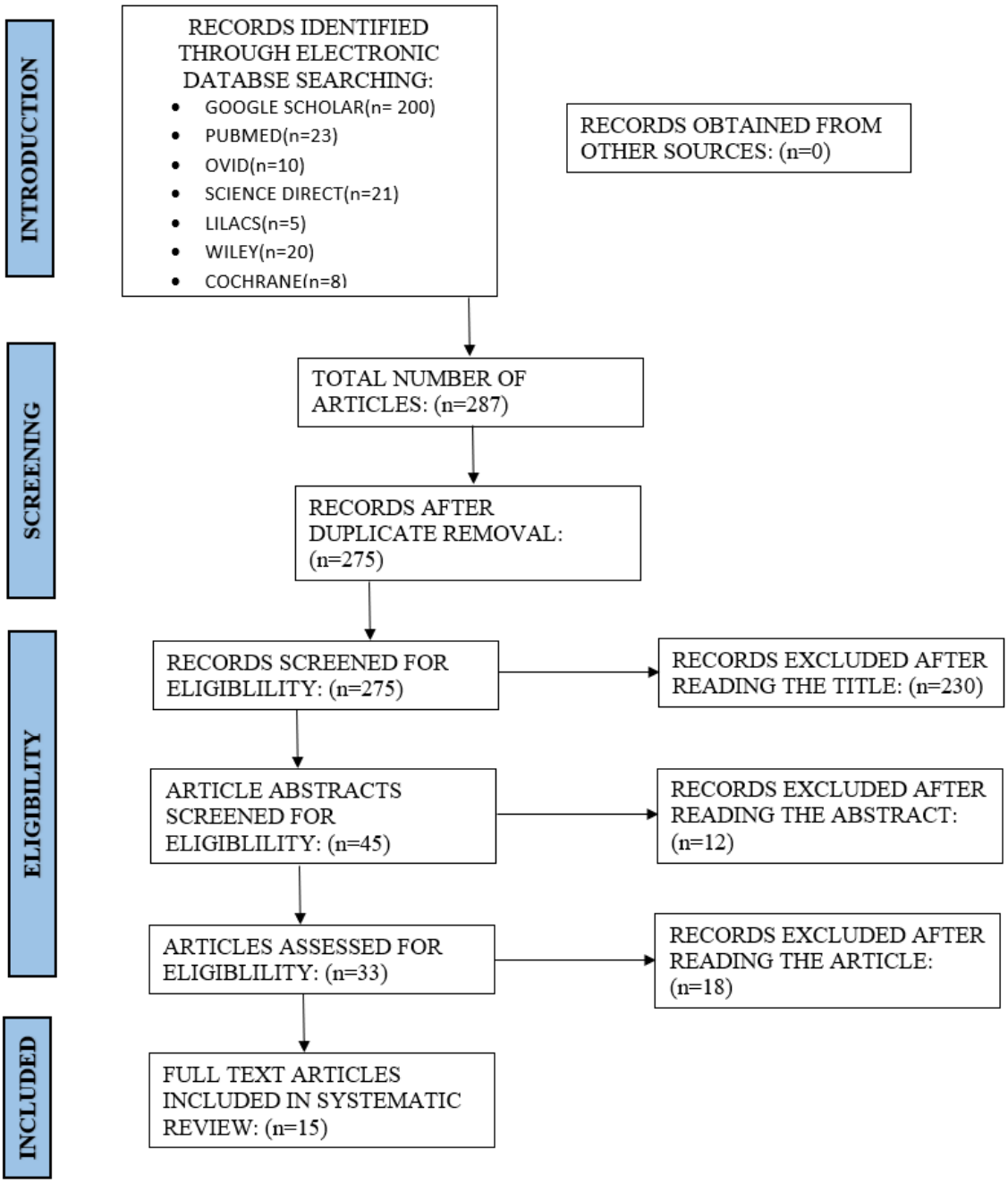
INCLUSION CRITERIA:

1. Full-text articles.
2. Randomized control trials.
3. Articles related to the aim of the systematic review.
4. Articles in English
5. No restriction regarding country, patient age, race, gender and date.

EXCLUSION CRITERIA:

1. Articles not related to the aim of the systematic review.
2. Articles with only abstracts available.
3. Review articles.
4. Editorials.
5. Articles published in other languages.
6. Case reports.

The screening was done in 4 stages. In the 1st stage, the duplicate articles were removed; in the 2nd stage, the title of the articles was screened for potential eligibility; in the 3rd stage, the abstract was read and, the articles not pertaining to the aim of the study were eliminated and, finally in the 4th stage the articles not meeting the eligibility criteria(inclusion criteria & exclusion criteria) were eliminated. The final number of articles included in the study were 15.



