Conceptualization of Bioactive Materials in Dental Caries Prevention

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ABSTRACT

Clinicians always face a challenge in selecting the appropriate material for clinical use. Presently, the term bioactive is being used judiciously and unquestionably in the field of dental materials. The introduction of nanotechnology brought about a revolution in material science leading to the development of bioactive materials for caries prevention and management. This review comprehensively evaluates the use of bioactive materials for modification of the oral biome, prevention of dental caries, and the management of dental caries as restorative materials. Six online database (PubMed, Scopus, Science Direct, Embase, Web of Science, and Cochrane library) were systematically searched using broad keywords. Published articles were scrutinized, analyzed and the full-text articles were selected. Data reveals relatively limited application of tissue engineering and regeneration for enamel and dentin due to their limited ability to remodel. However, many steps are being taken in biomimetic approach for the modification of dentin. The path to overcoming any challenges will require active collaboration among clinicians, a material scientist and pulp biologist.

Keywords: Bioactive material, dental caries, demineralization, nanoparticles, remineralization, restorations. (Siriraj Med J 2021; 73: 614-632)

INTRODUCTION

Larry Hench first suggested the concept of a bioactive material in the late 1960s, when he discovered the ability of special glasses to bond to the bone substrate.[1] Subsequently, a bioactive material was defined as one that elicits a specific biological response at the interface of the material resulting in a bond formation between the tissues and material.[2] The resulting bioactivities include the stimulation of cell differentiation and proliferation, stimulation of gene and tissue regeneration, and release of bioactive molecules to respond actively and effectively restore and repair the impaired functions of the organs.[3]

Bioactive materials (second generation) efficiently control interactions with the surrounding biological environment and contribute to tissue regeneration. Biomimetic bioactive materials (third-generation) that mimic the natural bioactive behaviour have been designed to modulate a particular gene, activating the process of tissue regeneration (in tissues like bone cartilage, vascular tissue, and nerves) via cell adhesion, proliferation, and

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Received 5 April 2021 Revised 13 July 2021 Accepted 14 July 2021
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http://dx.doi.org/10.33192/Smj.2021.80

differentiation.[4] Tissue regeneration has replaced the concept of tissue replacement through either *in situ* regeneration or tissue engineering strategies.[4]

Bioactivity is the property of a biomaterial to form apatite-like materials on its surface when immersed in simulated body fluid for some time.[5] A wide range of bioactive substances is used for caries management, a global infectious disease, where each individual of different age groups has experienced/undergone preventive measures. Hence, for a better understanding of dental caries management, bioactive materials can be categorized as a) bioactive agents/materials used for altering the oral microbiota in caries-prone individuals, b) bioactive agents/materials for dental caries prevention, c) bioactive agents/materials as a restorative material for dental caries management.

MATERIALS AND METHODS

Literature search

The Extensive data was compiled using search engines of Pubmed, Scopus, Science Direct, Embase, Web of Science, and Cochrane library. The search included the review articles, In vitro studies, and clinical studies. The Key terms were bioactive materials, biomimetic materials, bioactivity, and biomineralization in prevention and managing dental caries. The present review has discussed the applications, concepts, and advance potential uses of bioactive components in the management of dental caries.

Papers selection and data extraction

Following the preliminary search, terms more specific to each category were included to reduce the number of articles retrieved. Selected titles and abstracts were examined (SG, AJ). Specific keyword searched was "effect of bioactive materials on the carious tooth structure". Any potential conflicts were resolved by mutual discussion and consensus between the authors. An independent reviewer (NM) was consulted to resolve the complex studies.

Inclusion criteria

Systematic reviews and literature reviews on bioactive agents.

Chapters on bioactive agents.

Laboratory studies.

Studies on bioactive agents having antimicrobial action on caries micro-organisms.

Studies on bioactive agents helps in prevention of dental caries.

Studies on bioactive agents used as a restorative material.

Exclusion criteria

Studies on Bioactive agents used in endodontic therapy.

Studies on periodontal diseases.

