

Arginine in Preventive Dentistry: Mechanisms, Clinical Applications, and Future Perspectives

ANJORI RAUT¹, PUNIT RATNAKAR FULZELE², RIJUTA GUJAR³,
ISHANI RAHATE⁴, DHARUVI SOLANKI⁵, AMRUTA SURYAWANSHI⁶



ABSTRACT

Arginine, becoming a promising biomimetic agent in preventive dentistry, is uniquely positioned to modulate plaque biochemistry and enhance resilience on tooth surfaces. Extensive in-vitro, in situ, and clinical evidence demonstrates that arginine can elevate plaque pH, influence microbial ecology, and promote remineralisation, thereby allowing it to distinguish between active, caries prone biofilms and healthier plaque environments. Research across enamel, dentin, and root surfaces indicates that arginine-fluoride formulations enhance mineral gain, strengthen enamel structure, and slow lesion progression. At the same time, clinical trials consistently report meaningful reductions in dentin hypersensitivity due to rapid tubule occlusion. Beyond biochemical mechanisms, arginine promotes favourable shifts in oral microbiota via enhancement of arginine deiminase activity and suppression of acidogenic species such as *Streptococcus mutans* (*S. mutans*). Continuing developments in formulation chemistry and the incorporation of calcium rich carriers continue to expand its potential as a therapeutic ingredient in both dentifrices and professional care products. In the present review, arginine has been considered a valued adjunct to modern preventive dentistry, with established benefits in caries control, remineralisation, and the management of hypersensitivity. Nonetheless, further long-term large-scale clinical research needs to be conducted with a view to establishing standardised concentrations, optimally delivering systems, and validating completely its role alongside conventional fluoride-based strategies.

Keywords: Caries, Ecology, Oral biofilm, pH homeostasis, Synergistic effects

INTRODUCTION

More than 700 different types of bacteria that form intricate biofilms are found in the oral cavity. In addition to being a major factor in the development of periodontal and dental caries, these biofilms can have an effect on general systemic health [1]. Dental caries is a chronic, complex condition characterised by the demineralisation of the calcified structures in the teeth [2]. The breakdown of fermentable carbohydrates by bacteria leads to the demineralisation of dental hard-tissues and the generation of acid, which causes dental caries [3]. The primary cause of dental caries is the generation of acid by bacteria that break down food sugars and carbohydrates at the interface between vulnerable tooth surfaces and residual dental plaque. The severity of caries is influenced not only by the duration of acid exposure but also by factors such as salivary function, individual behaviour, education level, and socioeconomic conditions [4]. It is widely recognised that agents containing fluoride remain the most effective option for promoting the remineralisation of early carious lesions [2]. Fluoride helps prevent cavities by acting directly on the tooth surface, where it repairs early carious lesions by facilitating the re-deposition of calcium and phosphate into demineralised hydroxyapatite [5]. The potential of arginine to reduce dental caries has recently drawn attention [6]. It supports the maintenance of healthy oral biofilms by regulating pH levels and influencing the composition of the oral microbial community [7]. Recent advances in the study of arginine and its formulations have highlighted the need to review and update the current scope of research in this area.

Burden of Dental Caries in India

Dental caries negatively impacts quality of life by causing difficulties in chewing, speaking, disrupting sleep, and affecting social engagement in individuals of all ages. India has a population of 1.21 billion, accounting for approximately 17.5% of the global population [8]. Globally, approximately 3.58 billion people are affected by oral diseases, with caries in permanent teeth being the

most common. Around 2.4 billion individuals experience permanent tooth caries, while caries in primary teeth affects about 486 million people [2]. Although 54.16% of people have dental caries, the prevalence varies significantly based on age, type of dentition, and geographic region. Among different age groups, prevalence was 62% in individuals over 18 years and 52% in those aged three to 18 years. The mixed dentition showed the highest prevalence at 58%, followed by primary dentition at 54% and the permanent dentition at 46%. Regionally, western India reported the highest prevalence at 72%, followed by eastern India (36%), Northern India, central India, and southern India [9]. The dentist-to-population ratio in India shows considerable variation across states, ranging from 1:1,000 to 1:20,000. Regions with a limited dental workforce face a higher likelihood of undiagnosed dental caries, which may partly explain the observed regional disparities in caries prevalence [8,10]. Given the high prevalence of dental diseases and limited resources, implementing affordable, biologically effective, and easily applicable preventive strategies is essential [11]. Arginine-based interventions could provide added benefits by enhancing and complementing existing fluoride-based preventive programs.

