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A COMPARATIVE EVALUATION OF REMINERALIZATION POTENTIAL OF A BIOMIMETIC SYSTEM BASED REMINERALIZING AGENT Vs FLUORIDE BASED REMINERALIZING AGENT ON ARTIFICIALLY INDUCED ENAMEL LESIONS – AN IN VITRO STUDY

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ABSTRACT

AIMOF THE STUDY

To compare the Remineralization potential of two different fluoride-based materials to a biomimetic based materials onartificially induced demineralized lesion by Vickers micro hardness test

MATERIAL AND METHOD

Hundred and eighty human permanents, matured and intact single rooted teeth were selected by direct clinical examination for the study. To simulate the first stages of subsurface enamel lesions, the samples were immersed in a demineralization solution for a duration of 72 hours. Each sample was cut in half lengthwise. Based on the remineralization agents utilized, the remaining half of each tooth sample was separated into four groups. There were fifteen samples in each group.

There mineralization was carried for 1week,2-week,3week separately

Group1–control and suspending the sample in artificial saliva7,14,21 days

Group 2 – GC tooth mousse plus. The tooth samples were suspended in artificial saliva for7,14,21days

Group3–Clinprotooth crème. The tooth samples were suspended in artificial saliva for7,14,21 days

Group4–Curodontprotect. The tooth samples were suspended in artificial saliva for7,14,21days.

Group 5- Pretreatment group (demineralized half of teeth).The micro hardness of samples was evaluated by Vickers micro hardness testing. One-WAY ANOVA test followed by Tukey's post hocanalysis was used for statistical analysis.

Result - Vickers micro hardness value shows that highest amount of remineralization has occurred in Curodont Protect followed by ClinproTooth Crème and GC tooth mousse plus.

Conclusion–

Curodont protect dentrifice showed highest remineralization potential. This is attributed to its innovative self-assembling peptide (P11-4) causing biomimetic type of enamel remineralization. Second highes tremineralization was seen in clinpro tooth crème due to its fluoride combination with functionalized tricalciumphosphate. This was followed by GC tooth mouseplus

KEYWORDS-Casein Phospho Peptide– Amorphous Calcium Phosphate Fluoride, functionalized Tricalcium Phosphate, Self – Assembling peptide, Surface Microhardness.

INTRODUCTION

Demineralization and cavitation are symptoms of dental caries, a disease that affects teeth in the contemporary day. This condition causes pain and discomfort, limits function, and compromises face attractiveness.[1]

The demineralization and remineralization phases of dental caries are irreversible and occur throughout the process of tooth mineral content disintegration. Catavitation occurs when the demineralization process is too heavy.[2]

Minerals are lost near the front of the lesion during demineralization. Ions of acid go from the plaque to the carious lesion and back again at a level below the enamel surface. Remineralization is a natural process that fixes the hydroxyapatite (HAP) crystal lattice by restoring missing minerals in ionic forms. When the pH levels in the body are close to neutral, new, bigger, and acid-resistant HAP crystals may develop within the caries lesion by redepositing mineral ions like calcium and phosphate from saliva and plaque fluid.[1]

Minimal Intervention Dentistry (MID) is a modern approach to dental care that aims to reduce invasiveness while keeping patients comfortable. Key to MID is remineralization of early carious lesions; the method places more emphasis on a therapeutic or biological approach than on conventional methods of treating lesions on the enamel surface at this stage. [3]

Remineralizing materials are applied to tooth structure (enamel and dentin lesions) as the key component of the biological method. A new age in dentistry has begun, made possible in large part by these materials, which govern the demineralization/remineralization cycle. [4]

Plaque/Salivary Calcium (Ca2+)andPhosphate (PO4 3–) ions are deposited as a natural repair process into crystal voids of the demineralized toothstructure, resulting in net mineral gain.
Ca2+ and PO4 3– ions are incorporated into the Crystal Lattice from the oralenvironment in the presence of free Fluoride (F–) ions, resulting in significantly more resistant fluorapatite mineral.[5]

Most commonly used calciumphosphate compounds for Remineralization are:

- **GC Tooth Mousse** containing 0.2% fluoride is available as CPP–ACPF paste. Clusters of amorphous calciumphosphate contains casein phosphopeptide aggregated with calcium phosphate.[5]

- **Tricalcium phosphate (*f* TCP)** commercially available as Clinpro Tooth Crème which is produced bysodium laurylsulfate and beta-tricalcium phosphate with the solid-state ballmilling process.[5]

Though various remineralizing agents are available, their efficacy is still a question. Hence anewbiomimeticmaterialwhichremineralizestheenamelwithmatrix-mediatedmineralizationlikethe natural process is introduced.[6]
ThisSelf-assemblingpeptide(SAP)P11-4containsshort-chainpeptideswhichhavetheproperty of assembling into a three-dimensional structure resembling the extracellular matrix,therebypromotingregeneration.It iscommerciallyavailable as CurodontProtect.

