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Caries preventive potential of professionally deliverable fluoride-containing agents with incorporated arginine: A scoping review☆

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ABSTRACT

The scoping review objectives were to: 1) investigate the caries preventive potential of professionally deliverable fluoride (F)-containing agents with incorporated arginine (Arg); and 2) identify the future scope of research on Arg-F interventions for caries prevention. Of 150 identified records, 7 articles (6 *in vitro* investigations and 1 scoping review) were included for a complete review; with no clinical studies with/without appraisal. Arginine variants (L-Arg/Arg.HCl at 1% to 10% *w/v*.) were examined for a potential professional application aimed at caries prevention, as reported with *in vitro* studies. Of the included articles, four *in vitro* studies explored L-Arg enriched 5% NaF varnish (Duraphat®) as a promising caries preventive agent, while only one considered incorporating L-Arg in MI varnish®/nanohydroxyapatite and one investigated glass ionomer cement for primary/secondary and tertiary caries prevention. The scoping review highlighted the scope for incorporating Arg to professionally deliverable F-containing agents. No clinical data are available to make conclusive recommendations about the caries preventive potential of professionally deliverable F-containing agents with incorporated Arg. With Arg-F varnish being investigated predominantly through *in vitro* studies, the data so far suggest that Arg was incorporated exclusively in Duraphat®, while the potential of Arg to prevent caries in other F-containing varnishes remains unexplored.

1. Introduction

Dental caries, a multifactorial biofilm-mediated disease, affects around 3 billion people worldwide [1,2]. Cariogenic biofilm prevails in high-risk patients with harbouring chronic dysbiosis leading to prolonged acidification of the tooth-adhered biofilm, thereby causing net mineral loss [3,4]. Persistent mineral loss affects the remineralization-demineralization dynamics, eventually causing an irreversible process termed as cavitation. Efforts are needed to prevent these irreversible tooth-related changes with interventions targeting high-risk groups, including the low-income and socially deprived populations for whom the burden of oral care is huge. Several preventive agents countering the deleterious effects of globally affected dental caries have been proposed [5,6]. However, novel disease-process targeted preventive regimens are needed to alleviate the caries-related concerns of the affected population, including the prevention of biofilm dysbiosis and the subsequent effect of endogenous biofilm-generated biocorrodonts.

Fluorides (F) have been the mainstay of caries prevention for the past seven decades [7]. Incorporated in vehicles like pastes, gels, varnishes, foams, and dispensable liquids, F is well known to prevent demineralization and promote remineralization, primarily by forming a CaF_2-like complex at the enamel surface [8,9]. Although the effect of F on remineralization-demineralization dynamics is undisputable, its effect on cariogenic biofilms is little and unsustainable [10]. Given the limitations of F on cariogenic biofilms, interventions are needed to append the conceded effect of F, addressing biofilm microenvironments leading to further cavitation-related deleterious effects on teeth. The beseeched

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interventions are essentially microbiota-targeted and based on their fundamental role in the development of cariogenic biofilms causing continual acidic domains for eventual mineral loss.

Arginine (Arg), a semi-essential amino acid termed as a prebiotic aimed at caries prevention, can maintain supra-gingival ecological homeostasis and prevent biofilm dysbiosis [6,11–14]. The prebiotic selectively inhibits the growth of cariogenic pathogens like *Streptococcus mutans* while enhancing the growth of arginolytic commensals – *Streptococcus sanguinis, Streptococcus parasanguinis,* and *Streptococcus gordonii via* the arginine deiminase (ADS) pathways to produce ammonia (NH_3) metabolite for restoring biofilm pH [15,16]. The basic amino acid has been incorporated in vehicles like toothpastes and mouth rinses aimed at caries prevention. While including the primary studies, systematic reviews and meta-analysis examined the effects of self-deliverable Arg-F interventions for preventing primary and secondary caries at tooth grade and reported a superior anti-caries effect than F (alone) toothpaste, while concerns were expressed about potential risks of bias due to industrial collaboration [11,14]. However, none of the primary studies included a potential professional application of Arg-F as an intervention.

Formerly, in a clinical study, the investigators explored the effect of a customized 3% Arg varnish on a group of mentally disabled children over eight weeks [17]. Based on the study results, the researchers expressed the possibility of including the intervention as an adjunct to routine oral hygiene measures for high-risk patients. Although this is a professional intervention, it excluded the long-evident benefits of F which, otherwise, are available as F-varnishes for professional use. In recent years, the possibilities of incorporating Arg in F varnishes have been explored [18]. While the data on professionally deliverable Arg-enriched F interventions are indubitable, these data are scarce, emerging, and discursive for comprehensive perception. Being discrete and inceptive, a further predilection for the future scope of research with professionally deliverable Arg-F interventions is compelling. With the objective of investigating the concerns outlined above and systematically mapping the research in this area, a scoping review was planned to: 1) investigate the caries preventive potential of professionally deliverable F-containing agents with incorporated Arg; and 2) identify the future scope of research on Arg-F interventions for caries prevention. The following review question was formulated addressing the study objectives: To date, what is known from the literature regarding the caries preventive potential of professionally deliverable Arg-F interventions?