Arginine: Biological Role and Mechanism of Action

A semi-essential amino acid, arginine (Arg), is found in a variety of food sources and in saliva at micromolar amounts [7,12]. It is an essential substrate for the oral biofilms that cover the tooth surface to produce alkali [9].

Bacteria can accomplish the metabolism of arginine through two distinct pathways: The hydrolysis of urea into ammonia and Carbon Dioxide (CO₂) by ureases, and the metabolism of arginine and agmatine via deiminase systems {Arginine Deiminase System (ADS) and Agmatine Deiminase System (AgDS)}. While ureolysis and the ADS are primary routes for neutralising plaque acidity and promoting oral health, the AgDS is notably active in cariogenic species like *S.mutans*; as it helps these harmful bacteria survive acidic conditions. Additionally, Malolactic Fermentation (MLF) further

assists in acid resistance by converting malate to lactate and CO_2 , which helps drive ATP production. Together, these systems allow oral bacteria to manage environmental stress, though their specific roles vary between health-associated commensals and decay-causing organisms. The periods of alkalisation that occurs after phases of demineralisation promote remineralisation and restore the enamel integrity [Table/Fig-1] [9].

Pathway	Primary enzyme	Main product	Clinical result
ADS	Arginine deiminase	Ammonia (NH_3)	Alkalinisation: Neutralises the external environment, protecting enamel.
AgDS	Agmatine deiminase	ATP+Internal NH_3	Survival: Helps <i>S. mutans</i> survive the acid it creates, making the biofilm more "cariogenic."
Ureolysis	Urease	Ammonia+ CO_2	pH Recovery: Rapidly raises plaque pH after sugar consumption.
MLF	Malolactic enzyme	Lactate+ CO_2	Bioenergetics: Provides energy (ATP) for bacteria to pump out protons during acid stress.

[Table/Fig-1]: Metabolic pathways in oral bacteria and their clinical significance.
MLF: Malolactic fermentation

Maintenance of Plaque pH Homeostasis

Arginine plays a key role in supporting healthy oral biofilms, thereby contributing to the prevention of dental caries [13]. When fermentable carbohydrates come into contact with dental plaque, the pH level decreases rapidly before gradually returning to normal levels. Processes such as salivary clearance and alkali production play a crucial role in this pH recovery. In the ADS, ammonia generated by bacterial metabolism is protonated by acids to form ammonium ions, increasing the pH of the surrounding environment and the cytoplasm. At pH values below 7.0, over 99.4% of ammonia molecules are converted to ammonium [6]. The pH homeostasis of dental plaque is disrupted by the selective growth of acidogenic and acid-tolerant bacteria, which is encouraged by persistent acidification of oral biofilms [14]. Ammonia-mediated neutralisation of glycolytic acids maintains a balanced demineralisation-remineralisation process on the tooth surface [6].

Within the biofilm, arginine is efficiently taken up and metabolised by microbial cells, enhancing pH homeostasis and modulating the microbial ecology, thereby highlighting its potential as an effective anti-caries agent [15].

Modulation of Oral Biofilm Ecology

The amino acid arginine can influence both the pH and microbial composition of oral biofilms [16]. An alkaline environment is created in dental plaque by arginolytic bacteria's breakdown of arginine, which hinders the growth of bacteria. Additionally, arginine may disrupt Coaggregation of cells in plaque biofilms, thereby reducing biofilm biomass and inhibiting synergistic pathogenic interactions that arise from direct physical contact between different bacterial species [6]. Synergistic interaction with fluoride Fluoride is a well-established anticaries agent with dual action on both tooth mineral and oral microbes. It inhibits bacterial activity by acting as a glycolytic enzyme inhibitor and a transmembrane proton carrier, leading to cytoplasmic acidification [17].

L-arginine monohydrochloride, when combined with a Sodium Fluoride (NaF) solution, has been shown to inhibit *S. mutans* in cariogenic biofilms significantly [17]. It has also been suggested that this arginine variant may interact with NaF to form sodium chloride [3]. Arginine may enhance fluoride uptake in demineralised enamel lesions through its terminal guanidinium group, which attracts electronegative ions such as fluoride, facilitating the formation of an Arg-F complex. This complex acts as a stable and bioavailable source of fluoride [13].

Arginine and fluoride work in tandem to influence the pathogenicity and bacterial composition of dental biofilms, surpassing the impact of arginine alone [1,2].

