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REVIEW ARTICLE

Effects of phytochemical extracts on smear layer removal in root canal treatment

Efecto de los extractos fitoquímicos en la eliminación del barro dentinario en el tratamiento de conductos radiculares

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ABSTRACT

Introduction: Studies suggested that phytochemical products are considered potential solutions to smear layer removal due to their biological safety in cleaning root canal systems, lower toxicity, lower irritant effect and antimicrobial effect. **Objective**: The aim of the present study was to perform a systematic review to evaluate smear layer removal of root canal systems by different natural product solutions. **Methods**: systematic review. Search of the literature was performed on Pubmed, Scopus, Cochrane, Web of Science, Scielo and Google Scholar according the PRISMA protocol. Studies were included if they performed the experiments of smear layer removal on extracted permanent human teeth. Articles published in any language without restriction of year of publication were included in this review. The risk of bias assessment in the included studies was evaluated using the Joanna Briggs Institute Critical Appraisal Checklist for Quasi-Experimental Studies. The search strategy resulted in the retrieval of 6221 publications. After the eligibility criteria application, 8 articles were selected for analysis. **Results**: It was observed that some natural products solutions showed effects on smear layer removal, especially on coronal third. The phytochemical products such as Salvadora persica, chamomile alcohol extract and grape seed extract demonstrated good potential of smear layer removal, however, its effectiveness and clinical applicability are still unclear. **Conclusions**: Although the limitations of this study, it is possible to highlight those phytochemical products such as Salvadora persica, chamomile alcohol extract and grape seed extract that demonstrated good potential on SL removal.

Keywords: Endodontics; Natural products; Phytotherapy; Root Canal Irrigants.

RESUMEN

Introducción: Los productos fitoquímicos se consideran soluciones potenciales para la eliminación del barro dentinario debido a su seguridad biológica en la limpieza del sistema de conductos radiculares, menor toxicidad, menor efecto irritante y efecto antimicrobiano. **Objetivo**: Evaluar la eliminación del barro dentinario de los sistemas de conductos radiculares mediante diferentes soluciones de productos naturales. **Métodos**: La búsqueda de la literatura se realizó en Pubmed, Scopus, Cochrane, Web of Science, SciELO y Google Scholar, según el protocolo PRISMA. Los estudios se incluyeron si realizaron los experimentos de eliminación del barro dentinario en dientes humanos permanentes extraídos. En esta revisión se incluyeron artículos publicados en cualquier idioma, sin restricción de año de publicación. La evaluación del riesgo de sesgo en los estudios incluidos se evaluó mediante la lista de verificación de evaluación crítica del Instituto Joanna Briggs para estudios cuasiexperimentales. La estrategia de búsqueda resultó en la recuperación de 6221 publicaciones. Después de la aplicación de los criterios de elegibilidad, se seleccionaron 8 artículos para su análisis. **Resultados**: Se observó que algunas soluciones de productos naturales mostraron efectos sobre la eliminación del barro dentinario, especialmente en el tercio coronal. Los productos fitoquímicos como salvadora pérsica, extracto de alcohol de manzanilla y extracto de semilla de uva demostraron un buen potencial de eliminación del barro dentinario; sin embargo, su efectividad y aplicabilidad clínica aún no están claras. **Conclusiones**: A pesar de las limitaciones de este estudio, es posible destacar aquellos productos fitoquímicos como salvadora pérsica, extracto de alcohol de manzanilla y extracto de semilla de uva demostraron buen potencial de eliminación del barro dentinario.

Palabras clave: endodoncia; productos naturales; fitoterapia; irrigantes del conducto radicular.

INTRODUCTION

Irrigation of root canal system is considered one of the most important processes for successful root canal treatment.[1] The effects of irrigants are either physical, chemical or both in the treatment of the intracanal tooth surface.[2] One of the desired effects of irrigated solutions is the removal of the smear layer (SL) that raises when endodontic instruments touch the root canal walls.