2. Methods

The present scoping review was performed based on a seminal paper and a guidance document for the biomedical literature review type [19,20]. The details in this paper are reported as per the PRISMA extension for scoping reviews (PRISMA-ScR) with an essential checklist [21] for reporting items (Table S1), referring to the tip sheet for fine narration. The review was intended to synthesize the evidence on professionally deliverable Arg-F interventions for caries prevention and thereby assess the scope of research, hence, justifying the need for scoping reviews on an emerging science in the field.

Based on the review focus, the research question was conceptualized using the SPICE framework:

S – Setting/study type: Any (given the review type)
P – Perspective: Biotic strategies for caries prevention (novel caries preventive agents)
I – Intervention: Professionally deliverable Arg-F (review focus)
C – Comparison: No intervention or F (based on the study context)
E – Evaluation: Characterization/outcomes with respective studies (to estimate relevant outcomes)

2.1. Protocol registration

A study protocol was drafted prior to initiating the review process which was duly construed, acknowledged and revised by all the reviewers. The final protocol included the list of reviewers, review objectives, search strategy with duration, study inclusion/exclusion criteria, data charting variables, and synthesis process. The pilot-tested registered protocol for public access can be located at https://osf.io/y5rw8/ with availability from January 2023. To record, there was no deviation from the protocol during the entire review process.

2.2. Record sources, study search, selection, and inclusion

2.2.1. Record sources

The literature databases PubMed, SCOPUS, and Web of Science were searched using the refined search strategy developed after identifying the relevant keywords for the research question with an accordant Boolean operator (until December 2023), as established in the protocol after team discussion. In addition, a reference search of the eligible papers was performed and the expert opinion of an internal reviewer (MNB) was sought. For the purpose of this review, records available as titles and abstracts in English with the relevant databases were considered for further scrutiny. Gray literature database searches (conference proceedings, a google search for thesis/books, and trial registries) were conducted to supplement the level of searches with the intent of identifying literature categorically distinct from the identified components of the initial search phases. The final search results were exported to Mendeley Desktop v. 1.19.8 (Mendeley Ltd., Elsevier, Netherlands) and duplicates were removed before proceeding with further phases of study inclusion in the review by scanning relevant and eligible studies.

2.2.2. Study eligibility

To be included in the review, records (titles/abstracts/full-texts) that reported examining the caries preventive potential of professionally deliverable Arg-F interventions were deemed eligible. Peer-reviewed papers on the review focus published until December 2023 were included. Further, records/papers were excluded if they did not suffice within the aegis of the conceptual framework of the review. The inclusion/exclusion criteria for the review were as follows:

2.2.2.1. Inclusion criteria. *In vitro* studies, clinical trials, systematic reviews with/without meta-analysis, umbrella reviews, systematic scoping reviews, and narrative reviews examining the caries preventive potential of professionally deliverable Arg-F interventions.

2.2.2.2. Exclusion criteria. Studies with no keyword-specific components, observational studies, not professionally deliverable Arg-F interventions, non-English language papers, no title &/or abstract, commentaries/opinions, and studies not related to the review question.

2.2.3. Search strategy

Preliminarily and throughout, the record search was carried out by two reviewers (NAA & TKN) independently to justify the reproducibility of the review process and resolve any discrepancies that arose through discussion and seeking the opinion of a third internal reviewer (MNB). The search string included the essential components of the devised SPICE framework, as mentioned in the protocol, including wildcards, as and when required – (arginine) AND (caries prevent*) AND (fluoride*). The final detailed search strategy for PubMed is available in Table S2. The search strategy did not include any limitations and no filters were applied prior to the entry of relevant keywords in the search fields.

2.2.4. Study inclusion

For consistency, the two main reviewers (NAA & TKN) screened the identified records after removing the duplicates. Eventually, at each

study inclusion phase, the results were discussed with all the reviewers to obtain consensus for the pertinent phase. Sequentially, the titles, abstracts, and full-texts of the papers were reviewed independently by the two reviewers (NAA & TKN) to narrow down papers/records eligible for inclusion in the study. Any disagreements during the process were resolved by discussion with the third internal reviewer (MNB).

2.3. Data variables and extraction

The data charting process included extracting qualitative variables as outlined in the protocol, *viz.*, article characteristics (study type, author (year), country/city); contextual factors (population, intervention(s), control/alternative intervention(s), characterization(s) and/or outcomes); commercial entities (commercial products, if any); results (significant data); study conclusion(s), and potential application(s).

The data charting process was performed on a piloted data charting sheet, as available in the registered protocol. The process was carried out on an MS Excel 2019 sheet (Microsoft, Richmond, USA) independently by the two main reviewers (NAA & TKN). Again, any inconsistencies in the charting process were resolved by seeking clarification from the third reviewer (MNB). From the initial charting to the final presentation, the data sheets were referenced as versions to identify the iterative process and any justifiable deviations from what was intended to be recorded as extractable variables.