As there is little information available on remineralizing efficacy of SAPs compared with CPP– ACPF paste and Clinpro Tooth Crème, a study was aimedat assessing and comparing the surface structure and remineralizing efficacy of novel biomimetic SAP P11-4, with CPP-ACP, tricalcium phosphate on artificially induced enamel lesions.

MATERIALS AND METHOD

180 extracted non carious,intact and mature single rooted teeth were collected from the dept of oral & maxillofacial surgery of Raja Rajeswari Dental college, Bangalore.
The extracted teeth were washed with distilled water and ultrasonic scaling was performed. Vickers microhardness test is employed to check the baseline surface microhardness for all the samples.

FIG1-60 TEETHS AMPLEDIVIDED INTO 4GROUPS

DEMINERALIZATION

To simulate the early stages of subsurface enamel lesion, we immersed the tooth samples in a demineralization solution containing 20 ml for 72 hours. This created a carious lesion. A demineralizing solution is prepared by adding 50% NaOH to a solution containing 2.2 mM CaCl2, 2.2 mM NaH2PO4, 0.05 M lactic acid, 0.2 ppm fluoride, and a pH of 4.5. A subsurface demineralization of around 150 microns width with an undamaged surface mimicking an early enamel lesion was achieved by immersing the specimen in the demineralization solution for 72 hours at 37° C. The tooth samples are cut in half lengthwise. To expose the prepared enamel surface, the buccal and lingual halves of each tooth were set in cold cure acrylic resin. The Vickers microhardness test was used to measure the degree of demineralization for each half of the tooth sample.

FIG2-TEETH SAMPLE IN DEMINERALIZING SOLUTION

“REMINERALIZATION

Depending on remineralizing agents used, the other half of the tooth samples were divided into group consisting of 15 samples each.

The test was conducted for 7 days (1 week), 14 days (2 week), 21 days (3 week) separately

FIG 3- GC TOOTH MOUSE PLUS

FIG 4-CLINPROTOOTH CRÈME

FIG5- CURODONT PROTECT

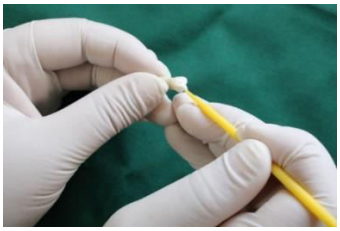


FIG 6 –APPLICATION OF REMINERALIZING AGENT

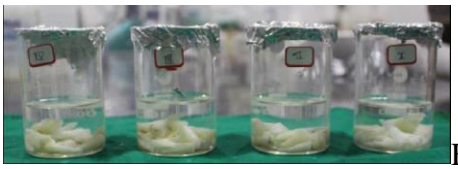


FIG 7-TEETHSAMPLEINREMINERALIZINGSOLUTION

FIG8– VICKERSMICROHARDNESSMACHINE

1 week test

Group 1a - (Control group) Tooth samples were suspended in the artificial saliva for 1 week.

Group 2a - Topical application of GC Tooth Mousse Plus and the samples were suspended in the artificial saliva for 1 week

Group 3a - Topical application of ClinproDentifrice and the samples were suspended in the artificial saliva for 1 week

Group 4a –Topical application of CurodontProtect and the samples were suspended in the artificial saliva for 1 week

Group 5a-Formed the Pretreatment group i.e the one halves of teeth from each group which are demineralized .Other halves of same teeth were subjected to remineralization. It consists of 15 samples randomly taken from the other four remineralizing group. This group were made in order to determine the demineralization value before subjecting it to

remineralization.It also helped in comparison of the degree of demineralization and remineralization that occurred after application of the remineralizing agent in the other groups.

2-week test

Group 1b - (Control group) Tooth samples were suspended in the artificial saliva for 2 weeks.

Group 2b - Topical application of GC Tooth Mousse Plus and the samples were suspended in the artificial saliva for 2 weeks

Group 3b - Topical application of Clinpro Dentifrice and the samples were suspended in the artificial saliva for 2 weeks

Group 4b – Topical application of Curodont Protect and the samples were suspended in the artificial saliva for 2 weeks.