SL consists of mineralized dentin, pre-dentin, pulp tissue remnants bacteria and biofilm[2,3] which can cause and obliteration on dentinal tubules and difficulties in root canal sealing. Its removal in endodontic therapy promotes better root canals sealing by obturation materials[4] and reduction on apical and coronal microleakage.[5]

Literature points out that an ideal solution for SL removal should present satisfactory dissolution of organic and inorganic components of pulp tissues, antimicrobial activity, minimal toxicity and biocompatibility with periapical tissues.[2,6,7]

Currently, EDTA has been the most commonly used solution for SL removal during endodontic treatment. However it has low or no organic dissolution activity[8] and it can cause root canal dentin erosion in case of prolonged application[9] and dentin microhardness reduction,[10] besides of having cytotoxic effects in periapical tissues and, in case of oral cavity touch, it can induce inflammatory reactions, as well as hypersensitivity reaction.[11,12]

Phytochemical products are considered potential solutions for SL removal due to their biological safety in cleaning root canal systems, lower toxicity, lower irritant effect[13] and antimicrobial effect.[14,15,16] Thus, these products such as *Morinda citrifolia*, *Salvadora persica*, *Citrus aurantifolia*, *Matricaria recutita* (German chamomile), *Origanum minutiflorum* (oregano) extract, grape seed oil, *Melaleuca alternifolia* (tea tree oil), *Fragaria vesca* (wild strawberries), *Sapindus mukorrossi*, propolis, saffron and many others have been investigated as possible antimicrobial agents and to SL removal.[10,15,17,18,19,20]

The effectiveness of natural products used to SL removal from root canals is still unknown. Thus, the objective of this systematic review was to evaluate the smear layer removal of root canal systems by different natural product solutions.

METHODS

This systematic review was developed according to PRISMA protocol for systematic review and it is registered in PROSPERO with CRD42018088911 protocol number.

PICOS Strategy

The question of this study was determined by PICOS strategy: population: root canal of extracted permanent teeth; intervention and comparison: root canal irrigation with different phytochemical product solutions compared to classical solutions used currently; outcome: removal of smear layer; and study: experimental in vitro studies. Thus, the question was established as: Can root canal irrigation with natural product solutions effectively remove smear layer in experimental in vitro studies?

Inclusion and exclusion criteria

Studies were included if they have performed smear layer removal experiments on extracted permanent human teeth with fully formed apices and if they have analyzed them with scanning electron microscope (SEM). Articles published in any language without restriction of year of publication were included in this review. Studies were excluded if they have done it *in vivo*, on animals, or in bovine teeth. In addition, case reports, case series, letters to the editor, conference summaries, literature reviews and animal studies were excluded.

Research strategy

This systematic review started in September 2018 and the searches were carried out until September 2019. Electronic databases such as Pubmed, Scopus, Cochrane, Web of Science, Scielo and Google Scholar were searched using the keywords “endodontic”, “natural products”, “phytotherapy” and “root canal irrigants”. The keywords were selected after preliminary analysis of articles about the topic and checked on MesH. Manual search in the reference lists of selected articles and gray literature (Google Scholar and thesis / dissertation databases) was also performed to complement the initial search. Two independent researchers performed the searches, and the references were organized using the EndNote X7 software.

Article selection and data extraction

Two independent researchers have selected articles based on title and abstract analysis (pre-selection), followed by full-text analysis of the pre-selected articles. The outcome sought was the use of natural products in root canals to remove smear layer. Data extraction was also performed independently by two reviewers. A data extraction form was created with the following variables: author/year/country in which the study was performed, sample size, type of intervention (type, volume and concentration of solutions), irrigation time, magnification/evaluation criteria and results. Differences of opinion in article selection or data extraction were solved by consensus between both researchers.

Qualitative analysis

To analyze the methodological quality of the articles, The Joanna Briggs Institute Critical Appraisal Checklist for Quasi-Experimental Studies was applied for evaluation of the articles by two researchers. The instrument consists of nine questions: 1) It is clear from the study what is the "cause" and what is the “effect” (there is no confusion about which variable comes first); 2) Were natural products included in any similar comparisons ?; 3) Were products included in any comparisons that received similar treatments other than exposure or intervention of interest ?; 4) Was there a control group ?; 5) Have there been multiple post-intervention outcome measurements?; 6) Was follow-up complete and, if not, were differences between groups described and adequately analyzed ?; 7) Were the results of the samples included in all comparisons measured in the same way ?; 8) Were the results measured reliably ?; 9) Was appropriate statistical analysis used? This last item was considered not applicable to all articles, given the individuality of the statistical analyzes performed on them. The answers “yes”, “no”, “not clear” or “not applicable” could be attributed to the questions. The risk of bias was rated high when the study reached up to 49% of yes scores, moderate when the study reached from 50% to 69% yes scores and low when the study reached more than 70% of this one [21, 22].