2.4. Synthesis of evidence

After the data were abstracted, the studies were grouped, based on the professionally deliverable Arg-F interventions. The data were pooled as a tabular representation to include the study types addressing the intervention under discussion and a synthesized outline based on the extracted primary data. Appraisal of the evidence was not an element addressed in the present review and, thus, no methodology for the critical evaluation of resources is reported here. However, the grouped interventions are commented upon in the results section of the paper.

3. Results

3.1. Study selection process

The study selection process for the present study is shown in Fig. 1. In total, 150 records were identified from the predetermined databases, of which 66 were duplicates and 74 records were excluded for reasons cited in the flowchart for the study selection process (Fig. 1). The remaining 10 articles were assessed for their eligibility and eventually, seven papers [18,22–27] were included in the systematic scoping review. These seven papers consisted of six *in vitro* studies [18,23–27] and one scoping review [22]. There was 100% agreement between all the reviewers about the final inclusion.

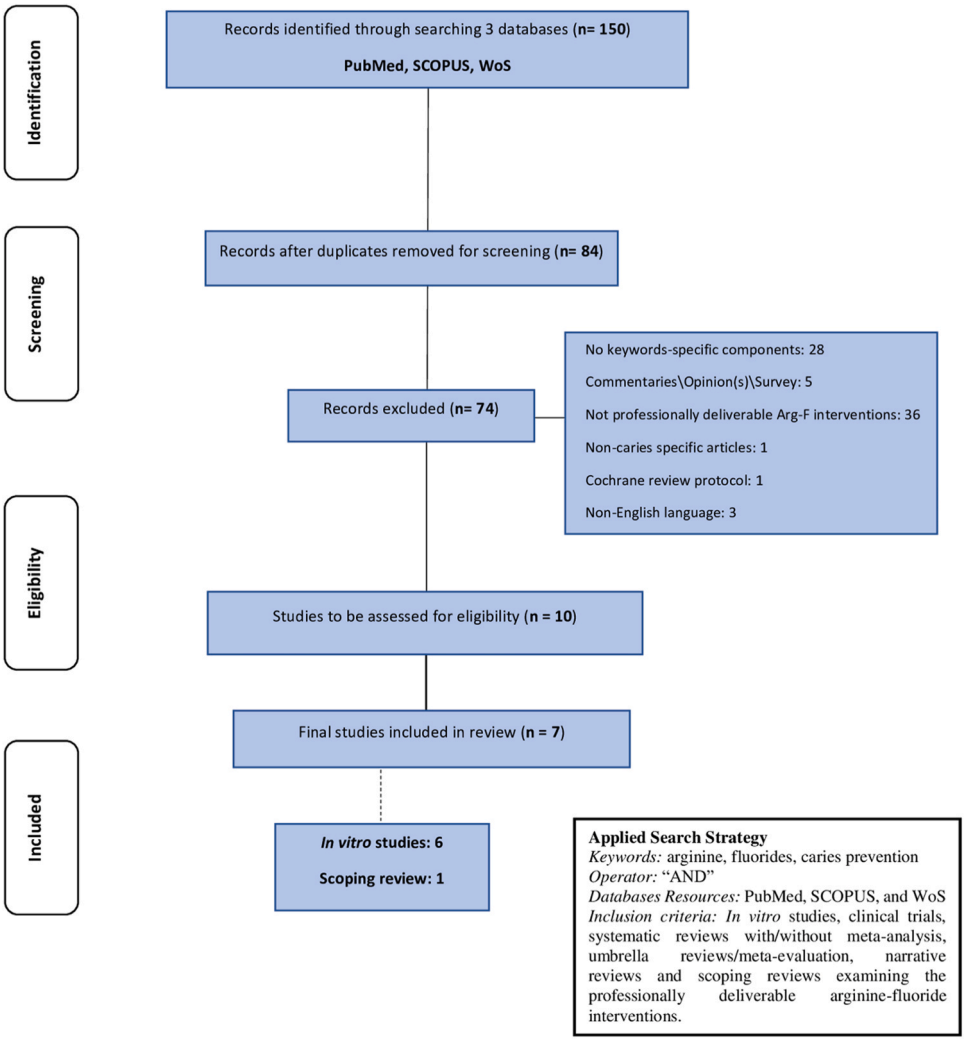

Fig. 1. Study search, selection, and inclusion.

3.2. Characteristics of included studies

The data abstracted for the included studies are presented in Tables 1 and 2. All of the included studies were from Asia – six [18,22–25,27] from Hong Kong SAR (South East Asia) and one [26] from India (South Asia – Indian subcontinent). Five papers were published in the year 2020 [18,22,25–27], while one was published in 2021 [23] and one in 2022 [24].