2.4 ASSESSMENT OF RISK OF BIAS IN INCLUDED STUDIES:

Bias analysis was done according to the Cochrane "risk of Bias" tool as described in the "*Cochrane handbook for systematic reviews of interventions."*

S.no	Author and year of publication	Random sequence generation	Allocation concealment	Selective reporting	Other sources of bias	Blinding (participants & personnel)	Blinding (outcome assessment)	Incomplete outcome data
1	Andrew joiner (2008)	?	+	+	+	?	?	+
2	Andréa Abi Rached dantas (2015)	+	+	+	+	+	?	+
3	Janaina Freitas bortolatto (2016)	+	+	+	+	+	?	+
4	Sônia Saeger Meireles (2020)	+	+	+	+	+	+	+
5	Vanessa Torraca Peraro (2018)	+	+	+	+	+	?	+
6	Danying Tao (2017)	?	+	+	+	+	?	+
7	Luisa Z. Collins (2008)	+	+	+	+	+	?	+
8	Carole J. Philpotts (2017)	+	+	+	+	+	?	+
9	Andrew Joiner (2008)	?	+	+	+	?	?	+
10	Rania Mossad Hassan (2019)	?	+	+	+	?	?	+
11	Ana LB Jurema (2018)	?	+	+	+	?	?	+

12	N Jiang (2019)	+	+	+	+	+	?	+
+13	Numan Aydın (2021)	?	+	+	+	?	?	+
1=4	Karen PINTADO-PALOMINO (2016)	+	+	+	+	+	?	+
15	Lourenço de Moraes Rego Roselino (2018)	?	+	+	+	?	?	+

3.0 CHARACTERISTICS OF INCLUDED STUDIES:

Fifteen randomized control trials were included in this study which was published from the year 2008 to 2021.

The characteristics of included studies are studied under the following headings:

1. The author and year of publication.
2. Type of study.
3. Materials and sample size
   - Type of tooth used
   - No. of teeth used
4. Measurement parameters and methods
5. Methodology
   - Pre-experiment interventions
   - Experimental interventions

Table 1: Characteristic of included studies and methodology

S. no.	Author and year of publication	Type of study	Materials and sample size	parameters	Methodology	
					Pre-experimental interventions	Experimental interventions
1	Andrew joiner (2008)	In-vitro Randomized control trial	36 Bovine teeth cut and embedded in an auto-polymerizing methacrylate resin. Group 1: silica-based blue covarine whitening toothpaste(n=9) Group 2: non-whitening	Pellicle cleaning ratio(PCR) was measured using the Baseline colour	The surfaces were polished, acid-etched and stained in coffee/tea/mucin And air at 50 degrees for four days.	The toothpastes were dispersed in water(38.5%) and 10ml of the slurry was added to the

			silica toothpaste(n=9) Group 3: silica-based whitening toothpaste A(n=9) Group 4: silica-based whitening toothpaste B(n=9)	measurement , which was done using Minolta CR-321 Chromameter in the CIE L*a*b* mode.		brushing machine and the teeth were brushed for 400 cycles, rinsed with water, air dried and colour measured.
2	Andréa Abi Rached dantas (2015)	In-vitro Randomized, paired and single blinded control trial	90 Bovine teeth were cut and embedded in neutral grey acrylic resin out of which 75 were used Group 1: control (C) (n=15) Group 2: bleaching with toothpaste containing blue covarine(BC)(n=15) Group 3: bleaching with toothpaste without blue covarine(WBC)(n=15) Group 4: in-office bleaching using 35% h_2o_2(HP35)(n=15) Group 5: at-home bleaching with carbamide peroxide(CP10)(n=15)	Colour difference, luminosity, green-red axis and blue-yellow axis were calculated using the CIE L*a*b*coordinates with reflectance spectroscopy at baseline time(T0), immediately after bleaching(T1), 7 days later(T2), 14 days later(T3), 21 days later(T4)	The teeth were stored in artificial saliva under stirring at a temperature of 36 +/- 1 degree for a week prior to testing. Each tooth paste was mixed in 0.5% sodium carboxymethyl cellulose solution and water in a 1:1:1 ratio.	The teeth were placed in a tooth brushing machine run for 3 min per day at 450 strokes per day and 150strokes/min with a load of 375g.
3	Janaina Freitas bortolatto (2016)	In-vitro, controlled, randomized, paired and single blinded study	90 Bovine teeth were cut and embedded in neutral grey acrylic resin Group 1: bleaching with 10% carbamide peroxide then brushing with toothpaste containing blue covarine (PC10%BC) (n=15) Group 2: bleaching with 10% carbamide peroxide then brushing with toothpaste without blue covarine (PC10%NBC) (n=15) Group 3: bleaching with 10% carbamide peroxide	Colour difference, luminosity, green-red axis and blue-yellow axis were calculated using the CIE L*a*b* coordinates with reflectance spectroscopy at baseline time(T0), immediately	Two bleaching sessions of 35% h_2o_2 were performed at 1 week interval with total bleaching time of 90min. bleaching with 10% carbamide peroxide in tray at 36 +/- 1 degree for a total time of 3360min was done The teeth were	The teeth were placed in a tooth brushing machine run for 3 min per day at 450 strokes per day and 150strokes/min with a load of 375g.