RESULTS

Selection of Studies

The initial search resulted in 6221 articles: 337 from Pubmed, 665 from Scopus, 680 from Cochrane, 4523 from Web of Science, 16 from SciELO and no articles were found in gray literature. After removing 2199 duplicated articles, 4022 were submitted to title analysis. Pre-selection by titles led to 3908 papers exclusion and, about the remaining, 114 were selected for reading the abstracts. After of reading full articles, 8 papers were considered eligible. From the manual search of the reference lists of the selected articles, 03 papers more were identified as eligible, however, they were excluded after full reading of the studies. Thus, 8 articles were included in this review and submitted to qualitative analysis (Fig. 1).[6,13,23,24,25,26,27,28]

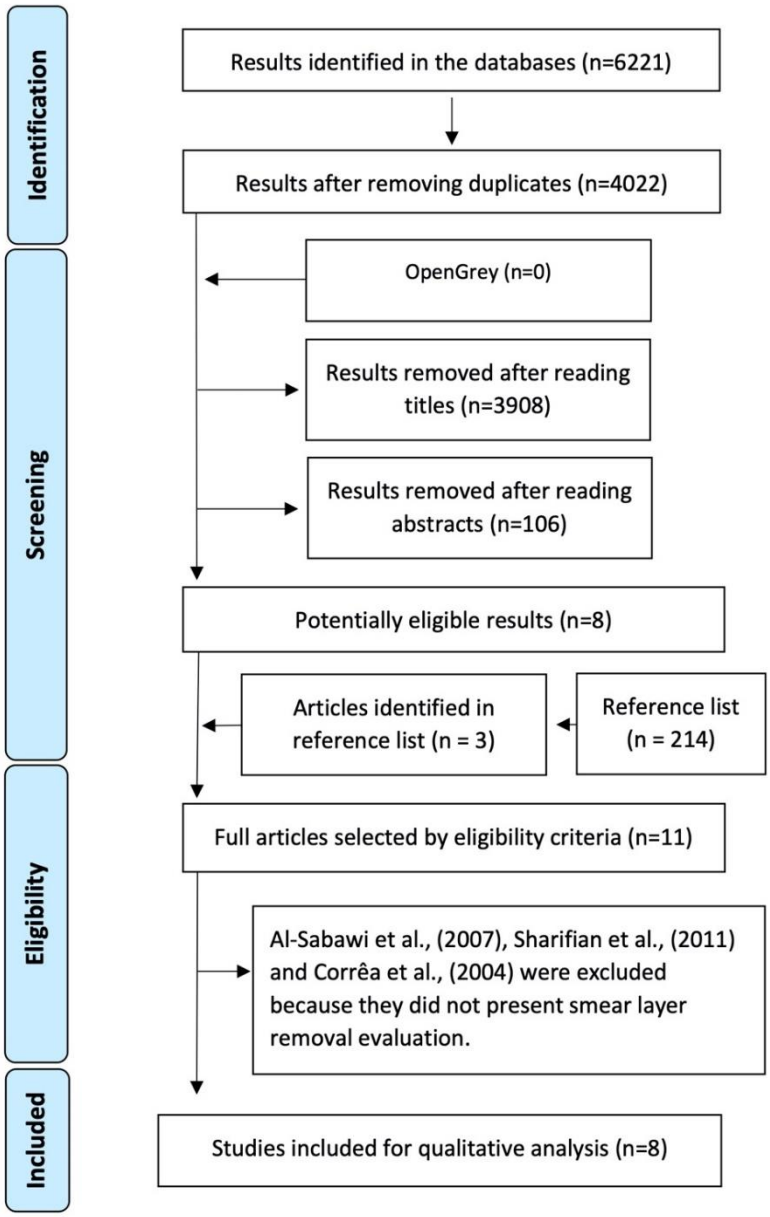

Fig. 1 - Flowchart of the bibliographic search and selection process, adapted from the Preferred Reporting Items for Systematic Reviews and Meta-Analysis protocol – PRISMA.