L-arginine enriched 5% NaF varnish (Duraphat®) was predominantly investigated and reported in four *in vitro* studies [18,23,24,27]. As well, the conception of such an intervention was suggested in a scoping review [22]. One paper each reported examining the effect of incorporating L-Arg in glass ionomer cement (GIC, GC Fuji II) [25] and MI varnish®/10% nanohydroxyapatite (nano-HA) [26] on material properties/antimicrobial activity and remineralization potential, respectively.

3.3. Investigations

3.3.1. In vitro studies

3.3.1.1. L-arginine in glass ionomer cement (GIC). The contributors of the included article [25] reported examining the effect of incorporating 1%, 2%, and 4% L-Arg in GIC (GC Fuji II, GC Corp., Tokyo, Japan) on the mechanical properties and antibacterial potential of GIC. The positive control in the study was GIC discs, while the negative control was acrylic discs. To estimate material properties, characterizations *viz.*, biaxial flexural strength, nanohardness, surface roughness, molecular and elemental release profiles for F, Al, Si, Ca, Arg were performed. To investigate the material antimicrobial potential quantitatively, bacterial DNA quantification, media pH, ADS activity by NH_3, H_2O_2, and lactic acid were measured. Further, confocal imaging was undertaken to qualitatively estimate the material antimicrobial potential. The results of the study suggested that incorporating 4% L-Arg in GIC inhibited the growth of viable *S. mutans* and *S. sanguinis* with higher F/Arg/Al/Si release, environmental pH, and H_2O_2 production than the other groups. The mechanical properties of 4% L-Arg in GIC were similar to the control. A potential application for tertiary caries prevention, addressing the development of secondary caries, was highlighted with 4% Arg in GIC as the combined material demonstrated an increased antimicrobial potential with no adverse effect on mechanical properties compared to the control. The authors of the study proposed that incorporating L-Arg at 4% *w/w*. might selectively enhance the growth of healthy commensals due to the prebiotic effect of Arg adjacent to the restoration, thereby limiting the development of secondary caries.

3.3.1.2. L-arginine in MI varnish and 10% nanohydroxyapatite. A study by Konagala et al. [26] evaluated the enamel remineralization potential of incorporating Arg in MI varnish® and with 10% nano-HA on their remineralization potential. MI varnish® is casein phosphopeptide – amorphous calcium phosphate (CPP-ACP) with 5% NaF varnish, thus referred to as CPP-ACFP. A 10% nano-HA solution was custom-prepared using distilled water. To examine the remineralization potential of experimental interventions and respective controls, characterizations *viz.*, Vickers microhardness testing and SEM-EDX elemental analysis for Ca, P, F were undertaken. The authors reported a significant increase in the remineralization-associated hardness and mineral gain (shown by SEM-EDX) with Arg-based interventions than the controls. It was further concluded that incorporating 10% L-Arg in MI varnish® or with 10% nano-HA significantly increased their remineralization potential to prevent primary and secondary caries. The authors advocated that interaction between positively charged guanidinium groups (of Arg) and negatively charged F, while the negatively charged COO group of L-Arg and HA facilitated the precipitation and deposition of calcium and phosphates in the decalcified areas of artificial incipient caries-like lesions thereby enhancing the remineralization potential of CPP-ACFP and nano-HA. A caution is laid on the extrapolation of these results on the caries preventive potential as no qualitative data were presented along with the reported quantitative data. Further, the authors recommended undertaking studies to evaluate crystal growth and morphology to discern the claimed enhanced remineralization potential with Arg-based interventions.

3.3.1.3. L-arginine in 5% NaF varnish. Several *in vitro* investigations [18,23,24,27] were undertaken to examine the caries preventive potential of Arg-enriched 5% NaF varnish under different experimental conditions, all aimed at preventing primary and secondary caries. The conditions varied from investigating the changes in the material properties [27], demineralization/remineralization assay [18], chemical pH cycling [18], bacterial pH cycling [23], and biofilm modulation potential [24]. *A priori* exploratory studies [18,27] incorporated two Arg variants: L-Arg and L-arginine monohydrochloride (L-Arg.HCl) in Duraphat® (5% NaF varnish) at concentrations 2%, 4%, and 8% *w/v*. to examine the effect of augmenting Arg to the varnish on the material properties and remineralization potential under different chemically-steered experimental cycles. In these studies, the relevant characterizations of F/Arg release, Ca^{+2}/PO_4^{3-} content analysis, F/Arg enamel uptake, SEM-EDX (Ca/F), and mineral density assessment using micro-CT were investigated. The first study in the series on material properties [27] highlighted that incorporating 2% Arg in Duraphat® exhibited higher and perpetual F/Arg release in the media and the varnish physical properties were improved with a stable matrix. However, L-Arg.HCl in Duraphat® exhibited a non-contributory effect on the varnish properties. Subsequently, the imminent study [18] explored the remineralization potential of Arg-F intervention and concluded that incorporating 2% Arg in Duraphat® enhanced the enamel F uptake (EFU) and remineralization potential of the control varnish (Duraphat®). In a nutshell, the preliminary studies of Arg-F varnish suggested that incorporating 2% Arg in Duraphat® might enhance the caries preventive potential of the varnish control.