Clinical Evidence on Arginine in Dentistry

Role in caries prevention and remineralisation: Arginine has several applications in caries management, particularly in prevention, involving the potential use of ADS+ bacteria as probiotics, its function as a prebiotic, and its integration into dental care products. Numerous oral products containing arginine have been released. The most popular and thoroughly researched of these are arginine-containing dentifrices with a calcium based abrasive mechanism, where arginine serves as the primary active ingredient or in combination with fluoride. 1.5% arginine with a calcium-based abrasive and fluoride is well-supported by multi-year clinical trials and *insitu* studies [5,18,19]. Research by Kraivaphan P et al., and Li X et al., consistently demonstrates that this formulation provides superior caries protection compared to standard fluoride-only toothpastes, resulting in a significant reduction in Decayed, Missing, and Filled Surfaces (DMFS) increments up to 21%- over a 2-year period [18,19]. This superiority is attributed to the synergistic interaction between arginine and the calcium carbonate base, which creates a mineral reservoir that enhances fluoride uptake and promotes superior remineralisation of both enamel and root dentin [5,20]. Furthermore, higher concentrations (8%) of this technology have proven effective for the immediate management of dentine hypersensitivity by physically occluding exposed dentinal tubules [21]. Other forms include mouthrinses and varnishes, which have demonstrated anticaries effects comparable to those of arginine-containing dentifrices [6].

Root caries and adult populations: Root caries is becoming increasingly common in older adults, driven by gingival recession, decreased salivary flow, and greater accumulation of dental plaque. Randomised controlled trials by Souza MLR et al., concluded that a dentifrice containing 1.5% arginine is significantly more effective than fluoride alone in arresting and reversing active root-caries lesions in adults [5].

Hu DY et al., (2013) showed that the arginine-containing dentifrice was significantly more effective at arresting and reversing root caries than the control dentifrices. These improved outcomes are linked to increased plaque alkalinity and a reduction in demineralisation of exposed root dentin surfaces [22].

Dentin hypersensitivity: The Dentin Hypersensitivity arginine has been widely investigated for managing dentin hypersensitivity. Comprehensive care may also involve effective plaque control, dietary modifications, and strategies to enhance salivary flow, improve buffering capacity, and increase salivary pH to achieve sustained relief [23].

In a double-blind trial, Schiff T et al., showed that a single application of an in-office desensitising paste consisting of 8% arginine+calcium carbonate significantly reduces dentin hypersensitivity after 28 days [21]. A summary of the impact of arginine on oral health is illustrated in [Table/Fig-2].

Summary of clinical outcomes: The reviewed clinical studies consistently demonstrate beneficial effects of arginine-containing dental products in terms of caries prevention, lesion arrest, and reduction of dentin hypersensitivity. These outcomes are attributed to the combined impact of plaque pH modulation, biofilm alteration, and synergistic interaction with fluoride as reported in the referenced clinical trials [Table/Fig-3] [2,3,5,7,11,18-20,24-27].

Clinical Implications

As a caries-preventive agent, arginine is becoming more well-acknowledged. This naturally occurring amino acid, found in

S. No.	Mechanism	Biological/chemical process	Key effects in oral environment	Clinical significance
1	Arginine Deiminase System (ADS) Activation	Arginine→Citrulline+Ammonia (NH ₃) via ADS enzymes (arcA, arcB, arcC, arcD)	Increases plaque pH by neutralising acids; raises ammonia levels	Reduces acidic challenges after sugar intake; suppresses demineralisation; protects enamel from caries
2	Ammonia-Driven pH homeostasis	Ammonia produced is protonated to ammonium (NH ₄ ⁺), buffering plaque acids	Rapid increase in plaque pH after sucrose challenge	Less enamel demineralisation; favourable environment for remineralisation
3	Modulation of oral microbiome	Promotes growth of ADS-positive commensals (<i>S. sanguinis</i> , <i>S. gordonii</i>) while reducing aciduric species (<i>S. mutans</i>)	Shifts biofilm from cariogenic→health-associated	Lowers caries risk by reducing pathogenic biofilm composition
4	Inhibition of <i>S. mutans</i> virulence	Downregulation of virulence genes (gtfB, spaP, comX, nlmA/B/D)	Reduced Extracellular Polysaccharide (EPS) formation and decreased biofilm mass	Weakens cariogenic potential; decreases plaque stickiness and acid production
5	Disruption of Co- aggregation and biofilm maturation	Arginine inhibits <i>Fusobacterium nucleatum</i> adhesins (RadD)	Prevents bridging of early-late colonisers; reduces biofilm structural integrity	Thinner, less mature plaque which is less cariogenic
6	Enhanced fluoride uptake	Arginine+fluoride→improved fluoride incorporation into enamel	Increases formation of fluorapatite	Stronger enamel, higher resistance to acid attacks
7	Synergistic interaction with calcium/phosphate	Forms calcium-rich complexes (calcium carbonate, dicalcium phosphate)	Faster enamel mineral deposition	Promotes remineralisation of early carious lesions
8	Prebiotic action	Selectively enhances beneficial bacteria that metabolise arginine	Healthier microbial balance; increased ADS activity	Long-term ecological stabilisation against caries
9	Tubule occlusion in dentin hypersensitivity	Arginine forms plugs with calcium carbonate inside dentinal tubules	Blocks fluid flow through tubules	Immediate+long-term reduction in dentin hypersensitivity
10	Reduction of biofilm EPS matrix	Arginine reduces insoluble glucans via gtfB inhibition	Less sticky plaque; reduced bacterial adhesion	Lowers cariogenic potential and biofilm load