RESULTS & DISCUSSION

Categorization of the Bioactive materials.

A total of 2859 in posse articles up to March 2020 were identified through the database and considered (Fig 1) After removal of duplicates the selected articles were categorized based on (a) bioactive material that can alter the oral microbiome in caries risk individual, (b) prevention of dental caries and, (c) as a restorative material in carious tooth. Full text reading was carried for 146 articles and 72 articles met the eligibility criteria. Out of 72 publications, 23 articles for category (a), 42 articles for (b), and 8 articles for (c) were included for the final review.

The types of bioactive compounds currently used, and their general applications are shown in Tables 1 and 2.[6] The two basic concepts of creating bioactive elements are the top-down and bottom-up approaches. The top-down approach is based on existing well-accepted biomaterials, either bio-inert or bioactive, and the addition of bioactive elements to meet the clinical requirements, (Fig 2). The bottom-up approach involves the designing of a bioactive material at the molecular level to produce new bioactive materials (Fig 3). As shown in Table 2, bioactive materials have vast applications in medicine and dentistry.[7]

Pathogenesis of dental caries

The pellicle, comprising of glycoproteins, is formed immediately on the tooth after brushing. Acid-induced demineralization of the hard tissue occurs due to the decrease in salivary pH and microbial metabolism of carbohydrates. The aetiology of dental caries involves three microbial hypotheses: a. specific plaque hypothesis, which proposes that a few species of the total microflora, such as *Streptococcus mutans (S. mutans), Streptococcus sobrinus (S. sobrinus)*, and lactobacilli, are actively involved in the disease; b. nonspecific plaque hypothesis, which suggests that caries is the consequence of the overall interaction of all groups of bacteria within the plaque; and c. ecological plaque hypothesis, which indicates that caries is the result of an imbalance in the microflora due to ecological stress, resulting in an enrichment of certain disease-related microorganisms.[8,9] The common supragingival microbes in the oral cavity are listed in Table 3.[10]

In the presence of carbohydrate substrates, *S. mutans* generate three forms of glucosyltransferase (GtfB, GtfC,