To explore the area further, the contributors working on Arg-F varnish examined the remineralization potential of Arg-F varnish under bacterial pH-cycling conditions [23] based on the premise that Arg is a prebiotic and its caries preventive potential might well be highlighted under an artificial mouth system with bacterial-induced pH changes on the tooth substrate with artificial incipient carious lesions. The concentrations of L-Arg tested in this and subsequent studies were 1%, 2%, and 4% *w/v*., possibly based on the promising results of the preliminary exploratory studies with 2% Arg in Duraphat® [18,27]. Based on the characterizations investigated (mineral density assessment using micro-CT, SEM-EDX for Ca/P, EFU, and plaque F uptake), the authors concluded that incorporating 2% Arg in Duraphat® enhanced the EFU and remineralization potential of Duraphat®, under the bacterial pH-cycling conditions. Thereafter, in a study, the biofilm modulation potential of Arg-F varnish was explored to investigate the effect of varnish release on established biofilms in high caries-risk patients [24]. Several characterizations were undertaken including the biofilm biochemical assessment (carbohydrates, proteins, eDNA), confocal imaging, DNA quantification, and relative gene expression. In this study, 2% and 4% Arg in Duraphat® enhanced the antimicrobial effect of Duraphat® in a dose-dependent manner with an antagonistic effect on the biofilm matrix. It was concluded that incorporating 2% Arg in Duraphat® enhanced the biofilm modulation effect of the control varnish.

In summary, it appears that incorporating 2% Arg in Duraphat® demonstrates a promising caries preventive potential that is superior to the existing professionally deliverable Duraphat®-based measures.

3.3.2. Scoping review

We were able to identify and include a scoping review on the subject

Table 1
In vitro investigations of the caries preventive potential of professionally deliverable fluoride-containing agents.

SN	Author (Year)	Country/ City	Intervention (s)	Control or Alternative intervention (s)	Characterizations and/or outcome	Commercial product	Results (Significant data)	Conclusion	Potential application (s)
1	Bijle et al. (2020)	Hong Kong, Hong Kong SAR	1%, 2%, and 4% of L-Arg	Positive control: Glass ionomer cement; Negative control: Acrylic discs	Biaxial flexural strength using UTM; nanohardness & surface roughness by AFM; SEM-EDX; molecular/elemental release by F-ISE, ICP-OES, & spectrophotometer; DNA quantification; pH estimation; ADS activity by ammonia measurement, lactic acid, and hydrogen peroxide measurements; and CLSM.	GC Fuji II (Fuji II, GC Corporation, Tokyo, Japan)	The 4% Arg in GIC exhibited growth inhibition of viable *S. mutans/ S. sanguinis;* higher F/Arg/Al/Si release, environmental pH, and hydrogen peroxide production than the other groups. The mechanical properties and surface roughness of 4% Arg in GIC were similar to the control.	Incorporating 4% L-Arg to the commercially available glass ionomer cement increased its antibacterial activity with no adverse effect on its mechanical properties.	Tertiary caries prevention
2	Bijle et al. (2020)	Hong Kong, Hong Kong SAR	2%, 4%, and 8% of L-Arg and L-Arg.HCl	5% NaF varnish	Varnish adhesion/ viscosity, F extraction, molecular interaction of Arg and F using computational dynamics, F and Arg release in lactate buffer and artificial saliva.	Duraphat® varnish (Colgate Palmolive Company, New York, USA)	Incorporating 2% Arg in NaF varnish significantly increased varnish viscosity and thereby improved retention. The total F extraction for 2% Arg in NaF varnish was lower than the control group thereby exhibiting Arg-F interaction. Also, 2% Arg in 5% NaF varnish exhibited a higher perpetual F and Arg release in the media.	L-Arg.HCl exhibited a non-contributory effect on varnish properties when incorporated in 5% NaF varnish. Incorporating 2% Arg in 5% NaF varnish improved varnish physical properties with a stable matrix and enduring F/Arg release.	Primary and secondary caries prevention
3	Bijle et al. (2020)	Hong Kong, Hong Kong SAR	2%, 4%, and 8% of L-Arg and L-Arg.HCl	5% NaF varnish	Demineralization assay: surface roughness using AFM; Remineralization assay: calcium and phosphate content analysis, F & Arg uptake; pH-cycling: mineral density assessment using micro-CT and SEM-EDX (Ca & F).	Duraphat® varnish (Colgate Palmolive Company, New York, USA)	2% Arg in NaF varnish significantly increased the Ca-content with a higher Ca/P ratio, and enhanced F/ Arg uptake in incipient carious lesions than the control. The pH-cycling experiments outlined a significantly increased remineralization potential of 2% Arg in NaF varnish than 5% NaF varnish.	Incorporation of 2% L-Arg in 5% NaF varnish enhanced the EFU and remineralization potential of 5% NaF varnish.	Primary and secondary caries prevention
4	Konagala et al. (2020)	Andhra Pradesh, India	10% of L-Arg	MI Varnish (CPP-ACFP) and 10% Nanohydroxyapatite (nano-HA)	Microhardness testing using a Vickers hardness testing machine and SEM-EDX (Ca, P, F)	MI varnish® (GC Corporation, Tokyo, Japan)	A significant increase in the remineralization-associated hardness and mineral gain was shown with L-Arg incorporated interventions compared to the controls, while a significant increase in F gain was observed with	Incorporating 10% L-Arg in CPP-ACFP varnish and nano-HA significantly increased their remineralization potential.	Primary and secondary caries prevention