Group 5b- Formed the Pretreatment Group i.e the one halves of teeth from each group which were demineralized .other halves of same teeth was subjected to remineralization. It consists of 15 samples randomly taken from the other four remineralizing group.

3-week test

Group 1c - (Control group) Tooth samples were suspended in the artificial saliva for 3 weeks

Group 2c - Topical application of GC Tooth Mousse Plus and the samples were suspended in the artificial saliva for 3 weeks

Group 3c - Topical application of Clinpro Dentifrice and the samples were suspended in the artificial saliva for 3 weeks

Group 4c– Topical application of Curodont Protect and the samples were suspended in the artificial saliva for 3 weeks

Group 5c- Formed the Pretreatment Group i.e the one halves of teeth from each group which were demineralized .other halves of same teeth was subjected to remineralization. It consists of 15 samples randomly taken from the other four remineralizing group.

Using Vickers hardness testing machine, the specimens were subjected to microhardness testing after each period of 7days, 14 days and 21 days.Five indentations were made for each specimen with a spacing of 100 microns with a load of 25g applied for 5 sec. Microhardness of the corresponding specimen were considered with their average value.

STATISTICAL ANALYSIS

Statistical analyses will be performed using Statistical Package for Social Sciences [SPSS] for Windows Version 22.0 Released 2013. Armonk, NY: IBM Corp.

Descriptive Statistics:

Descriptive analysis includes expression of micro hardness using mean and standard deviation in each study group.

Inferential Statistics

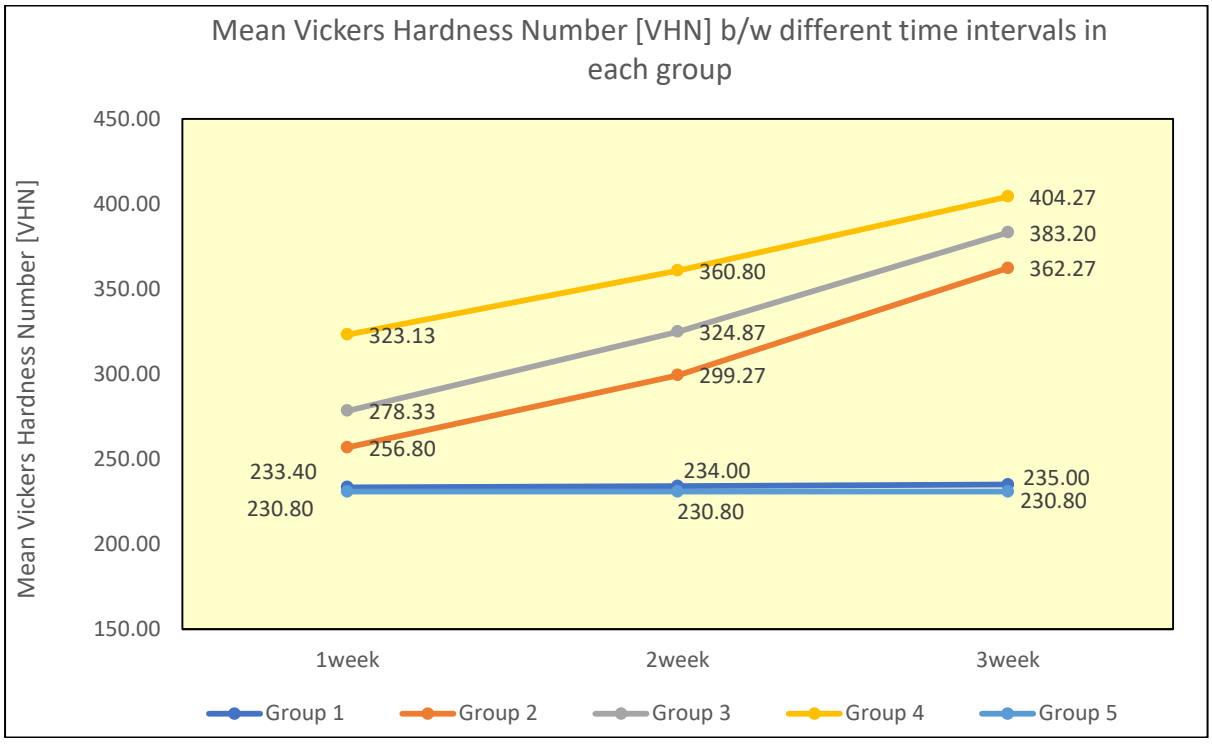
One-way ANOVA test followed by Tukey's HSD post hoc analysis will be used to compare the mean micro hardness scores between 04 study groups.