			alone (PC10%) (n=15) Group 4: in-office bleaching using 35% h_2o_2 alone (HP35) (n=15) Group 5: in-office bleaching using 35% h_2o_2 then brushing with toothpaste containing blue covarine (PC10%BC) (n=15) Group 6: in-office bleaching using 35% h_2o_2 then brushing with toothpaste without blue covarine (PC10%NBC) (n=15)	after bleaching(T1), 7 days later(T2), 14 days later(T3), 21 days later(T4)	stored in artificial saliva under stirring at a temperature of 36 +/- 1 degree for a week prior to testing. Each tooth paste was mixed in 0.5% sodium carboxymethyl cellulose solution and water in a 1:1:1 ratio.	
4	Sônia Saeger Meireles (2020)	parallel controlled double-blind randomized clinical trial	75 individuals (18-32yrs) Group 1: conventional toothpaste (n=25) Group 2: whitening toothpaste (n=25) Group 3: 10% carbamide peroxide (n=25)	Spectrophotometer that decides tooth shade using two methods: using the 16 shade tabs in the Vita shade guide (B1-C4) and the CIE L*a*b* colour system. Colour evaluation using visual analogue scale	Pea sized toothpaste and floss to be used. No mouthwash.	Subjects were asked to brush for 90 seconds, twice a day with the respective toothpaste for 2 weeks.
5	Vanessa Torraca Peraro (2018)	In-vitro randomized double blind control trial.	90 bovine teeth with pulp chambers embedded in red acrylic resin. Group 1: activated charcoal (B&W) (n=15) Group 2: blue covarine (WAD) (n=15) Group 3: hydrogen peroxide (LWA) (n=15) Group 4: microbead abrasive (3DW) (n=15) Group 5: optimized abrasives (XW4D) (n=15) Group 6: control (TA) (n=15)	Previously calibrated examiners score based on Vita Classical shade guide, then the recorded tones were converted into scores and the whitening efficacy into shade guide	Pulp chamber was cleaned and then the tooth was immersed in concentrated tea solution for 18 hours followed by air drying for 6 hours. This was repeated 4 times and the teeth were fixed in silicon impression material.	Two brushing cycles were done: 1st cycle180 movements and 2nd cycle16,200 movements at 36+/- 1 degree and 200g/cm^2 using the corresponding toothpaste mixed with artificial saliva and water in

				units (ΔSGU).		the ratio of 1:1:1.
6	Danying Tao (2017)	Two In-vitro single blind randomized control trial (study 1 & 2) & double blind cross-over randomized control clinical trial.	In-vitro study 1: Extracted human anterior teeth mounted in acrylic resin blocks. Group 1: blue covarine (BC) (n=15) Group 2: silica-based toothpaste with increased levels of blue covarine (BC+) (n=15) Group 3: silica-based toothpaste without blue covarine (n=15) In-vitro study 2: extracted human incisors and premolars were used. Group 1: toothpaste with increased level of blue covarine (BC+) (n=32) Group 2: control silica-based toothpaste without blue covarine (n=32) Clinical trial: 80 participants (18-65 yrs.) Brushing with toothpaste with blue covarine. Brushing with toothpaste containing increased level of blue covarine.	Study: 1 Minolta CR321 chromameter in the CIELAB mode and whiteness values based on tooth whiteness index (WIO) Study: 2 baseline CIE L*a*b* values and shade of each tooth was measured using a VITA Easyshade in the 3D-Master mode. Clinical trial: CIE L*a*b* and WIO were used to analyse the pre and post treatment images.	Study 1 & 2: The teeth were cleaned with prophylactic paste and sterilized whole human saliva (gamma irradiated) for 2 hours. Clinical trial: A pre-brushing image of two upper central incisors was taken	Study 1& 2: The teeth were brushed for 1 min with the corresponding toothpaste and water mixture in 1:2 ratio and colour was measured 2 hours later. Clinical trial: Subjects brushed with 1.5gms of the assigned toothpaste for 90s followed by 5ml mouth rinse. Immediately a post brushing picture is taken
7	Luisa Z. Collins (2008)	A controlled, single blind, cross-over randomized study	83 participants aged 18 or older. Brushing with silica-based toothpaste containing blue covarine. Brushing with silica-based toothpaste without blue covarine	digital imaging system (Adobe Photoshop CS2 version 9) which was expressed as CIE L*a*b* and WIO whiteness index values.	subjects underwent prophylaxis prior to start of experiment. Pre brushing picture was taken of the upper two central incisors.	Subjects brushed for 90s with the assigned toothpaste followed by 5s 5ml mouth rinse. Post brushing pictures were taken.
8	Carole J. Philpotts	Randomized control trial	Extracted human incisors and premolars were restored	The digital images were	The tooth were restored with 3X1	The specimen were placed in