Features of included article

Table 1 presents data characteristics of the 8 articles included in this review. All experimental in vitro studies were randomized controlled blinded trials with scanning electron microscopy (SEM) analyzes. The publication date of the included articles ranged from 2006 to 2018. Five

studies used permanent teeth,[6,23,24,25,27] and 3 studies did not report the type of teeth used.[13,26,28] In addition, all studies used extracted uniradicular teeth to perform the tests.

Table 1 – Data extraction of included studies

Author/Year/ Country	Sample size	Experimentals groups (type of intervention)	Irrigation time	Magnification/ Evaluation criteria	Results
Sadr Lahijani et al., 2006, Iran	n=40	*Group 1*: 10ml HCE *Group 2*:10ml Tea Tree Oil *Group 3*: 10ml NaOCl 2.5% *Group 4*: Control +: NaOCl 2.5% + 10ml EDTA 17% *Group 5*: Negative Control: distilled water	2 minutes	2000x 5000x *Hulsmann et al.* 2002	Data not shown
Murray et al., 2008, USA	n=60	*Group 1*: MCE 6% + EDTA 17% + MCE 6% *Group 2*: MCE 6%/CHX 2% (1:1) + EDTA 17% + MCE 6%/CHX 2% *Group 3*: MCE 6% + saline solution + MCE 6% *Group 4*: Positive Control = NaOCl 6% + EDTA 17% + NaOCl 6% *Group 5*: Positive Control = 2%CHX *Group 6*: Negative Control = saline solution 0.9%	Uninformed	2000x *Madison & Hokett*, 1997	Complete removal of smear layer and all visible dentinal tubules: *Coronal third* *Group 1*: 60% *Group 2*: 0% *Group 3*: 20% *Group 4*: 80% *Group 5*: 0% *Middle third* *Group 1*: 70% *Group 2*: 0% *Group 3*: 30% *Group 4*: 80% *Group 5*: 30% *Apical third* *Group 1*: 40% *Group 2*: 1% *Group 3*: 20% *Group 4*: 60% *Group 5*: 10%
Balto et al., 2012, Saudi Arabia	n=60	*Group 1*: 1mg/ml ASPE (5ml) + NaOCl 1% *Group 2*: 5mg/ml ASPE (5ml) + NaOCl 1% *Group 3*: Positive Control = EDTA 17% (5ml) NaOCl 1%	5 minutes	1000x 1500x *Torabinejad et al.* 2003	Mean of SL scores covering surfaces and tubules: *Coronal third* *Group 1*: 56.5 *Group 2*: 46.5 *Apical third* *Group 1*: 60.92

		Group 4: Negative Control = saline solution (5ml) + NaOCl 1%			*Group 3*: 46.5 *Group 4*: 110.5 *Middle third* *Group 1*: 65.3 *Group 2*: 49.2 *Group 3*: 30.5 *Group 4*: 103.5	*Group 2*: 61.83 *Group 3*: 24.5 *Group 4*: 93.0
Bolhari et al., 2012, Iran	n=39	*Group 1*: 1ml EDTA 17% *Group 2*: 1ml CCAE *Group 3*: 1ml ACAE *Group 4*: Negative Control: 1ml distilled water	20 minutes 20 minutes 20 minutes 1 minutes	2000x *Schafer e Lohmann* 2002	Data not shown	
Chhabra et al., 2015 India	n=50	*Group 1*: Negative Control = distilled water (3ml) *Group 2*: Positive Control = EDTA 17% (3ml) *Group 3*: 3ml 1:1 0.1g/ml CA 0.1g/ml SM aqueous solution (CA/SM) *Group 4*: 3ml 1:1 CA/SM Solution + sonic agitation *Group 5*: 3ml 2:1 0.12g/ml CA 0.06g/ml SM aqueous solution *Group 6*: 3ml CA/SM (2:1) + sonic agitation	5 minutes	1000x *Hülsmann et al.* 2003	Mean score of SL remaining: *Coronal third* *Group 1* = 3.6 *Group 2* = 1.4 *Group 3* = 2.2 *Group 4* = 2.3 *Group 5* = 1.6 *Group 6* = 1.6 *Middle third* *Group 1* = 4.6 *Group 2* = 2.2 *Group 3* = 3.7 *Group 4* = 3.8 *Group 5* = 3.5 *Group 6* = 2.6	*Apical third* *Group 1* = 4.0 *Group 2* =1.8 *Group 3* = 2.9 *Group 4* = 2.9 *Group 5* = 2.7 *Group 6* = 2.1
Davoudi et al., 2015, Iran	n=40	*Group 1*: 10ml FVE *Group 2*: FVE + EDTA *Group 3*: Positive Control: NaOCL 5.25% + EDTA	10 seconds	1500x *Hülsmann et al.* 1997	Mean score of SL remaining: *Coronal third* *Group 1* =3.2 *Group 2* = 2.4	*Apical third* *Group 1*= 3.8