[Table/Fig-2]: Arginine mechanisms and their impact on oral health.

Author and year	Place of study	Study design/ Sample	Intervention/Groups	Parameters assessed	Key findings	Conclusion
Bijle MN et al., (2020) [7]	The University of Hong Kong	In-vitro; 6 varnish formulations	NaF varnish+2%, 4%, 8% arginine vs NaF alone	Varnish physical and chemical characterisation, Mean fluoride release profiles of tested varnishes, Mean arginine release	2% Arg-NaF showed best long-term fluoride release and strongest retention	2% arginine improves NaF varnish performance
Nascimento MM (2019) [24]	University of Florida (UF) in Gainesville, Florida, USA	Clinical; 83 adults	1.5% arginine toothpaste vs 1100 ppm fluoride	Plaque ADS activity Plaque acidogenicity Bacterial community profiles and global metabolomics	Arginine increased ADS activity and plaque pH; distinct metabolic profiles	Arginine modifies plaque metabolism differently from fluoride
Carda-Diéguez M et al., (2022) [11]	King's College London, London, UK	Metagenomic+ metatranscriptomic	Fluoride vs Fluoride+Arginine dentifrice	Taxonomic composition, genetic potential, and functional activity of the oral microbiota	Fl+Arg decreased caries-associated organisms and increased ADS gene expression	Arg enhances microbiome stability and anti-caries function
Bijle MNA et al., (2018) [3]	The University of Hong Kong, Hong Kong SAR, China, Sir John Walsh Research Institute, University of Otago, Dunedin, New Zealand	In-vitro; 50 enamel specimens	2%, 4%, 8% Arg-NaF vs NaF vs water	pH measurement, fluoride estimation, Na-Cl element analysis, Mineral density, Ca/P ratio and surface fluorine concentration were determined and Enamel Fluoride Uptake (EFU)	2% Arg-NaF had highest remineralisation and fluoride uptake	2% arginine optimises enamel remineralisation
Konagala RK et al., (2020) [2]	People's College of Dental Sciences and Research Centre	In-vitro; 100 extracted teeth	Arg, Fluoride varnish, nHAP, Arg+F, Arg+nHAP	Microhardness, Surface morphology, Elemental composition and Calcium-to-Phosphorus (Ca:P) ratio	Arg+F and Arg+nHAP groups showed maximum mineral gain	Arginine shows synergistic effect with F and nHAP
Cheng X et al., (2015) [25]	Colgate-Palmolive Technology Center in Piscataway, New Jersey, USA	In-vitro; 6 treatment groups	DI water, Arg, NaF, Arg+NaF, F-TP, Arg-F TP	Surface microhardness, cross-sectional microhardness, Enamel Fluoride Uptake (EFU)	Arg+NaF increased fluoride uptake significantly	Arginine enhances fluoride incorporation
Li X et al., (2015) [19]	Primary schools in Sichuan Province, China	2-yr double-blind RCT; 5500 children	1.5% Arg+MFP+Ca vs NaF	DMFT and DMFS	20.5% reduction vs fluoride alone	Arg dentifrice showed superior caries reduction
Petersen PE et al., (2015) [26]	Southern Thailand	School-based intervention; 3706 children	1.5% Arg+F toothpaste	DMFT and DMFS increments ("enamel and dentine")	Cooperative schools saw up to 41% reduction in DMFS	School programs with Arg dentifrice highly effective
Kraivaphan P (2013) [18]	Bangkok, Thailand	2-yr RCT; 6000 children	1.5% Arg+Ca+F vs F	DMFT and DMFS	16-21% lower increments vs F	Arg provides superior caries protection
Acevedo AM et al., (2008) [27]	Central University of Venezuela	1-yr clinical; 200 children	Arginine bicarbonate-CaCO ₂ mint vs placebo	DMFS, defs, and DMFS+defs	50-76% fewer caries in Arg group	Arginine-Arg group based mints significantly inhibit caries progression