	(2017)		with 4 restorative materials and each set of tooth restoration materials (n = 30) was subdivided into 3 treatment groups (n = 10 for each treatment) Group 1: water (control) (n=10) Group 2: silica-based toothpaste containing blue covarine (test group) (n=10) Group 3: red wine (positive control group) (n=10).	analysed in Adobe Photoshop CS2 version 9 then the RGB values were converted into CIELAB values and a subjective evaluation was done by a panel of assessors by rating the colour from 1-100.	mm A2 spectrum composite restoration, A2 supreme composite, light cured GIC restoration and chemical cure GIC restoration. The specimen were stored in demineralised water for 4 weeks and baseline picture was taken.	the respective solutions for 24 hours and then a 24hr picture was taken. The teeth were brushed for 1min with a slurry of 1:2 ratio of silica-based toothpaste and water. A post brushing picture was taken.
9	Andrew Joiner (2008)	Randomized control trial	Study 1: Extracted human anterior teeth embedded in acrylic Group 1: patent blue V (n=7) Group 2: FD&C no.1 (n=7) Group 3: brilliant black BN (n=7) Group 4: blue covarine (n=7) Study 2: 68 extracted human anterior and premolar teeth mounted in acrylic was used. Group 1: water (n=39) Group 2: 0.2% blue covarine in water (n=39) Study 3: Human enamel blocks were prepared. Group 1: blue covarine 0.02% (n=4) Group 2: blue covarine 2% (n=4) Study 4: Extracted human anterior teeth mounted in acrylic with silicon based toothpaste with corresponding conc. of blue covarine was used. Group 1: BC at 0% (n=5) Group 2: BC at 0.01% (n=5)	Chromameter in the CIE L*a*b*mode Visually assessed by three trained assessors using a Vita Shade Guide. Ion mass spectrometer.	Study 1: The surfaces were cleaned with prophylactic paste and placed in sterile(gamma irradiated) pooled human saliva for 2 hrs. the base colour was measured using chromameter. Study 2: Same as study 1 and 3 trained accessors measure the baseline shade using vita shade guide. Study 3: The tooth were placed in sterile human saliva for 16hrs and the baseline colour was measured using chromameter. Study 4: Same as study 1. The slurry of the given conc. of	Study 1: Blue dyes at 0.2% conc. in water were used and the teeth were dipped in their given solution for 30s, then placed in water and removed at 5, 10, 20, 60 and 120min interval to measure the colour and then returned. Study 2: Teeth are dipped in respective groups for 30s and the shade was evaluated. Study 3: The tooth were treated with the given material for 1 min, then colour was measured

			Group 3: BC at 0.05% (n=5) Group 4: BC at 0.1% (n=5) Group 5: BC at 0.2% (n=5)		toothpaste, water and sodium carboxymethyl cellulose is made in the ration of 1:1:1. Baseline colour measured using chromometer.	using ion spectrometer. Study 4: The teeth are brushed for 1min with the given conc. of material then the colour is measured.
10	Rania Mossad Hassan (2019)	In vitro randomized control trial	70 extracted human premolars were embedded in gypsum blocks. Group 1: Close up White now (with blue covarine) (n=10) Group 2: Sensodyne True White (abrasion/sodium triphosphate) (n=10) Group 3: Colgate Optic White (abrasion/sodium monophosphate with hydrogen peroxide) (n=10) Group 4: Close Up (n=10) Group 5: Sensodyne (n=10) Group 6: Colgate (n=10) Group 7: (Control) No tooth paste application (n=10)	Vita easyshade spectrophoto meter with CIE L*a*b*setting	The teeth were cleaned using prophylactic paste and stored in sterilized artificial saliva for 2hrs. Toothpaste to water ratio was 2:1. The baseline colour was measured.	The teeth were brushed using 120 strokes/min at 250g load for 3.5 min for 4 weeks and 3 times a day using corresponding toothpaste. The colour was measured.
11	Ana LB Jurema (2018)	In vitro randomized control trial	70 extracted bovine incisors and 3 specimen of size 3X2.1 mm were obtained from each tooth. Each specimen was embedded in acrylic resin. The specimen were divided into 14 groups, 7 groups were treated with OTC whitening treatments and 10% carbamide peroxide at-home bleaching while the other 7 groups were treated with OTC whitening treatment alone with n=15 in each group. The CP-CloseUpW and CloseUpW groups had blue covarine as one of its components.	Spectrophoto meter using CIE L*a*b*syste m.	The specimen were stained for 14 days in a staining broth containing instant coffee and tea of 136.5g, 30ml of red, 30ml of yellow colour, 3.8L of red wine, then the specimens were polished with abrasive paper to remove excessive stain.	For the specimens with carbamide peroxide(CP) and OTC product treatment, 10% CP gel is applied 8hrs/day and brushed for 10s with the corresponding OTC product and stored in artificial saliva until completion of the 24 hour cycle for 2 weeks. For specimen

						with only OTC product treatment, the corresponding OTC products were brushed for 10sec and stored in artificial saliva until completion of the 24 hour cycle for 12 weeks.
12	N Jiang (2019)	Double-blind randomized controlled clinical trial	63 volunteers (34 females & 29 males) were enrolled but a total of 60 participants completed the trial. Group 1: C (Crest Cavity Protection, a regular dentifrice) (n=20) Group 2: CW (Crest 3D Whitening, a conventional whitening dentifrice) (n=20) Group 3: CU (Close Up White, a whitening dentifrice containing blue covarine) (n=20)	CIE L*a*b* colour space using a spectrophoto meter (Vita Easyshade).	They underwent oral prophylaxis and then in-office bleaching using 40% h_2o_2 gel for 30 min was done once a week for 4 weeks. Tooth colour was evaluated prior to treatment(T1).	The participats brushed their teeth twice daily for 2 min for 4 weeks. Tooth colour was evaluated immediately after the 1st bleaching session(T2), immediately after the 2nd bleaching session (T3), and one week (T4) and three weeks (T5) after the completion of the bleaching treatment.
13	Numan Aydın (2021)	Randomized control trial	40 extracted human incisor teeth (40-65 yrs.) were used. Group 1: activated charcoal toothpaste (n=10) Group 2: h_{2o2} (n=10) Group 3: blue covarine (n=10) Group 4 : complete protection (n=10)	Single point measurement mode (L*, a*, b* values) and bleach shade mode of the spectrophotom eter. If the bleach shade mode is SGU (Shade Guide Units), the measured colour was set according to	The teeth were stored in artificial saliva for 24 hours at 37 degrees Celsius after being treated with a prophylactic paste. The toothpastes were made in 1:1 ration with distilled water.	The teeth were brushed for 8 seconds everyday twice a day with electric toothbrush and respective toothpaste then rinsed and stored in artificial saliva.