(*continued on next page*)

Table 1 (*continued*)

SN	Author (Year)	Country/ City	Intervention (s)	Control or Alternative intervention (s)	Characterizations and/or outcome	Commercial product	Results (Significant data)	Conclusion	Potential application (s)
							L-Arg in NaF group as compared to the other groups.		
5	Bijle et al. (2021)	Hong Kong, Hong Kong SAR	1%, 2%, and 4% of L-Arg	5% NaF varnish	Bacterial pH-cycling: Mineral density assessement using micro-CT, SEM-EDX (Ca, P), EFU and PFU	Duraphat® varnish (Colgate Palmolive Company, New York, USA)	L-Arg in 5% NaF varnish significantly increased the EFU than the control, while 1%/2% Arg in NaF varnish significantly increased the remineralization potential of 5% NaF varnish.	1%/2% L-Arg in 5% NaF varnish enhanced the EFU and remineralization potential of the conventional 5% NaF varnish under bacterial pH-cycling model.	Primary and secondary caries prevention
6	Bijle et al. (2022)	Hong Kong, Hong Kong SAR	1%, 2%, and 4% of L-Arg	5% NaF varnish	Biochemical assays: carbohydrates (total, water-soluble, and water-insoluble), proteins, and eDNA; CLSM; DNA quantification and qPCR; relative gene expression	Duraphat® varnish (Colgate Palmolive Company, New York, USA)	2% and 4% L-Arg in 5% NaF varnish enhanced the biofilm modulation effect of NaF varnish by a dose-dependent antimicrobial effect and antagonistic effect on biofilm matrix	Incorporating 2%/ 4% L-Arg in 5% NaF varnish enhances the biofilm modulatory effect of the control 5% NaF varnish.	Primary and secondary caries prevention

UTM: Universal Testing Machine; AFM: Atomic Force Microscopy; SEM-EDX: Scanning Electron Microscopy-Energy Dispersive X-Spectroscopy; F-ISE: Fluoride Ion Selective Electrode; ICP-OES: Inductively Coupled Plasma-Optical Emission Spectroscopy; CLSM: Confocal Laser Scanning Microscopy; CPP-ACFP: Casein Phosphopeptide-Amorphous Calcium Fluoride Phosphate; Arg: Arginine; F: Fluoride; micro-CT: microcomputed tomography; EFU: Enamel Fluoride Uptake; PFU: Plaque Fluoride Uptake; qPCR: quantitative polymerase chain reaction.

[22], with 39 articles reviewed from 105 identified records, including *in vitro* studies, clinical trials, narrative reviews, and systematic reviews with/without meta-analysis. Three Arg variants could be identified with the review *viz.*, L-Arg, L-Arg.HCl, and L-Arg bicarbonate used with commercially available F-containing toothpaste. No conclusive recommendations with regard to caries preventive effects of Arg/Arg formulations could be established due to the primary studies, being industry-supported, having a high risk of bias. None of the articles included in the review addressed professionally deliverable Arg-F intervention. However, within the purview and scope of a systematic scoping review the authors suggested that, although Arg (alone) was tested in a clinical trial [17] as a professionally deliverable agent, a more inclusive case appears for Arg-F varnish/other vehicle as a possible long-standing professional intervention for caries prevention. A further note was added that such a professional and targeted delivery Arg-F needs further development for effective standardization and clinical implementation.

3.4. Synthesis of results

The results of the synthesized evidence with the present scoping review are shown in Table 3. L-arginine in MI varnish® [26], with 10% nano-HA [26], and in GIC [25] at different concentrations significantly improved the material properties of the control for enhanced caries preventive effect. However, the reported effect was based on a solitary *in vitro* investigation. Thus, the reported effect might be encouraging, although unlikely to be regarded as conclusive without any further investigations and clinical trials. While 2% Arg in Duraphat® appeared to be a promising professionally deliverable Arg-based caries preventive agent, no appraised/non-appraised clinical data could be identified for inclusion in the present review and thereby conclusive recommendations could not be drawn. Conversely, compared to other Arg-F-based professionally deliverable agents referred to in the review, several *in vitro* studies [18,23,24,27] investigated the caries preventive effect of Arg-F varnish with a mention of research scope in a systematic scoping review paper [22], implying published baseline reports/data with translational potential. Furthermore, Arg was incorporated exclusively in Duraphat® with the effect of the intervention remaining unexplored in other professionally deliverable F-containing agents.