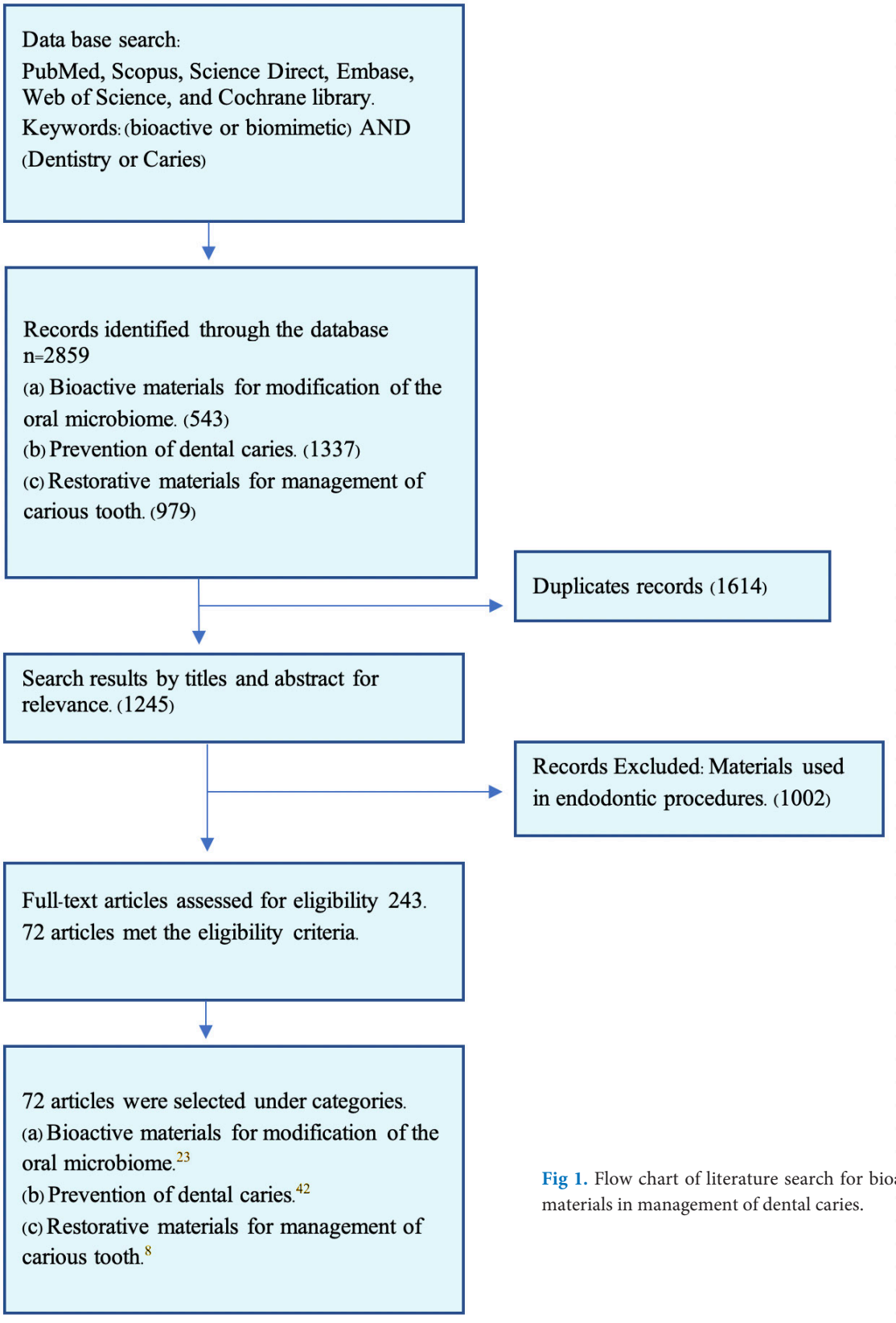

Fig 1. Flow chart of literature search for bioactive materials in management of dental caries.

and GtfD), which polymerize into α-1,3-and α-1,6-linked glucans. Attracting glucans via glucan-binding proteins (lectin-like molecules GbpA, GbpB, GbpC, and GbpD) and Gtfs promotes bacterial adherence, interbacterial adhesion, and biofilm formation on the tooth surface. GtfB, GtfC, and GtfD, and GbpA, GbpB, GbpC, and GbpD combined with their adhesive extracellular glucans, constitute the sucrose-dependent pathway by which the *S. mutans* is established on the tooth surface, leading to acid production and localized enamel decalcification.[11]

TABLE 1. Types of bioactive compounds (*Zhao X et.al., 2011*)

Class	Application
Enzymes	Electrochemical Biosensors, active packaging, formation of extracellular matrix bioreactors, Immunoassays, microanalytical devices.
Peptide	Self-assembling peptide including regeneration, encapsulation of chondrocytes, osteoblast differentiation. Tissues engineering, regulation of matrix metalloproteinase(MMP), antimicrobial surfaces, focal adhesion kinase (FAK) phosphorylation, bioactive gene delivery systems, Gel-based drug delivery system.
Polysaccharide	Skin regeneration, angiogenesis, Tissue engineering, hemocompatible materials, antimicrobial surfaces.
Phospholipid analogue	Tissue remineralization, phospholipid-mediated nucleation of apatite crystals, Biocompatible/hemocompatible materials, copolymer formulations in methacrylate-based composites materials, Nano/microparticulates, and drug conjugates
Antibody	Immunologic activity, antibody-secreting hybridomas, biosensors
Polyethylene glycol	Cell adhesion motifs, hemofiltration membranes, drug conjugates, development of zirconia-based composite material, dental implants
Antimicrobial agent	Prevention of bacterial colonization
Oligonucleotide	Biosensors Scaffolds for growth factors Biocompatibility Active packing, antimicrobial textiles Microarrays, biosensors.
Collagen	Recombinant human collagen, graft material