		Group 4: Negative Control: saline solution			*Group 3* = 1.8 *Group 4* = 3.9 *Middle third* *Group 1* = 3.8 *Group 2* = 2.9 *Group 3* = 2.6 *Group 4* = 4.0	*Group 2*= 3.4 *Group 3*= 2.6 *Group 4*= 4.0
Margono et al., 2017, Indonesia	n=50	*Group 1*: GSE 3.25% *Group 2*: GSE 6,5% *Group 3*: GSE 13% *Group 4:* EDTA 17% *Group 5*: Negative Control: distilled water	Uninformed	1000x *Margono et al.* 2017	% of apical third cleaning	
					Group 1: Score 0 = 30% Score 1 = 40% Score 2 = 30% *Group 2:* Score 0 = 10% Score 1 = 70% Score 2 = 20%	*Group 3:* Score 0 = 40% Score 1 = 20% Score 2 = 40% *Group 4:* Score 0 = 30% Score 1 = 70% Score 2 = 0% *Group 5:* Score 0 = 0% Score 1 = 20% Score 2 = 80%
Ok et al., 2015, Turkey	n=60	*Group 1*: 3ml NaOCl 5.25% + 3ml EDTA 17% *Group 2*: 3ml OE 1% *Group 3*: 3ml OE 2% *Group 4*: 3ml OE 5% *Group 5*: 3ml OE 1% + 3ml EDTA 17%	1 minute	1000x *Ok et al.* 2018	Data not shown	

		Group 6: 3ml OE 2% + 3ml EDTA 17% *Group 7*: 3ml OE 5% + 3ml EDTA 17% *Group 8*: 3ml saline solution + 3ml EDTA 17%			

Phytochemical extracts

The most natural products used in the 8 articles included in this systematic review were *Marticaria recutita L.* (German chamomile),[23] *Melaleuca alternifolia* (tea tree),[23] *Morinda citrifolia*,[24], *Salvadora persica*,[25] *Citrus aurantifolia*,[26,27] *Sapindus mukorrossi*,[27] *Fragaria vesca* (wild strawberries),[28] grape seed oil[13] and oregano.[6]