The level of significance will be set at $P<0.05$."

RESULTS

Comparison of mean Vickers Hardness Number b/w 3 time intervals in each group using One-way ANOVA test followed by Bonferroni's Post hoc Test

Groups	Time	N	Mean	SD	p-value [a]	Sig. Diff	p-value [b]
Group 1	1week	15	233.40	8.35	0.89	1w vs 2w	..
	2week	15	234.00	10.56		1w vs 3w	..
	3week	15	235.00	8.90		2w vs 3w	..
Group 2	1week	15	256.80	7.46	<0.001*	1w vs 2w	0.001*
	2week	15	299.27	31.88		1w vs 3w	<0.001*
	3week	15	362.27	16.47		2w vs 3w	<0.001*
Group 3	1week	15	278.33	9.74	<0.001*	1w vs 2w	<0.001*
	2week	15	324.87	20.62		1w vs 3w	<0.001*
	3week	15	383.20	11.07		2w vs 3w	<0.001*
Group 4	1week	15	323.13	18.97	<0.001*	1w vs 2w	<0.001*
	2week	15	360.80	15.78		1w vs 3w	<0.001*
	3week	15	404.27	24.56		2w vs 3w	<0.001*
Group 5	1week	15	230.80	4.11	1.00	1w vs 2w	..
	2week	15	230.80	4.11		1w vs 3w	..
	3week	15	230.80	4.11		2w vs 3w	..



"The mean Vickers Hardness Number in Group 2 at 1-week time interval was 256.80 ± 7.46, at 2-weeks' time interval was 299.27 ± 31.88 and at 3-weeks' time interval was 362.27 ± 16.47. This difference in the mean Vickers Hardness Number between different time intervals in Group 2 was statistically significant at p<0.001. Multiple comparison of mean difference b/w time intervals revealed that 3-weeks' time interval showed significantly highest mean Vickers Hardness Number as compared to 2-weeks' time interval & 1-week time interval at p<0.001. This was then followed next by 2-weeks' time interval showing significantly higher mean Vickers Hardness Number as compared to 1-week time interval at p=0.001.

The mean Vickers Hardness Number in Group 3 at 1-week time interval was 278.33 ± 9.74, at 2-weeks' time interval was 324.87 ± 20.62 and at 3-weeks' time interval was 383.20 ±

11.07. This difference in the mean Vickers Hardness Number between different time intervals in Group 3 was statistically significant at p<0.001. Multiple comparison of mean difference b/w time intervals revealed that 3-weeks' time interval showed significantly highest mean Vickers Hardness Number as compared to 2-weeks' time interval & 1-week time interval at p<0.001. This was then followed next by 2-weeks' time interval showing significantly higher mean Vickers Hardness Number as compared to 1-week time interval at p<0.001.
The mean Vickers Hardness Number in Group 4 at 1-week time interval was 323.13 ± 18.97, at 2-weeks' time interval was 360.80 ± 15.78 and at 3-weeks' time interval was 404.27 ± 24.56. This difference in the mean Vickers Hardness Number between different time intervals in Group 4 was statistically significant at p<0.001. Multiple comparison of mean difference b/w time intervals revealed that 3-weeks' time interval showed significantly highest mean Vickers Hardness Number as compared to 2-weeks' time interval & 1-week time interval at p<0.001. This was then followed next by 2-weeks' time interval showing significantly higher mean Vickers Hardnes2s Number as compared to 1-week time interval at p<0.001.
The mean Vickers Hardness Number in Group 1 at 1-week time interval was 233.40 ± 8.35, at 2-weeks' time interval was 234.00 ± 10.56 and at 3-weeks' time interval was 235.00 ± 8.90. However, this difference in the mean Vickers Hardness Number between different time intervals in Group 2 was not statistically significant [p=0.89]
The mean Vickers Hardness Number in Group 5 at all the time intervals remained the same [230.80 ± 4.11] and there was no significant difference noted between different time intervals [p=1.00]."

DISCUSSION

As part of the mineralization process, inorganic material continuously deposits onto the organic matrix. The scaffolding for a highly structured arrangement of uniaxially arranged calcium phosphate crystals is provided by collagen in the hard connective tissues of the human body, which includes dentin. A better comprehension of the biological mechanism of mineral deposition is crucial for the creation of treatments for disorders associated with mineralization and for advancements in scaffold development.