Cantore R et al., (2013) [20]	USA and UK (Colgate-Palmolive Technology Center, NJ, USA and University of Manchester, UK)	3 in-situ studies	Arg+Ca+F dentifrices	Percent Mineral Change (%MC), Surface Microhardness (SMH) Ammonia Production, Lactic acid levels	Significantly improved remin/de-min balance	Arginine enhances remineralisation and pH regulation
Souza MLR et al., (2013) [5]	Rome, Italy (Sapienza University of Rome)	6-mo RCT; 284 adults	1.5% Arg+F vs F	Lesion hardness clinical texture, colour/pigmentation	70.5% vs 58.1% lesion hardening	Arg beneficial in root caries

[Table/Fig-3]: Experimental evidence [2,3,5,7,11,18-20,24,25-27].

dietary proteins and saliva, is metabolised by arginolytic bacteria to produce ammonia, which raises the pH within the oral biofilm and counteracts the acidic environment that favours the growth of aciduric bacteria [28]. Adding arginine to oral products containing fluoride can boost their remineralisation effect. Remineralisation is a conservative strategy aimed at replenishing minerals in teeth to prevent decay. In this way, arginine supports enamel health by promoting tooth remineralisation [9]. The primary challenge is heterogeneity of formulations which limit direct comparisons between studies. There is considerable heterogeneity in arginine formulations across studies. Arginine has been combined with different remineralising agents, including calcium carbonate, dicalcium phosphate, nanohydroxyapatite, and various fluoride compounds. Fluoride concentration and type also vary (commonly 1450 ppm, but sometimes lower; sodium fluoride or sodium monofluorophosphate). Because these agents differ in their properties and mechanisms, it is difficult to determine whether clinical outcomes are due to arginine alone or its combined effect with specific adjunct components. Also depending on the delivery type - sugarless mints (CaviStat), toothpaste, varnish- affects the substantivity. Varnish provides long-term contact, whereas a mint or toothpaste relies on a transient “burst” of concentration. While many commercial toothpaste have 1.5% arginine concentration for caries prevention and 8% for sensitivity, the true “optimal” dose is still a subject of debate for several reasons.

Limitation(s)

Prolonged use of arginine may lead to excessive alkalinisation of plaque and the overgrowth of oral anaerobes, including *Porphyromonas gingivalis*, a key pathogen associated to periodontitis [29]. Long-term safety, optimal concentrations, and independent multicentric trials especially in developing countries are required. Future research should also explore personalised approaches based on individual microbial profiles and arginolytic capacity.

CONCLUSION(S)

By addressing the disease’s metabolic and ecological causes, arginine represents a significant breakthrough in the prevention of dental caries. Arginine-based formulations offer a biologically sound and clinically useful addition to conventional caries prevention strategies by increasing alkali production, stabilising plaque pH, and amplifying fluoride’s effects. The future of preventive dentistry may be shaped, and the worldwide burden of dental caries may be lessened by incorporating these formulations into regular oral care.

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PARTICULARS OF CONTRIBUTORS:

1. Postgraduate Student, Department of Paediatric and Preventive Dentistry, Datta Meghe Institute of Higher Education and Research, Wardha, Maharashtra, India.
2. Professor, Department of Paediatric and Preventive Dentistry, Datta Meghe Institute of Higher Education and Research, Wardha, Maharashtra, India.
3. Postgraduate Student, Department of Paediatric and Preventive Dentistry, Datta Meghe Institute of Higher Education and Research, Wardha, Maharashtra, India.
4. Postgraduate Student, Department of Paediatric and Preventive Dentistry, Datta Meghe Institute of Higher Education and Research, Wardha, Maharashtra, India.
5. Senior Resident, Department of Paediatric and Preventive Dentistry, Datta Meghe Institute of Higher Education and Research, Wardha, Maharashtra, India.
6. Postgraduate Student, Department of Paediatric and Preventive Dentistry, Datta Meghe Institute of Higher Education and Research, Wardha, Maharashtra, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:

Anjori Raut,
Postgraduate Student, Department of Paediatric and Preventive Dentistry,
Sharad Pawar Dental College and Hospital, Wardha, Maharashtra, India.
E-mail: anjorir@gmail.com

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