Root canals analysis

Smear layer analysis in root canals was performed in different ways in the included articles. Sadr *Lahijani et al.*[23] used the method described by *Hülsmann et al.*[29] (score 1: fully open dentinal tubules; score 2: more than 50% of open dentinal tubules; score 3, less than 50% of open dentinal tubules; score 4: almost complete SL covering). *Murray et al.*[24] used the criteria by *Madison* & *Hokett*[30] (score 0: no smear layer removal and no visible dentinal tubule; score 1: some smear layer removal and some visible dentinal tubules; score 2: complete removal of smear layer and all visible dentinal tubules). *Balto et al.*[25] used the methods established by *Torabinejad et al.*[8] (score 1: represents the absence of smear layer on the root canal surface and all tubules are cleaned and opened; score 2: moderate SL on tubules but no SL on root canal surface; score 3: much SL covering the root canal surface and tubules). *Bolhari et al.*[26] used the work of *Schäfer* & *Lohmann*[31] as a criteria for root canal evaluation (score 1: root canal walls cleaning, only with few remaining particles; score 2: few small clumps of debris; score 3: many debris agglomerations covering less than 50% of the canal walls; score 4: more than 50% of the walls covered; score 5: completely or almost completely covered by debris). *Chhabra et al.* (2015) employed the methods described by *Hülsmann et al.*[32] (score 1: no SL and all open tubules; score 2: little amount of SL and some open tubules; score 3: Homogeneous SL covering the canal wall and only a few open dentinal tubules; score 4: canal wall completely covered by a homogeneous SL and no open dentinal tubule; score 5: heavy homogeneous SL completely covering the canal wall). *Davoudi et al.* (2015) evaluated smear layer removal by the criterion mentioned by *Hülsmann et al.*[33] (score 1: completely open dentinal tubules; score 2: more than 50% of open dentinal tubules; score 3: less than 50% of open dentinal tubules; score 4: almost all dentinal tubules occluded with SL). Smear layer removal level in *Margono et al.* (2017) study was evaluated like the system described by *Iona* & *Vasile*[34] (score 0: > 75 % of SL removal; score 1: 50-75% of SL removal; score 2: > 50% covered by SL). *Ok et al.* (2018) has used an own smear layer removal evaluation

criteria: (whether there was complete removal of the smear layer from the dentinal tubules, whether the tubules were completely open or not, and whether there was erosion in the peritubular and intertubular dentin).

Analysis of article quality

Table 2 presents detailed information of the risk of bias in the included studies. Five studies showed low risk of bias[23,25,26,27,28] and 3 studies showed a moderate risk of bias[6,13,24]. Additionally, no studies were classified as high risk of bias. Regarding item 5, *Margono et al*. (2017), *Murray et al*. (2008) and *Ok et al*. (2018) studies were unclear to show how measurements were taken. Therefore, the evaluation of item 8 was considered "no" for these studies. Item 9 of table 2 was considered not applicable for all studies due to the heterogeneity of the data presented.

Table 2 - Risk of bias assessed through the Joanna Briggs Institute Critical Appraisal Checklist for Quasi-Experimental Studies

	Q. 1	Q. 2	Q. 3	Q. 4	Q. 5	Q. 6	Q. 7	Q. 8	Q. 9	% Yes	Risk
Sadr Lahijani et al., 2006	Y	Y	Y	Y	Y	Y	Y	Y	NA	88,88	Low
Murray et al. 2008	Y	Y	Y	Y	UC	Y	Y	N	NA	66,66 %	Moderate
Balto et al., 2012	Y	Y	Y	Y	Y	Y	Y	Y	NA	88,88 %	Low
Bolhari et al., 2012	Y	Y	Y	Y	Y	Y	Y	Y	NA	88,88 %	Low
Chhabra et al., 2015	Y	Y	Y	Y	Y	Y	Y	Y	NA	88,88 %	Low
Davoudi et al., 2015	Y	Y	Y	Y	Y	Y	Y	Y	NA	88,88 %	Low

Margono et al., 2017	Y	Y	Y	Y	N	Y	Y	N	NA	66,66 %	Moderate
Ok et al., 2018	Y	Y	Y	Y	UC	Y	Y	N	NA	66,66 %	Moderate

Q.1: Is it clear in the study what is the 'cause' and what is the 'effect' (i.e. there is no confusion about which variable comes first)?

Q.2: Were the natural products included in any comparisons similar?

Q.3: Were the products included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?

Q.4: Was there a control group?

Q.5: Were there multiple measurements of the outcome both pre and post the intervention/exposure?

Q.6: Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed?

Q.7: Were the outcomes of samples included in any comparisons measured in the same way?

Q.8: Were outcomes measured in a reliable way?

Q.9: Was appropriate statistical analysis used?

Risk of bias was assessed as high when "yes" scores got 49%, moderate when it ranged 50 to 69% and low risk when it got more than 70%.

Y=Yes; N=No; UC= Unclear; NA= Not applicable.

Statistical analysis

No meta-analysis was performed due to the great heterogeneity of data presentation of selected articles, especially regarding of the criteria for evaluating smear layer removal from root canals.