When the pH rises over the threshold level, certain minerals precipitate out, a process known as remineralization occurs. When the pH drops below a certain threshold, demineralization takes place.[34]

In a clinical setting, an enamel lesion looks white when the enamel's natural translucency is removed. The surface of early enamel lesions seems intact, much like healthy enamel, but they really have a far lower microhardness value due to their very low mineral content.[34]

"In the present study the tooth samples were placed in 20ml of demineralization bath for 72 hours to create a carious lesion which represents preliminary stage of subsurface enamel lesion. Demineralizing solutions containing $CaCl_2$ = 2.2 mM NaH_2PO4 = 2.2 mM Lactic acid = 0.05 M, Fluoride = 0.2 ppm, is adjusted with 50% NaOH to a pH of 4.5. The samples will be placed in the demineralization solution for 72 hrs at 37° C to form subsurface demineralization of approximately 150 microns width with an intact surface simulating an early enamel lesion.Universal Incubator was used to mimic oral conditions, where the specimens were stored in the demineralizing solution at 37°C."

A variety of remineralizing materials can be utilized in improving the remineralizing process remains as best method of caries management.[34]

The effectiveness of milk products containing bioactive CPP-ACP in healing early enamel carious lesions has been shown in several in vitro and in vivo investigations. They restore the body's calcium and phosphate ion stores. In contrast to salivary calcium, the CPP-ACP complex aids in keeping phosphate and calcium at a supersaturated level. Holding the CPP-ACP complex close to the enamel lesion reduces demineralization and increases remineralization.[35]One of the materials with this technology is GC Tooth mousse plus.

GC Tooth Mousse plus

In this study G C Tooth Mousse plus was used to evaluate the remineralizing potential. It is a combination of 0.2% w/w (900 ppm) fluoride and milk-derived protein called RECALDENT.[36]

Clinpro tooth crème (3M ESPE)

Another remineralizing agent used in this study was Clinpro tooth crème (3M ESPE) Tricalcium phosphate (*f* TCP) commerciually available as Clinpro Tooth Crème."The solid-state ball milling technique with 0.21% NaF is used to make it, together with beta-tricalcium phosphate and sodium lauryl sulfate. With a neutral pH base that includes water, titanium dioxide, sorbitol, sodium lauryl sulfate, carboxymethyl cellulose, sodium saccharine, and tricalcium phosphate, Clinpro Crème has 0.95 mg of fluoride ion per gram. In addition, functionalized tricalcium phosphate and fluoride (950 ppm) are present. The system's stability in water and its inability to interfere with the fluoride activity of dentifrice are its main selling points. The effectiveness of the several remineralizing agents now on the market remains an open subject.[37]

A new class of bioactive materials has emerged that mimics biological structures in order to encourage biomimetic remineralization and induce mineral deposition in situ. One possibility for this strategy is the novel self-assembling peptide (P11-4). P11-4 mimics the function of the extracellular enamel matrix proteins present during tooth formation by self-assembling into three-dimensional fibrillar scaffolds under certain environmental circumstances. P11-4 mimics histogenesis by attracting, binding, and stabilizing calcium ions, which in turn causes hydroxyapatite production.

In situ dental tissue engineering is made possible by newer, smart dental biomaterials that modulate mineral behavior via this technique.[20].

One of the commercially available dentifrices is Curodont Protect.

Curodont™ Protect (Credentis AG, Dorfstrasse, Windisch, Switzerland)

This toothpaste contains the following ingredients: water, hydrated silica, cellulose gum, hydrogenated starch hydrolysate, sodium monofluorophosphate, aroma, sodium saccharin, citric acid, sodium hydroxide, dicalcium phosphate, oligopeptide-104, calcium glycophosphate, sodium chloride, sodium sulfate, limonene, cinnamon."[38]

This study set out to fill that knowledge gap by comparing the surface structure and remineralizing efficacy of two different SAPs—CPP-ACP, tricalcium phosphate, and a novel biomimetic SAP called P11-4—on artificially induced enamel lesions.