				the VITA bleachedguide 3D-MASTER.		
14	Karen PINTADO-PALOMINO (2016)	double-blind randomized controlled trial	60 participants aged 18 and above were selected. Group 1: Colgate Luminous White (G1) (n=20) Group 2: Close Up White Now (contains blue covarine) (G2) (n=20) Group 3: and Sorriso (G3 – Control) (n=20).	Vita Easyshade spectrophotometer in CIELAB setting.	Tooth colour was assessed at baseline (prior to the treatment) and once weekly at the 1st (t1), 2nd (t2), 3rd (t3) and 4th (t4) assessment points.	Participants were asked to brush thrice a day for 2-3 min for 4 weeks using the corresponding toothpaste.
15	Lourenço de Moraes Rego Roselino (2018)	Randomized clinical trial	30 students (20-35 yrs.) (18 women & 12 men) were selected. Group 1: SDB (non-whitening toothpaste) (n=10) Group 2: Colgate Luminous White (CLW) (n=10) Group 3: Close up White Now (containing blue covarine) (n=10)	Spectrophotometer Easyshade in CIE L*a*b*mode.	The patients were treated with a prophylactic paste and rubber cup.	The participants brushed their teeth with their corresponding toothpaste thrice a day for 90 days. The initial colour was evaluated at 7th day and the subsequent colour evaluation was done at 30 and 90 days.

4.0 OUTCOME ASSESSMENT AND RESULT:

The outcome assessment and tabulation of the result is done under the following headings:

1. The author and year of publication.
2. outcome.
3. Result.
4. Notes.

Table 2: Outcome assessment and result

S. no.	Author and year of publication	Outcome assessment	result	notes
1	Andrew joiner (2008)	Silica-based blue covarine whitening toothpaste is significantly more effective ($p < 0.05$, ANOVA) in PCR stain removal than the non-whitening silica-based toothpaste. It was not significantly different to the two silica-based	Toothpastes containing blue covarine are significantly more effective in	The other parameters: toothpaste Abrasivity and fluoride efficacy are

		whitening toothpastes A and B.	tooth whitening than silica-based non-whitening toothpastes.	not discussed.
2	Andréa Abi Rached dantas (2015)	Colour difference was significant between experimental groups, and the interaction between evaluation times and experimental groups ($p<0.001$). Luminosity: Significance was found in relation to the factors, experimental group ($p<0.001$) and evaluation time ($p=0.006$). Green-red axis: there is significant differences in significance threshold for significance threshold for time evaluation ($p=0.049$) but no significant difference between the evaluation times. Blue-yellow axis: there is significant differences for the factors evaluation time, experimental group, and the interaction between factors ($p<0.001$).	Blue covarine has the ability to whiten teeth but there is no significant difference between whitening caused between the different experimental groups.	Hydrogen peroxide and carbamide peroxide have better bleaching efficacy than blue covarine. The tooth colour with the Vita EasyShade reflectance spectrophotometer.
3	Janaina Freitas bortolatto (2016)	Colour alteration: there was significance for evaluation time ($p < 0.001$), for the interaction between evaluation time and experimental groups ($p = 0.002$) but different experimental groups did not result in any differences ($p = 0.107$). Luminosity: Significance was found for the different experimental groups ($p = 0.041$), for the interaction between experimental groups and the evaluation time ($p < 0.001$). Green-red axis: There was statistically significant difference only for the experimental groups ($p < 0.001$) Blue-yellow axis: there was significant differences ($p < 0.001$) for the evaluation time, the experimental group ($p < 0.001$) and also the interaction of factors ($p < 0.001$)	Blue covarine showed no statistically significant whitening ability on previously bleached teeth.	The tooth colour was measured using Vita EasyShade reflectance spectrophotometer.
4	Sônia Saeger Meireles (2020)	The two-way ANOVA measurement showed significant interaction between the factors, treatment groups and evaluation periods ($P = 0.001$). At 2- and 4-week evaluations, higher L* and lower a* and b* values were observed from CP10 when compared to WT and CT ($P = 0.001$). There was no significant statistical difference noted between the WT and CT groups for tooth shade medians or L*a*b* parameters in all evaluation periods ($P > 0.05$). A decrease in b* values for WT was observed after the first application and at 2-week compared to baseline ($P< 0.01$). The patient's satisfaction with tooth appearance was significantly higher for CP10 than the CT and WT groups ($P < 0.001$).	Statistically significant difference between the whitening capacity of the conventional toothpaste and the whitening toothpaste which contains blue covarine was not seen.	The bleaching capacity of 10% carbamide peroxide was significantly higher than the conventional or whitening toothpaste. The tooth colour was measured with the Vita EasyShade reflectance spectrophotometer.
5	Vanessa	Statistically significant differences were observed	There was a	Previously