DISCUSSION

Scientific research on use of natural oils and extracts in Dentistry has been highlighted over the years. In Endodontics, natural-based irrigants have been tested for SL removal compared to conventional EDTA, citric acid, MTAD irrigators. This systematic review

examined whether natural product-based irrigating solutions are capable of removing SL from root canals of permanent teeth. Natural products identified in the included studies were: *Matricaria recutita* (German chamomile), *Melaleuca alternifolia* (tea tree oil), *Morinda citrifolia*, *Salvadora persica*, *Citrus aurantifolia*, *Sapindus mukorrossi*, *Fragaria vesca* (wild strawberries), grape seed oil, *Origanum. minutiflorum* (oregano).

Chamomile (*Matricaria recutita*) has acidic components such as capric acid, caprylic acid, chlorogenic acid, o-coumaric acid, p-coumaric acid and dihydroxybenzoic acid that may have an effect on SL removal.[35] *Lahijani et al*. (2006) demonstrated that the efficacy of hydroalcoholic chamomile extract in SL removal was lower than 17% EDTA and Biopure MTAD, respectively. However, this study showed that chamomile extract had more pronounced effect on coronal and middle thirds compared to apical third of the root canals.

Melaleuca alternifolia, more commonly known as tea tree oil, is an Australian plant composed mainly of terpinen-4-ol[20,23] that has anti-inflammatory activity and 1,8-cineole with anti-inflammatory and antimicrobial activity [20,36]. *Sadr Lahijani et al*. (2006) demonstrated that tea tree oil was not able to clean SL on three thirds of root canals. According to the authors, low effectiveness of tea tree oil may be related to its high surface tension. Therefore, it is possible to suggest that tea tree extract added to an on-greasy vehicle or aqueous extract could have better SL removal results, considering the lower surface tension of the solution.

Morinda citrifolia L., also known as noni (Hawaii), Indian mulberry, nunaakai (Tamil Nadu, India), Kumuda (Balinese), among other common names, has been suggested for use as endodontic irrigant.[10] *Murray et al*. (2008) described that *Morinda citrifolia* extract showed good efficacy in removing SL from root canals, but only when accompanied by a 17% EDTA rinse. The combination of *Morinda citrifolia* extract with chlorhexidine had a similar effect to saline solution. Additionally, *Saghiri et al*. (2013) also concluded that 6% *Morinda citrifolia*, followed by 17% EDTA final flow, can be considered an effective solution for SL removal, without side effect on root canal dentin microhardness property.

Salvadora persica has several chemical compounds in its extracts, such as sodium chloride, potassium chloride, salvadourea, salvadorine, saponins, tannins, vitamin C, silica and resin,[37] which have cleaning action. *Balto et al*.[25] found that 1 mg/ml of *S. persica* alcohol extract was able to partially remove SL from coronal and middle thirds of root canals, and 5mg/ml of *S. persica* alcohol extract was as effective as EDTA 17% in the SL

removal from coronal third. On middle and apical thirds, EDTA was more effective than both concentrations of *S. persica* alcohol extract in SL removal.

Citrus aurantifolia (lemon) composed of 6-8% citric acid has been studied as a possible irrigating solution due to its action on SL removal.[26,27,38] *Bolhari et al*. (2012) concluded that concentrated and alcoholic extracts of *Citrus aurantifolia* were not able to completely remove SL layer when compared to 17% EDTA. The authors believe that it is due to the low concentration of citric acid in the solutions. The efficacy of concentrated extract was better than alcohol extract on middle and coronal thirds. It was suggested that increased concentrations may lead to increased SL removal.

Chhabra et al. (2015) associated aqueous solutions of *C. aurantifolia* and *S. mukorrossi* in two different proportions (1:1 and 2:1), with and without ultrasonic shake, and they found that only *Citrus aurantifolia* and *Sapindus mukorrossi* group (2:1) with ultrasonic agitation were comparable to EDTA group on all 3 thirds, suggesting that an increase of *C. aurantifolia* concentration, and consequent an increase of citric acid concentration, associated with sonic activation, improved solution efficacy. Therefore, the action of natural products may be potentiated by increased concentrations and sonic activation. Ultrasonic agitation within an instrumented root canal produce a hydrodynamic effect and improve the displacement of the solution, that will result in better contact of irrigating solutions with root canal walls.[39]

Sapindus mukorrossi is a biosurfactant that dissolves water-insoluble substances composed mainly of triterpene saponins[40] and it was also used to potentiate *Citrus aurantifolia* action, but in a unique concentration. Thus, the authors suggest studies with solutions of alcoholic extract and variations in *S. mukorrossi* concentrations to evaluate its ability to remove SL.