TABLE 2. Medical & Dental Applications of bioactive materials (*Zhao X et.al., 2011 and Santin M et.al 2012*)

Medical & Dental Applications of bioactive materials				
Bioactive materials		**Medical/Dental applications**	**Common Type of material**	**Products/technology/medical application**
1. Hap (hydroxyapatite) 2. Bioglass (BAG) contains silicon, sodium, calcium, and phosphorus oxides 3. TCP (tricalcium phosphate) 4. Hap/TCP 5. Calium hydroxide 6. Mineral trioxide aggregate 7. Nanoparticles of Calcium phosphate compounds	Hard tissue repair	Hard tissue repair; Bone defect repair/bone grafts; Joint replacements; Restorative materials; Remineralization of teeth; Anticarcinogenic agent; Dentin hypersensitivity; Dental implant; Pulp capping materials and scaffolds in pulp tissue engineering.	Polymers	Poly(methyl methacrylate; PMMA) bone cement/twist or PrePack® Artelon implant – biodegradable polyurethane urea for tissue repair Artificial disc – Freedom® lumbar disc using a viscoelastic polymer Polyurethane foam, co-foam for vascular occlusion device DASCOR® device – artificial disc Cemex®, antibiotic-impregnated bone cement; OpteMx® Porous Tissue Matrix™ (PTM) technology based on polylactides, polylactide-co-glycolides, polycaprolactones, polycarbonates (e.g., TMC), polyurethanes. Elastomer: polycarbonate polyurethane (PCU) Precision polyurethane manufacture (PPM). Bioscorp – cervical bioresorbable corpectomy implant (polyester tube coated with PLLA). Dental composite: 3M, Ivoclar Vivadent. Dentures, Glass ionomer cements, Impression materials.
8. Metal/polymers containing bioactive molecules such as antimicrobial substances Biodegradable polymers + bioglass 9. Casein phosphopeptide and amorphous calcium phosphate (CCP-ACP)		Dental applications Bone tissue repair; Dentin hypersensitivity; and remineralization of dentin.	Biopolymer	Collagen-guided tissue repair membranes Collagen/ceramic bone graft substitutes New generation of collagen matrix for repairing cartilage, degenerative disc disease Vitoss®; Vitagel® – control bleeding and facilitate healing HEMA based copolymer used in bonding systems and restorative materials for remineralization and desentization.

TABLE 2. Medical & Dental Applications of bioactive materials (*Zhao X et.al., 2011 and Santin M et.al 2012*) (Continue)

Medical & Dental Applications of bioactive materials				
Bioactive materials		**Medical/Dental applications**	**Common Type of material**	**Products/technology/medical application**
10 Collagen n-Hap/collagen Hap/collagen/chitosan Biodegradable polymer + Hap + cells	Soft tissue	Soft tissue augmentation as cosmetic surgery Vascular grafts, tendons, and ligaments Skin substitutes	Bioceramics	Demineralized bone matrix putties/gels 40% β-TCP + 60% Hap CELLPLEX® TCP graft CopiOs™ bone void filler NuCore® injectable nucleus chronOS is a fully synthetic cancellous bone graft substitute comprising pure β-tricalcium phosphate Medicrea® OSMOSYS® sticks (60% Hap + 40% β-TCP) DuoFix™ Hap (hydroxyapatite coatings) CERAMENT™ injectable bone substitute materials CERAMENT™ (bone void filler) CERAMENT™ (spine support) (calcium sulfate + hydroxyapatite) Ostim® – 100% synthetic, nanoparticular, phase hydroxylapatite bone matrix in paste form. Novamin, Toothmin, GC tooth Mouse, Remin pro for remineralization and anticarcinogenic
11 Zinc polyalkenoate cements 12. Glass polyalkenoate cements		Pulp protection Sandwich techniques, restorative materials		
13. Chitosan		Wound tissue repair	Composites	BILOK TCP/PLLA screw (absorbable); PLLA (2–3 years) GraftLock screws. High-density, long carbon fiber-reinforced polymer (LCFRP) for spinal defect repair . Mozaik™ osteoconductive scaffold (80% highly purified beta-TCP granules + 20% highly purified type-1 collagen); Polyactive (1000PEGT-70PBT30); OsSatura BCP (biphasic calcium phosphate) and OsSatura TCP (synthetic bone void fillers). Origen DBM with bioactive glass. OsteoMax synthetic bone graft for enhanced bone regeneration.