	Torraca Peraro (2018)	between the ΔSGU(difference of shade) values after the first use (p=0.0001) and also after the continuous use(p=0.0001). Wilcoxon test showed a statistically significant increase in whitening (pUE=0.001), due to the continuous use for all whitening toothpastes however the control toothpaste (TA) showed no significant whitening change.	significant increase in the whitening capacity of all whitening toothpastes as compared to the control.	calibrated examiners score based on Vita Classical shade guide, then the recorded tones were converted into scores and the whitening efficacy into shade guide units (ΔSGU).
6	Danying Tao (2017)	The in-vitro studies revealed a greater statistically significant (p<0.05) change in b* and WIO values in toothpastes with blue covarine as compared to the control. The toothpaste formulated as BC+ showed a greater increase in b* and WIO values than the BC toothpaste. And BC+ toothpaste showed a greater shade change than the control toothpaste. The clinical results demonstrated that the toothpastes with BC+ and BC formulas gave a significant reduction in b* values(p<0.0001) and a significant increase in WIO values(p<0.0001) from the baseline shade indicating significant whitening of tooth. On brushing with BC+ toothpaste, significantly greater WIO values were observed than with BC toothpaste. (WIO value, p=0.006; b* value, p=0.013).	Blue covarine + has statistically significant whitening capacity as compared to blue covarine alone, while blue covarine had statistically significant whitening capacity as compared to control.	Blue covarine has a dose dependant effect. Minolta CR321 chromameter in the CIELAB mode and whiteness values based on tooth whiteness index (WIO) was used in study 1. CIE L*a*b* values was measured using a VITA Easyshade in the 3D-Master mode in study 2. CIE L*a*b* and WIO were used to analyse the pre and post treatment images in clinical trial.
7	Luisa Z. Collins (2008)	The WIO whiteness index for the test toothpaste showed that teeth became significantly whiter (p < 0.05) immediately after brushing with the silica-based whitening toothpaste containing blue covarine. A statistically significant change in WIO whiteness index was not observed for the control toothpaste. The comparisons made between the baseline and post brushing showed statistically reduced yellowness in the test group (p < 0.05) while it was not significant in the control group.	The silica-based whitening toothpaste containing blue covarine had statistically significant whitening capacity as compared to control.	Images were analysed in Adobe Photoshop CS2 version 9 and the values were converted to CIELAB values and WIO whiteness index values.
8	Carole J. Philpotts (2017)	The blue covarine toothpaste group gave a greater overall colour change for whole specimens and restoration margin than the water group, which was of statistical significance only for the Spectrum restored specimens (p < 0.05, ANOVA). The colour change for the blue covarine group were	There was a significant colour change after treating the specimen with blue covarine	The digital images were analysed in Adobe Photoshop CS2 version 9 then the RGB values were then converted

		lower than before brushing and there were no significant differences between this group and the water treated group for the whole specimen and margins of all restoration types. Subjective evaluation showed no significant differences ($p > 0.05$, ANOVA) between the water and the blue covarine treatment groups for either the whole specimen or the restoration margin.	toothpaste slurry as compared to water group but after brushing with silica-based toothpaste the colour change was not significant as compared to water group.	into CIELAB values. Subjective evaluation was done by a panel of assessors.
9	Andrew Joiner (2008)	Blue Covarine gave a statistically greater increase in mean Vita Shade change as compared to water($p < 0.0001$, Student's t-test). The differences between treatments for the other colour parameters were also of statistical significance as follows; L* ($p < 0.05$); a* ($p < 0.0001$); b* ($p < 0.0001$), and WIO ($p < 0.0001$). The mean b* and WIO values versus Blue Covarine concentration in a silica-based toothpaste showed a linear increase in whiteness and a decrease in yellowness.	There was a significant increase in whiteness of the teeth when blue covarine was used.	A chromameter (Minolta CR-321) in the CIELAB mode was used to assess colour. The tooth colour was assessed by three trained assessors using the Vita Shade Guide.
10	Rania Mossad Hassan (2019)	One-way ANOVA showed that the mean colour changes seen were statistically significant between the groups ($p=0.01$). Toothpaste containing blue covarine (Group I) had a statistically significant colour difference when compared to the non-whitening control group, group IV ($p = 0.02$, Student's t-test) and a substantially significant difference seen with other whitening tooth pastes not containing blue covarine group II ($p=0.005$) and group III ($p=0.04$).	There was a statistically significant colour change in toothpastes containing blue covarine as compared to other toothpaste groups.	Measurement of colour was done using VITA Easyshade spectrophotometer Advance 4.01 in accordance to the CIE L*a*b* colour order system. Other parameters are not discussed here.
11	Ana LB Jurema (2018)	Negative changes were noted for Δb^* values, except for Water which lead to decreased yellowness. The ANOVA results revealed a significant difference between the groups and the Tukey 't' test showed that colour change was significantly greater in all the groups bleached with 10% CP associated with OTC products. The teeth treated with toothpaste containing blue covarine also presented similar results to those of 10% CP.	There was a statistically significant decrease in yellowness and increase in whiteness when blue covarine was used.	Spectrophotometer using CIE L*a*b*system. Other parameters are not discussed here.
12	N Jiang (2019)	The mean ΔE(average values of L*, a*, and b*) were 8.19 for group C, 7.62 for group CW, and 6.90 for group CU. Significantly lower ΔE values were observed in group CU, ($p=0.008$). After bleaching, the tooth colours of the participants in all groups became whiter, with increased L* and W values and decreased a* and b* values (all $p<0.001$). An increase in the DE values (from T4 to T5) was observed in groups CW and CU, whereas a decrease	There was a statistically significant decrease in yellowness and increase in whiteness when blue covarine (CU) was used	Blue covarine had a synergistic effect with bleaching whereas other OTCs used in this clinical trial did not. CIE L*a*b* colour space using a spectrophotometer

