# Enamel remineralisation-inducing materials for caries prevention

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Review article

# Enamel remineralisation-inducing materials for caries prevention

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## ABSTRACT

***Background:*** *Dental caries is a multifactorial disease indicated by the progressive demineralisation process of dental tissue. It is caused by an imbalance between the remineralisation and demineralisation processes. The focus of caries management is on prevention. Providing materials that can induce remineralisation is one management of caries prevention. Various materials have been or are being researched, such as casein phosphopeptide amorphous calcium phosphate (CPP–ACP), tricalcium phosphate (fTCP), bioactive glass (BAG), and nanotechnologies such as nano-hydroxyapatite (n-HAP) and silver nano fluorine (NSF).* ***Purpose:*** *This study aims to review the development of enamel remineralisation inducing materials as a newer approach in caries prevention.* ***Review:*** *Various ingredients have been shown to increase enamel remineralisation through different mechanisms in preventing the development of carious lesions.* ***Conclusion:*** *CPP–ACP, fTCP, BAG, n-HAP, and NSF can induce enamel remineralisation as caries prevention agents. n-HAP and NSF are the most effective agents to enhance enamel remineralisation to prevent caries.*

***Keywords:*** *caries; enamel; fluoride; remineralisation; BAG; CPP–ACP; n-HAP; NSF; TCP*

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## INTRODUCTION

Caries is considered one of the most common dental and oral health problems globally, including in Indonesia. Based on National Basic Health Research (2018), the prevalence of dental and oral health problems in Indonesia is 57.6%, while the prevalence of dental caries reaches 88.8%.[1] Dental caries is a disease with a multifactorial aetiology. Caries is caused by the imbalance of the remineralisation and demineralisation processes. It is influenced by pathological factors such as microbes, a carbohydrate diet, poor oral hygiene and time, as well as protective factors such as antimicrobial agents, hosts, saliva and minerals in particular fluor, calcium and phosphate.[2]

Based on the International Caries Classification and Management System (ICCMS), caries management is based on the level of progress. Preventive measures are the most important ways to maintain tooth structure, while restoration and recovery from damage are secondary treatments in dental practice.[3] Preventive dental treatment will inhibit tooth decay and maintain tooth vitality, one of which is through the principle of remineralisation.

The most common therapy for dental remineralisation is fluorine therapy, which is the gold standard in increasing remineralisation.[4] The remineralisation ability of fluor relies on mineral ions such as phosphate and calcium found in the oral cavity. Physiologically, these ions can be found in saliva, but the amount of phosphate and calcium in the saliva is limited; thus, an extrinsic source is needed. Although various studies on alternative materials to improve enamel remineralisation have been carried out, more need to be done to optimise treatment. Materials that can be used include casein phosphopeptide amorphous calcium phosphate (CPP–ACP), tricalcium phosphate (fTCP), bioactive glass (BAG), and most recently, nanoparticles. Nano-hydroxyapatite (n-HAP) is a nanoparticle ranging in size from 50–1000 nano that is biocompatible with good affinity to the enamel surface.[5]

Differing from conventional restorative approaches, consensus currently states that caries must be detected and



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monitored in the earliest stage when non-invasive methods can still be used, and the development of caries can be prevented. The purpose of this paper is to review enamel remineralisation inducing materials as a newer approach in caries prevention.

## REVIEW

Caries is the destruction of the hard dental tissue due to the fermentation of food carbohydrates, especially sucrose, by acidic bacteria. Caries is a multifactorial disease with three main factors: microorganisms, diet and host, with time as an additional factor.[2] Caries occurs when there is an imbalance in the remineralisation and demineralisation processes in the oral cavity. Remineralisation happens when calcium and phosphate ions in the oral cavity are deposited into enamel crystals.

The fluor ion binds with calcium and phosphate ions, forming a fluorapatite unit [$Ca_{10}(PO_4)_6F_2$]. Fluorapatite then will replace the dissolved enamel hydroxyapatite structure. Fluorapatite is more acid resistant, insoluble and stronger than hydroxyapatite.[6] Fluor antimicrobial properties can inhibit plaque formation on teeth.[7]

Various calcium-phosphate-based remineralisation technologies have been used and are continually being developed. This technology can improve remineralisation, especially when used in conjunction with fluorine and include CPP–ACP, fTCP, BAG, and n-HAP. These materials provide exogenous minerals such as calcium and phosphate ions for the oral cavity. Both CPP–ACP and fTCP contain calcium and phosphate ions that are needed in the formation of fluoroapatite.[8] BAG releases calcium, phosphate, sodium and silica ions, which helps enamel remineralisation.[9] The material n-HAP utilises nanoparticles with morphology and properties that resemble original enamel crystals and can improve enamel integrity.[5]

Another technology developed in the remineralisation approach is biomimetic material. It is developed by adapting the original structure of a tissue, which in this case is enamel. The biomimetic material used to increase remineralisation is amelogenin. Amelogenin is one of the enamel matrix proteins that controls the growth and formation of enamel crystals and helps mineral deposition in them.[10]

## DISCUSSION

Fluor affects the chemical and physical properties of apatite minerals by increasing the hardness and stability of enamel and maintaining the apatite structure. Fluor can be added through various sources such as toothpaste, varnish, mouthwash, water fluoridation or supplements.[11] Fluor compounds commonly used in dentistry include sodium fluoride (NaF), stannous fluoride and silver diamine fluoride.[7] The use of fluor in various dosages and concentrations has been shown to increase enamel remineralisation. However, the anti-caries properties of fluor depend on the availability of phosphate and calcium ions in the oral cavity. The lack of availability of these ions can be a barrier to remineralisation after fluor application. A strategy to improve the anti-caries properties of fluor is therefore needed.[4,11]