TABLE 2. Medical & Dental Applications of bioactive materials (*Zhao X et.al., 2011 and Santin M et.al 2012*) (Continue)

Medical & Dental Applications of bioactive materials				
Bioactive materials		**Medical/Dental applications**	**Common Type of material**	**Products/technology/medical application**
14. Graphene oxide		Dental prostheses Graphene composite (few-layer graphene); Drug delivery carriers; Imaging agents; Bimolecular analysis; Tissue engineering scaffolds.		Provides optimal osteoconduction. Reduces the time for the bone to regain its full structural function. Osteotech's Plexur™ – bone void filler. Neudisc™ – tubular, fabric-reinforced hydrogel designed to mimic the behavior of a normal disc nucleus. Dental composite as a restorative material.
15. Gelatin		Implant for urinary incontinence. Hemostasis, as scaffolds for soft tissue healing	Biomatrix	OsteoSponge® demineralized bone matrix (DBM) OsteoSponge® Block and Filler, 100% cancellous form of DBM derived from donor bone DiscCell/to restore the function of a degenerated; intervertebral disc; NuBone® DBM putty; NuBone® DBM gel (gelatine) Novocart 3D (biophasic matrix) – autologous chondrocyte transplantation (collagen-based matrix)
16. Demineralized bone matrix (DBM) containing bone growth factors	Tissue engineering	Tissue engineering bone and cartilage repair		

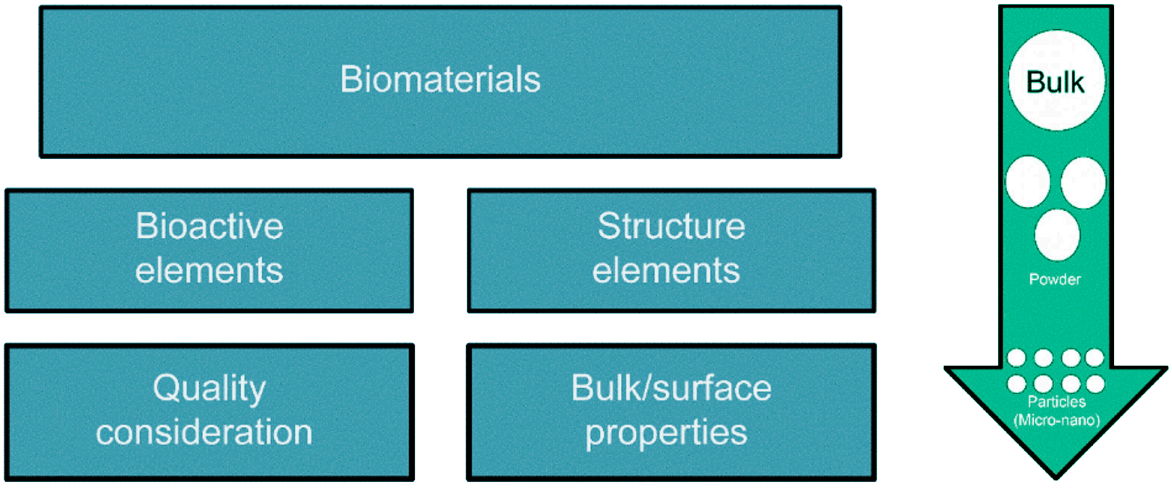

Fig 2. Illustrate the basic concept of bottom-up approach of bioactive material.