		was observed in group C. A decrease in tooth yellowness was observed in groups CW and CU, whereas there was an increase in group C from T4 to T5.	before in-office bleaching using 40% h_2o_2 gel as compared to other groups.	(Vita Easyshade) was used to measure the shade.
13	Numan Aydın (2021)	The toothpaste containing blue covarine showed statistically the least whitening effect ($p < 0.05$). The toothpaste containing activated charcoal showed statistically higher whitening effect in 7th, 14th and 28th days as compared to other groups including blue covarine. No statistically significant difference was between the whitening effect produced by hydrogen peroxide containing toothpaste and traditional toothpaste ($p > 0.05$).	Although blue covarine produces good whitening effect according to ΔE00 and ΔSGUBG values, it's not the best whitening agent when compared to other groups.	Toothpastes containing charcoal produce better whitening as compared to ones containing blue covarine. Single point measurement mode (L*, a*, b* values) and bleach shade mode of the spectrophotometer. If the bleach shade mode is SGU (Shade Guide Units), the measured colour was set according to the VITA bleachedguide 3D-MASTER.
14	Karen PINTADO-PALOMINO (2016)	The values for ΔE(change in colour) showed no statistically significant differences ($p > 0.05$) during the initial period of study. Despite ΔE showing no significant results, its values were significantly higher after 4 weeks, implying visible changes in tooth colour in Group 1 ($\Delta E = 5.1$), Group 2 ($\Delta E = 6.8$), and Group 3 ($\Delta E = 4.4$). Group 2 showed significant change in Δa between t2-t3 and t3-t4 interval. Tukey's test showed, after 4 weeks of treatment, Δb was significantly different for Group 2 when compared with Group 1 and Group 3 (control).	There was greatest change in colour observed in the dentifrice containing blue covarine(G2).	A Vita Easyshade spectrophotometer was used to determine change in colour based on CIEL*a*b* parameters.
15	Lourenço de Moraes Rego Roselino (2018)	With ($P > .05$), the difference for any of the variables studied (ΔE, ΔL, Δa, Δb, and ΔRa(surface roughness)) were not statistically significant in all three groups, except for ΔL, after 90 days with CLW, which showed the highest ΔL ($P < .05$) when compared with brushing with SDB (control). CWN(containing blue covarine) resulted in an intermediate value of ΔL ($P > .05$) when compared with the other toothpastes used in the study.	There was no statistically significant difference in whiteness produced by all the involved groups. The toothpaste containing blue covarine only produced intermediate luminosity.	The Abrasivity of the toothpaste played a significant role in determining the whiteness of the specimen. CLW had the highest amount of abrasives. Spectrophotometer Easyshade based on CIEL*a*b* parameters was used to determine the colour.

5.0 DISCUSSION:

In this systematic review, two hundred and eighty seven articles were screened, after through screening for duplicates and eligibility criteria, fifteen articles were selected to be included in this study.

The main purpose of doing this systematic review was to verify whether blue covarine was effective in increasing the whiteness of teeth. According to our results, twelve of the randomized control trials showed significant increase in whiteness of the tooth specimen (Andrew joiner(2008)[14], Andréa Abi Rached dantas (2015)[15], Vanessa Torraca Peraro (2018)[16], Danying Tao (2017)[17], Luisa Z. Collins (2008)[18], Carole J. Philpotts (2017)[19], Andrew Joiner (2008)[20], Rania Mossad Hassan (2019)[21], Ana LB Jurema (2018)[22], N Jiang (2019)[23], Numan Aydın (2021)[24], Karen PINTADO-PALOMINO (2016)[25]), whereas three of the randomized control trials reported no significant increase in whiteness of teeth (Janaina Freitas bortolatto (2016)[26], Sônia Saeger Meireles (2020)[27], Lourenço de Moraes Rego Roselino (2018)[28]).

The effectiveness of blue covarine in whitening of teeth depends on multiple factors. One of the most important factor is the specimen chosen. The randomized control trials included in this study used extracted bovine teeth, extracted human teeth and human volunteers. A study was conducted by Ghaeth H. Yassen et al[29], where they compared the effectiveness of usage of bovine teeth as a replacement for human teeth in research studies. According to the study, there seems to be no significant difference in relation to the surface abrasiveness between bovine teeth and human teeth. However, the whiteness of the teeth not only depends on the amount of enamel wear due to abrasion, which helps in removing mild superficial internal stains, it also depends on the optical properties of the teeth, which have not been explained. Hence it is difficult to conclude if bovine teeth are a suitable replacement for human teeth when the results depend more on the optical property rather than the physical property.