CPP–ACP is a material that interferes with the progression of carious lesions by increasing enamel remineralisation. CPP stabilises ACP by binding calcium and phosphate ions to form nanoclusters with ACP. It is used to maintain a supersaturation state of calcium and phosphate around the enamel to prevent demineralisation and increase remineralisation.[12]

In vitro studies have shown that topical application of CPP–ACP can improve enamel microhardness and reduce lesion depth better than fluor.[13,14] However, CPP–ACP has the disadvantage of having low solubility in acidic conditions, and this causes a decrease in its ability to retain calcium and phosphate ions.[15] Combining fluor with CPP–ACP to form CPP–ACPF can increase its ability to enhance remineralisation. During in vitro studies, CPP–ACPF increased enamel microhardness and reduced the depth and area of the lesion.[4,16] This increase in remineralisation can be caused by the presence of calcium, phosphate and fluoride ions that will easily form fluorapatite on the enamel surface layer.[17] Attiguppe et al.[12] reported that CPP–ACPF varnish (MI Varnish) showed superior effects compared to conventional fluor varnish. Clinical studies have shown that patients who get fluor varnish, CPP–ACP and CPP–ACPF can inhibit the development of white spot lesions (WSL), which are the initial lesions of caries. Both CPP–ACP and CPP–ACPF can regress WSL, with the CPP–ACPF group showing the greatest percentage of regression.[18]

Tricalcium phosphate in beta form that is then modified to functionalised TCP (fTCP), is another material that provides calcium-phosphate ions, which can then be administered with fluor.[19] In vitro studies measuring the depth of a lesion using a polarised light microscope show that dentifrice containing fluorine fTCP can improve enamel remineralisation better than dentifrice containing fluor alone.[20,21] Dentifrice containing a combination of NaF and fTCP showed better enamel surface microhardness than dentifrice with twice the fluor content.[21] Combining fTCP with fluor reduces the required fluor concentration. Incorporating fTCP in fluor varnishes increases enamel microhardness and reduces the incidence of lesions better than fluor varnish alone in both in vitro and clinical studies.[21] Although NaF varnish is considered sufficient to protect tooth enamel from caries, the addition of fTCP in the varnish should be considered.

BAG is a synthetic material containing ions needed for the remineralisation of enamels such as calcium, phosphate, sodium and silica. These ions will be released by BAG when it comes into contact with saliva, and they will directly form a calcium-phosphate layer such as hydroxyapatite on the surface of the enamel and will continuously release mineral

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ions.[22] Based on the results of an in vitro study carried out by looking at the surface microhardness of enamel, BAG has a better ability to increase enamel resistance to caries development compared to fluor.[23]

Compared with CPP–ACP, BAG showed a better effect on increasing remineralisation. The two ingredients have a similar effect, and they can both increase remineralisation and prevent enamel demineralisation in the initial carious lesion.[24,25] However, regarding the enamel microhardness, compared to TCP, BAG has a better remineralisation effect than TCP.[26]

The most recent remineralisation treatment is nanotechnology that utilises materials with sizes between 1–100 nm. Nano-hydroxyapatite (n-HAP) has a similar structure and morphology to dental apatite crystals, so it has a good affinity with enamel by forming ionic interactions with it. n-HAP acts as a provider of calcium and phosphate ions and maintains the supersaturation of these ions in the oral cavity. The nanoscopic particle size of n-HAP allows it to fill in the tiny holes that form when a tooth is demineralised. n-HAP will continue to bind calcium and phosphate ions, thereby increasing crystal integrity and growth.[27,28]

In vitro studies have shown that n-HAP has a better remineralisation enhancement effect when compared to fluor. It showed good mineral content as well as increased enamel surface microhardness, and it forms a mineral-rich layer on the enamel surface so that the lost enamel structure can be restored.[29,30] The use of n-HAP in combination with fluor exhibits a superior effect.[31]

The material n-HAP also showed better remineralisation effects compared to other materials such as CPP–ACP, fTCP, and BAG.[32,33] A clinical trial proved that n-HAP, fTCP and fluor varnish exhibited significant remineralising effects on early caries with n-HAP use having the best effect.[34]

Another nanotechnology is nanosilver fluorine (NSF), which contains silver nanoparticles, chitosan and fluor. Dentifrice containing NSF has a bacteriostatic effect and exhibits a remineralising effect like NaF. The use of NSF for enamel remineralisation can improve the performance of fluorides by the antimicrobial action of silver nanoparticles added to this compound.[35,36]

Biomimetic material is a new development in remineralisation therapy. Amelogenin is the predominant protein in forming enamel, and it plays a role in modulating and controlling the growth of calcium hydroxide crystals in enamel.[37,38] Amelogenin is a biomimetic material that is used to induce remineralisation. It can bind calcium and phosphate ions, facilitate ion transport into the enamel, and form a mineral layer on the surface of the enamel to increase enamel remineralisation.[39] The use of amelogenin and fluor showed less mineral loss and lesion depth than fluor alone because amelogenin helps bind fluor, calcium and phosphate.[40] Studies on the comparison of the effectiveness of amelogenin biomimetic material with other remineralisation materials is still not widely done, so it cannot be concluded that amelogenin biomimetic material is the most superior technology.

CPP–ACP, fTCP, BAG, n-HAP and NSF are materials that can induce enamel remineralisation as caries prevention. Nanotechnologies such as n-HAP and NSF are the most effective ingredients to improve enamel remineralisation to prevent caries. Their nano-size enhances their ability to remineralise enamel because they can penetrate deeper and form a tighter bond. It is recommended to conduct further studies regarding the development of materials that can induce enamel remineralisation.

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PAGE 1

PAGE 2

PAGE 3

PAGE 4