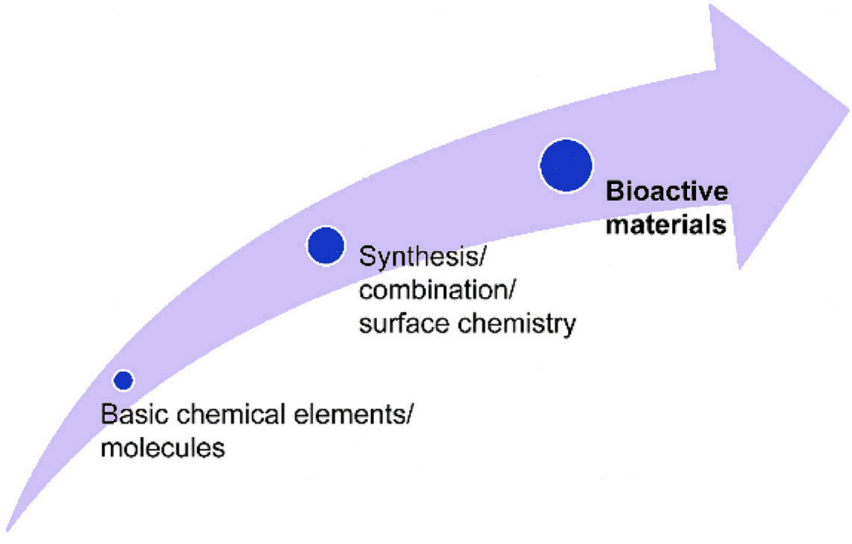

Fig 3. Illustrate the basic concept of bottom-up approach of bioactive material.

TABLE 3. Common microorganism that cause dental caries.

Common oral microbes	Disease
Actinomyces israelii	Gingivitis, periodontitis, and pericoronitis
Actinomyces naeslundii	Bacterial infections and one of the pathogenic bacteria in root caries
Actinomyces viscosus	Carcinogenic bacteria found in root caries and related to periapical infections, dacryosolenitis, and abdominal and faciocervical actinomycos
Bifidobacterium dentium	Biochemically active; can ferment d-ribose, l-arabinose, lactose, sucrose, cellobiose, trehalose, raffinose, melibiose, mannitol, salicin, starch, galactose, maltose, fructose, xylose, mannose, and glucose to produce acid; cannot ferment sorbitol and inulin; Isolated from adult dental caries
Lactobacillus acidophilus, Lactobacillus casei	Found in material from deep caries
Lactobacillus fermentum	Oral infectious diseases such as dental caries and root canal infections
Streptococcus mutans	Glucan and fructan from sucrose colonization; key virulence factors in of dental caries formation
Streptococcus sobrinus	Second highest rate of carcinogenicity after *S. mutans*

(a). Bioactive agents/materials used for altering the oral microbiota in caries-prone individuals, and categorized into natural and synthetic biomaterials.

Natural biomaterials

The bioactive plant compounds derived from secondary metabolism (phytochemicals) have antioxidant activity with low potency as a bioactive compound; however, regular consumption may have distinct unceasing physiological effects. Based on extraction type[12,13], materials are classified as hydrophilic or polar compounds (e.g., phenolic acids, flavonoids, organic acids, and sugars) and lipophilic or nonpolar compounds (e.g., carotenoids, alkaloids, terpenoids, and fatty acids).[14] The most commonly available natural materials are as follows:

Flavonoids. Geismann and Hinreiner 1952 (correlated the group of natural substances with variable phenolic structures to the 2-phenylchroman heterocyclic system (flavan).[15]

- *Propolis* is a nontoxic resinous natural substance that inhibits the adherence of *S. mutans* and *S. sobrinus* and is mainly associated with the control of *Candida albicans*; besides, *propolis* is known to have immunomodulatory effects.[15,16]
- *Nidus Vespae* (honeycomb) is a conventional Chinese medicine used for caries treatment. The chloroform/methanol (CHL/MeOH) chemical extract from this medicine has anti-F-ATPase and anti-lactate dehydrogenase activity against *S. mutans*, along with anti-acidogenic properties. The isolated quercetin and kaempferol flavonoids present in the CHL/MeOH extract exhibit potential preventive and therapeutic actions against dental caries.[17]
- *Polyphenols* are an exclusive class of bioactive natural products with antioxidant, anti-cariogenic, anticancer, and anti-inflammatory effects. An analysis of the literature[18,19] suggests that *polyphenols* can directly act against *S. mutans*; they can inhibit the adherence of bacterial cells and functions of glucosyltransferase and amylase as well as interact with the microbial membrane proteins. Some examples of these compounds include xanthorrhizol, macelignan, magnolol, artocarpin, artocarpesin, quercetin, tannins, myricetin, proanthocyanidin,[11] naringin, and hesperidin.[20]