4. Discussion

The purpose of this systematically approached scoping review was to investigate the existing literature related to the caries preventive potential of professionally deliverable Arg-F interventions. The results of the data synthesized through the review process signify that there are no clinical studies available to make conclusive recommendations on the caries preventive potential of professionally deliverable Arg-F interventions. Clearly, there is a need to explore the area further with appraised reports. The synthesized data leaned towards the possibility of Arg-F varnish as a professionally deliverable caries preventive agent. While exploring such an intervention, Arg was incorporated exclusively in Duraphat®, while the caries preventive effect of incorporating Arg in other commercially available F-containing varnishes remains unexplored. The concept of Arg-enriched F-containing varnish is based on the premise that varnish is known to adhere to tooth surfaces for prolonged periods while releasing adequate concentrations of active ingredients for caries prevention per case being Arg and F.

Arginine, a semi-essential amino acid, is available in micromolar concentrations in the oral cavity. The Arg-utilized metabolic ADS pathway with arginolytic commensals is associated with dental caries to an extent, being regarded as a caries risk indicator [28]. The relationship is quantitatively inverse – a higher ADS activity is associated with a lower risk of dental caries and *vice versa* [29–32]. In addition, self-applied Arg-F interventions have shown a superior caries preventive effect than the conventional F (alone)-containing vehicles for daily use [33,34]; however, the systematic reviews of clinical trials have raised concerns about a high risk of bias [11,14]. Further, it has been explored

Table 2
A review paper on the caries preventive potential of professionally deliverable fluoride-containing agents.

Study type	Author (Year)	Country/ City	Population	Intervention (s)	Control or Alternative intervention (s)	Characterizations and/ or outcome	Commercial product	Results (Significant data)	Conclusion	Potential application (s)
Scoping review	Bijle et al. (2020)	Hong Kong, Hong Kong SAR	No specific population	Arg/Arg formulations	Respective controls as per primary studies	Several characterizations independent to the included primary studies while being relevant to the study design	Commercially available Arg formulations (*e.g.* Arg-F toothpaste, Arg-non-fluoridated toothpaste, Arg sugarless confection)	Arg/Arg formulations investigated through *in vitro* studies, clinical trials, and reviews demonstrated a superior caries preventive effect compared to the controls. However, the evidence cannot be considered conclusive due to a high risk of bias.	Conclusive recommendations with the caries preventive effect for currently available Arg/Arg formulations are unlikely due to the included primary studies with a high risk of bias.	Primary and secondary caries prevention

Table 3
Synthesis of evidence.

SN	Intervention	Study references	Study types	Synthesized outline
1	L-Arg in Duraphat®	*In vitro* studies -[18,23,24,27]; scoping review -[22]	*In vitro* studies (4) and a scoping review (1)	2% L-Arg in Duraphat® appears to be a promising caries preventive intervention with no appraised/non-appraised clinical data for conclusive recommendations.
2	L-Arg in MI varnish®	*In vitro* study -[26]	An *in vitro* study	10% L-Arg in MI varnish® significantly improves the remineralization properties of the varnish; however, the suggestive evidence is based on 1 *in vitro study*.
3	L-Arg with 10% nanohydroxyapatite (nano-HA)	*In vitro* study -[26]	An *in vitro* study	10% L-Arg with 10% nano-HA significantly improves the remineralization properties of nano-HA; however, the suggestive evidence is based on 1 *in vitro study*.
4	L-Arg in glass ionomer cement (GC Fuji II)	*In vitro* study -[25]	An *in vitro* study	4% L-Arg in commercially available GIC improves the material antimicrobial properties; however, the suggestive evidence is based on 1 *in vitro* study.

that Arg with F enhances the remineralization potential, antimicrobial effect, and EFU of F (alone) interventions under different experimental conditions [18,23,24,27,35]. Given the literature available over the past two decades, it appears that Arg with F exhibits multifold benefits for an enhanced caries preventive effect which is much needed in this era where around 40% of the global population is still affected with dental caries [1,2] . With the sustained availability of both Arg and F in the oral environment, the intervention can further reduce the caries-related burden of oral care, with the intention of achieving a 'prevention prevails' philosophy. Therefore, based on the limited literature and considering that this is still an inceptive intervention, there are opportunities for research on several aspects that are unrecognized as yet, to unfold additional benefits or mechanistic facts on the subject.

In this systematic scoping review, we identified only seven studies for final inclusion in the review process, thereby indicating a paucity of research on professionally deliverable Arg-F interventions. All papers included in the review were published in the past three years, ranging from 2020 to 2022, implying that such an intervention is novel and contemporary. Furthermore, the reported literature is region-specific, limited to Asia and with a majority of the studies from Hong Kong, suggesting that a research group from the region has conceptualized professionally deliverable Arg-F and thereby studied the intervention under different experimental conditions. Thus, a need arises for further appraisal of this subject, particularly for the intervention to be tested by other peri-regional research groups working in this research area to demonstrate their understanding. Although it is a distinct intervention with limited data to support the concept, the professionally deliverable Arg-F expresses a possibility of a much-needed superior caries

preventive agent that can extend an effect on cariogenic biofilms and demineralization-remineralization dynamics.