Fragaria vesca 20% extract (wild strawberry) showed marked ability to remove SL, on middle and coronal thirds, when it was associated with EDTA.[28] The authors suggest the use of more concentrated EFV solutions, as well as higher volumes and irrigation times, in future studies.

Ok et al. (2015) demonstrated that *Origanum minutiflorum* (oregano) was not able to remove SL when used alone. However, 17% EDTA and oregano at 1%, 2% or 5% in combinated concentrations removed SL and opened dentinal tubules on coronal, middle and apical thirds without dentin erosion. One of side effects of EDTA is erosion of

peritubular dentin and it was suggested that the use of EDTA in combination with natural products may minimize this unwanted effect.

The 6.5% grape seed extract, composed of a weak acid called proanthocyanidin, has shown SL removal potential from apical third of the root canals, but it was not as effective as 17% EDTA [13]. The same product at 13% concentration showed lower efficacy, and further studies with higher concentrations are necessary to verify if the increase in concentration does not influence its action.

In this systematic review, it was observed that some natural-based solutions alone are effective in removing SL, especially on coronal third, followed by lower middle third. Some of these showed very close efficacy to EDTA on coronal third (*Salvadora persica* 5mg/ml, chamomile alcohol extract), medium (chamomile alcohol extract) and apical (grape seed extract). Products such as *Morinda citrifolia*, *Citrus aurantifolia*, *Fragaria vesca* and *Oreganum minutiflorum*, used without final EDTA rinse, were not able to remove SL satisfactorily.

The previous irrigation of the root canal system with sodium hypochlorite (NaOCL) in different concentrations reduces side effects such as dentin erosion of the intracanal tubules and improves the performance of some natural solutions. In addition, NaOCl promotes the effective removal of organic components from SL.[41] In this sense, the association of irrigating solutions based on natural products associated with previous irrigation with NaOCl may be an important alternative for SL removal.

The canal diameter narrowing on apical third leads to a lower flow of irrigating solution and, consequently, fewer effects of solutions, which may compromise the success of endodontic treatment. Operator skill, file type and technique used for canal enlargement on apical third should be considered.[3,23,28,42] In addition, the use of auxiliary methods such as ultrasound, sonic agitation, pulsed light, diode laser, endovac irrigation system negative pressure can improve quality of biomechanical preparation on apical third, enhancing the action of irrigating solutions.[27,43,44]

The criteria used to evaluate SL removal by the studies including in this review was SEM analysis. This method has some limitations such as being subjective, less comparativeness and with a low reproducibility and providing variety of results. *Murray et al*. (2008), *Balto et al*. (2012) and *Margono et al*. (2017) used methods of 3 scores. *Sadir Lahijani et al*. (2006) and Davoudi *et al*. (2015) used 4-point classification methods. *Bolhari et al*. (2012) and *Chhabra et al*. (2015) used 5-score methods. Additionally, *Ok et al*. (2015) described

their own evaluation method. Although there are others SL removal analyses methods, SEM technique is still acceptable for research on new irrigation solutions and protocols.[28] However, it is important to note that heterogeneity between SL removal classification and different evaluation strategies used by the authors were considered as a limitation on comparativeness of data studies. The difference in presentation of results such as mean SL remnant scores and mean SL remnant percentages became impossible the real analyze of the effectiveness of the natural products for SL removal.

Although the limitations of this study, it is possible to highlight those phytochemical products such as *Salvadora persica*, chamomile alcohol extract and grape seed extract that demonstrated good potential on SL removal. Nevertheless, the applicability of these products in endodontic therapy is still unknown and more studies are necessary to elucidate its real potential for SL removal as well as their biological proprieties.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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