Another important factor is the method used in evaluating the whiteness of the teeth. whiteness of teeth can be measured using various parameters, which mainly include lightness, hue and chroma. The lightness can be measured by determining the luminescence (L*), while the hue and chroma can be calculated from the a* and b* which represent the red-green and the yellow-blue components of light respectively[30]. The CIELAB system determines the true colour of the object measured[31], it measures the L*, a* and b* values and measures the colour difference. Different methods have been used to measure the whiteness of the specimen in the RCTs included in this study. According to Vanessa Torraca Peraro (2018)[16],most of the studies that have concluded that

blue covarine is effective in whitening teeth have measured the tooth colour by visual comparison, while most of those disproving the effectiveness of blue covarine in whitening teeth have measured the tooth colour using Vita EasyShade reflectance spectrophotometer, although this is not applicable to all the studies. The method of measurement of colour by Vita EasyShade reflectance spectrophotometer is said to be different. The explanation for this difference was given in a technical document that was published by the manufacturer #20030915-1[32]. According to this, although Vita EasyShade reflectance spectrophotometer was reliable for studies measuring the whiteness caused by peroxides, it was not accurate in measuring the colour change caused by blue covarine as it did not take into consideration the reflectance of light from enamel and only considered the scattered light from dentin. Although theoretically this may seem plausible, clinically as seen in this study, the three studies that have disproved the effectiveness of blue covarine measured colour using CIELAB system through visual comparison. Hence it maybe safe to say that although the method of measurement of colour is an important factor, it does not significantly alter the result of the study.

When the trials are done using toothpastes, it is important to keep the composition of the toothpaste in mind. The most important component that significantly effects the outcome of the study is the abrasives present, specifically the type and the amount of abrasive[11][12]. The use of abrasive toothpaste causes loss of the surface of the teeth[13]. This may lead to removal of any extrinsic stains present on the tooth surface or the superficial layer of the enamel, which may cause the tooth to appear whiter. But this effect is not produced by the blue covarine and hence may lead to false positive results. But the RCTs in this study are such that the composition of the toothpastes used for the test groups and control groups are similar in exception to the presence/absence of blue covarine or any other whitening agent. Hence the significance of the effect caused by the abrasive in the toothpaste is reduced.

According to the study done by Danying Tao (2017)[17], the effect of blue covarine is dose dependant. Increased levels of blue covarine significantly increased the whiteness of teeth. This kind of trial which studied the dose dependency of blue covarine was not done by any other person so far, hence a definite conclusion cannot be drawn based on one RCT. Further studies on blue covarine are required to obtain more insight into the properties of blue covarine.

Another interesting phenomenon reported by N Jiang(2019)[23] was that blue covarine had synergistic effect when combined with 40% h2O2 gel bleaching. This was not observed in any other over-the-counter whitening agents. Similar

to the report by Danying Tao (2017)[17], only one RCT reporting the synergistic effect of blue covarine currently exists. Hence further studies are required to discover other properties of blue covarine and to solidify the existing reports on blue covarine.

There RCTs included in this study not only compared blue covarine with a control, there were comparisons made with other agents as well. Although blue covarine was said to be effective in increasing the whiteness of teeth, it paled in comparison to some other agents like hydrogen peroxide bleaching, 10% carbamide peroxide bleaching and charcoal containing toothpastes. In a society where aesthetic dentistry is rapidly making its mark, the ever growing demand for better whitening agents is endless. In such cases, the whitening caused by in-office bleaching using hydrogen peroxide and 10% carbamide peroxide is significantly better than the whitening caused by blue covarine.

Hydrogen peroxide and carbamide peroxide work on the principle of oxidation of the double bonds present in the chromophores which leads to whiter teeth[33]. It is a more long lasting solution than blue covarine which only forms a thin film on the surface of the teeth, which may be lost on aggressive brushing. Charcoal on the other hand is an adsorbent which adsorbs the colouring pigments present on the teeth leading to whiter teeth[24]. Although these agents have better whitening capacity than blue covarine, blue covarine has fewer adverse effects as compared to the bleaching agents which are known to cause tooth sensitivity[34] and charcoal which can cause tooth abrasion.

In this age and time, large attention is given to facial and dental esthetics, esthetic concern is more in less deprived individuals with higher socioeconomic status than in those with lower socioeconomic status who are more deprived[35]; but especially post covid, the socioeconomic problems faced by the general population is still prevalent[36], during such situations the less expensive method of whitening of teeth using blue covarine tooth paste which provides significant results in whitening the teeth is a better alternative to more expensive bleaching methods used in dental clinic.

6.0 AUTHOR'S CONCLUSION:

Overall there is adequate evidence to conclude that blue covarine is effective in increasing the whiteness of the teeth. The adverse effects of blue covarine have not been studied, but it does help in overcoming the adverse effects caused by hydrogen peroxide and carbamide peroxide bleaching and other over-the-counter abrasive whitening agents. Blue covarine is a new and emerging

whitening agent that has shown promising results in whitening of teeth as concluded from this systematic review.

7.0 CONFILCT OF INTEREST:

The authors have no conflict of interest.

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