The concentrations of L-Arg (a primarily incorporated variant) used with different professionally-deliverable interventions ranged from 1% to 10% *by wt*. For Arg-F varnish, a 2% *w/v*. Arg appears to be a promising concentration to incorporate for an enhanced anti-caries effect. Thus, any subsequent exploration of Arg-F varnish must include the concentration for comparative analysis with previously published data. Also, with a closer analysis of the baseline experiments and characterization for understanding Arg-F varnish, it can be construed that, fundamentally, an initial exploratory phase can include estimating the varnish chemical properties including the F release, media pH changes, and molecular interaction which are based on a previous study [27] and relevant to the caries preventive effect. Subsequent studies can follow up by estimating the effect of the intervention on cariogenic biofilms and enamel with artificially induced incipient carious lesions.

The majority of studies included in this review explored the possibility of incorporating Arg in F-containing varnish, predominantly Duraphat®. The authors of these studies suggested that incorporating 2% Arg in Duraphat® enhances the caries preventive potential of the control. It appears that studies exploring Arg in Duraphat® were limited exclusively to a research group functional in an Asian region (Hong Kong), as mentioned previously with other reviewed professionally deliverable Arg-F interventions. While all studies included in this review were *in vitro* investigations, they were conducted under different experimental conditions seeking data on associated areas in caries development and progression. Comprehensively, these *in vitro* studies on Arg-F varnish examined the caries preventive potential based on F/Arg release, remineralization potential and a direct effect on a simulated cariogenic biofilm. Since an indirect effect assessment of the intervention was not within the scope of this paper, an article reporting such an element was excluded from this review exercise [36]. Nonetheless, the results of the included studies reveal that Arg-F varnish is a promising caries preventive intervention which is yet to be explored in preclinical (animal studies) and clinical (clinical trials) milieux for conclusive recommendations following appraisal.

As scoping reviews serve to synthesize evidence on niche areas of emerging science, the literature on the caries preventive potential of professionally deliverable Arg-F interventions was reviewed systematically and comprehensively. Subsequently, scoping reviews aid in determining whether a systematic review for literature appraisal and further meta-analysis is needed. Hereto, it can be considered to rule out the need for further systematic reviews and/or meta-analyses on this subject until published clinical data are available for scrutiny. Despite being comprehensive, the reported review has limitations pertaining to the articles/records screened in the English language, non-appraisal of the data due to the types of included articles, and the evidence reviewed being experimental *in vitro* investigations performed in environments with controlled variables. Another conceivable limitation could be a potential risk of bias in the articles that were included finally for the review; since one of the listed authors of these articles (MNB) was also a reviewer (MNB) in the present scoping review. However, the review process was primarily administered by two independent reviewers (NAA and TKN), which is a prerequisite for systematically conducted reviews, and therefore aids in reducing any potential risk of bias. Despite these few limitations, this review is sufficient to determine the future scope of research on Arg-F interventions and satisfies the objective of performing a systematic scoping review.

5. Future scope of research

Explicitly, the results of the present review highlight that amongst the professionally deliverable Arg-F interventions reviewed for their caries preventive potential, Arg in Duraphat®, has been reported substantially with *in vitro* studies. Duraphat® has long been used in clinical practice and trials in different countries. The Duraphat® varnish might not be available in certain places where other varnishes are available. Furthermore, Duraphat® is a colophony-based 5% NaF varnish which has triggered a Type I hypersensitivity reaction in the past and, thus, an alternative colophony-free F varnish is recommended for allergic patients. Hence, it is necessary to identify if Arg in other F-containing varnishes exhibits caries-preventive potential similar to that seen with Arg-enriched Duraphat®. Furthermore, it is imperative to identify if Arg incorporated in different F-containing varnishes will demonstrate an enhanced caries-preventive effect compared to the controls, as seen with Duraphat®-based Arg-F varnish.

6. Conclusion

Within the confines of this scoping review, it can be concluded that:

1. No clinical data are available to make conclusive recommendations on the caries preventive potential of professionally deliverable F-containing agents with incorporated Arg.
2. With Arg-F varnish being predominantly investigated through *in vitro* studies, the data so far suggest that Arg was incorporated exclusively in Duraphat®, while its caries-preventive potential in other F-containing varnishes remains unexplored.

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CRediT authorship contribution statement

Nouf Ali Alblooshi – Contributed to the conception, design, review process, data collection, performed critical analysis, and drafted the manuscript. **Tiba Kahtan Naseer** – Co-contributed to the review process, data collection, and critically revised the manuscript. **Mohammed Nadeem Bijle** – Co-contributed to the conception, funding acquisition, supervised the project, and critically revised all the drafts of the manuscript.

Conflict of interest

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

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jdsr.2024.05.002.

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