This research used a Universal Incubator set to 37°C to keep samples in a demineralizing solution, simulating circumstances in the mouth. In order to examine the surface layer alterations caused by caries development, the tooth samples were placed in artificial saliva, which mimics the circumstances found in the mouth.[39]

Since SMH evaluations are simple, rapid and straightforward to quantify nondestructively, it has been frequently employed for assessment of demineralization and remineralization

changes happening in enamel surface. When testing the microhardness of enamel, Vickers microhardness is the method to use.[40]

Prior to and during the remineralization procedure, the microhardness values of every specimen were recorded. Indenting a sample of teeth with a diamond indenter is the basis of the Vickers hardness test. The microhardness of the matching specimen is the mean value.[40]

In the present study remineralization of artificially created lesion on the enamel of extracted teeth were done using two fluoride baseddentifrice that is Gc tooth mouse plus,clinpro tooth crème and biomimetic based remineralization that is curodont protect for 7 days,14 days,21 days.

INTERGROUP RESULT ASSESSMENT

In this study the SMH values was higher in group 4 that is Curodont protect compared to group 3(Clinpro tooth crème) followed by group 2(GC tooth mousse) which was followed by group1(Control). least value was seen in group 5(Pretreatment)

INTRAGROUP RESULT ASSESSMENT

There was significant increase in SMH values between each intragroup of a particular dentrifice group.

In group 2

The SMH values was higher for group2c (3 week) followed by group 2b (2 week). least values were seen in group 2a (1 week).

In group3

The SMH values was higher for group 3c (3 week) followed by group 3b (2 week) and least values were seen in group 3a (1 week).

In group 4

The SMH values was higher for group 4c (3 week) followed by group 4b(2 week) and least values was seen in group 4a(1 week).

There was a statistically significant difference between group 4, group3, and group 2 in intergroup analysis and the same differences were noticed in sub groups.

Statistically significant difference was not found between control group1 and pretreatment group 5.

The Statistically significant difference in intra group comparisonis explained by the basic principle, that is remineralization process is a time dependent phenomenon. Increasing the duration of contact between tooth structure and remineralizing tooth paste, there is increase in remineralization.

Inter group comparison group 4 that is Curodont protect dentifrice showed highest remineralizing potential.The internal structure and mechanism are responsible for this.

SAP P11-4 initiates hydroxyapatite nucleation by forming three-dimensional fibrillar scaffolds in response to certain environmental conditions. A caries lesion's cations and high ionic strength cause it to spontaneously transform into an elastomeric 3D scaffold gel under certain circumstances, such as a low pH, where it forms a strong chemical interaction with the tooth surface. Similar to Odontogensis, these scaffold-like structures encourage subsurface remineralization and de novo hydroxyapatite precipitation, which in turn promotes enamel regeneration.[20]Second highest remineralizing potential was noted in group 3, This can be explained by its specialized mechanism of action.

Calcium, Phosphate, and Fluoride ions leach out when TCP comes in contact saliva. Initiation and enhancement of mineral growth takes place when these ions react with weakened enamel, delivering more Fluoride and Calcium to tooth tissue. Dentifrices or Mouthwashes containing functionalizing beta-TCP prevents premature fluoride-calcium interactions when applied to teeth with targeted low dose delivery.[41]

In comparison to Curodont and Clinpro tooth crème,remineralization was seen least in GC tooth mouse plus group(CPP-ACPF). This is explained by its mechanism of action. Acidic environmentis required for release of ACP, but it is washed away by the saliva even before the CPP-ACP complex is activated. This attributes for lower remineralizing potential of CPP-ACPF. [41]Functionalized Tricalcium Phosphate Paste (f-TCP) outperformed CPP-ACP with fluoride in terms of remineralization potential, according to a research.[42]

In contrast to fluoride and CPP-ACPF, biometic SAP P11-4 had the greatest remineralizing efficiency in an invitro research conducted on experimentally produced enamel defects.[20] They also found P_{11}-4 able to induce biomimetic regeneration of early caries lesions.[43]Another study on same materialwith fluoride varnish revealed that they both have the same remineralizing efficacy, as an alternative remineralizing agent to fluoride.[43]

CONCLUSION

It may be concluded that Curodont Protect Dentifrice had the best potential for remineralization within the constraints of this investigation. Its unique self-assembling peptide (P11-4) is responsible for a biomimetic kind of enamel remineralization, which is why it works so well. Due to its fluoride combination with functionalized tricalcium phosphate, Clinpro tooth crème exhibited the second-highest level of remineralization. Next on the agenda was GC teeth mouse plus. Conclusions drawn from this research indicate that, when compared to fluoride-based remineralizing agents, biomimetic-based remineralizing agents have the greatest remineralizing potential. Between the first and twenty-first days, the remineralization capacity increased in all of the dentrifice groups. Since remineralization is a process that depends on time, our research concludes that it is time dependent.

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