Prebiotic and probiotic bacteria. Prebiotic and probiotic bacteria are beneficial bacteria that can improve the microecological balance of the host. Generally, the microbiota of subjects with mature oral microbiota plays an insignificant role in the process of permanent colonization in the oral cavity. The probiotic bacteria include the genus *Lactobacillus, Bifidobacterium,* and *Streptococcus. In vitro* studies have shown favourable inhibition of the growth of cariogenic bacteria and *Candida albicans*.[21,22] The common strains of bacteria used are *Lactobacillus rhamnosus* GG, *Lactobacillus casei, Lactobacillus reuteri, Lactobacillus plantarum, Lactobacillus brevis* CD2, *Bifidobacterium* spp., *Streptococcus thermophilus*, and *Streptococcus salivarius* (K12, M18, and JH).[23,24]

Xylitol. Xylose (wood sugar) is a naturally occurring five-carbon sugar alcohol derived from hardwood.[25] Xylitol disrupts the energy-producing process in *S. mutans*, leading to a futile energy consumption cycle and cell death. Furthermore, it inhibits enamel demineralization (i.e., reduces acid production), reduces plaque formation and bacterial adherence, and has a direct inhibitory effect on *S. mutans*. It is readily available in the form of gums, gummy bear snacks, syrups, mouth rinses, and dentifrices. Xylitol acts by forming xylitol-5-phosphate through the phosphoenolpyruvate phosphotransferase system in the cell of *S. mutans* and inhibits its growth and ability to produce acids. It increases the concentration of ammonia and amino acids in plaque, thereby neutralizing the plaque acids; thus, microorganisms in the plaque cannot ferment the xylitol.[26]

Green tea extract. This is a natural bioactive component containing fluoride, catechin, and polyphenols. The indirect antibacterial effect of green tea is exerted by the stimulation of protective components such as immunoglobulins, lysosome, lactoferrin, histatin, and mucin. Green tea can control the pH by inhibiting the action of lactate dehydrogenase, leading to a decrease in acid production after sugar consumption.[27] This extract is effective against the growth of *S. mutans* and *Lactobacillus*.[11,28]

Synthetic biomaterials (biochemicals)

Cetylpyridinium chloride. Cetylpyridinium chloride (CPC) is a cationic quaternary ammonium compound, which exhibits antibiofilm activity during early biofilm formation. It acts as an antiplaque agent at a concentration of 0.025% - 0.1%. Long-term use of this compound causes tooth stains. Furthermore, CPC exhibits strong anti-*S. mutans* biofilm activity.[29,30] A reduction in fluoride ion (F^-) uptake by the action of chloride ions (Cl^-) will lead to an increased incidence of caries. NaCl solution (0.5 mol/L) does not cause any damage to the carious root surface, whereas cerium chloride alone or in combination with F^- can significantly reduce mineral loss from the carious lesion and inhibit its progression.[31]

Chlorhexidine gluconate. This is a cationic bisbiguanide and an antimicrobial agent that inhibits the growth of *S. mutans*. Chlorhexidine varnishes have been reported to cause the most persistent reduction in *S. mutans*, followed by gels and mouth rinses. However, the results of chlorhexidine-fluoride therapy for the prevention of caries are inconclusive.[32-34]

Quaternary ammonium methacrylates (QAM). These are widely used as antibacterial agents. The antimicrobial activity is because the negatively-charged bacterial cells come in contact with the positively-charged quaternary amine (N^+), there is a change in osmotic pressure, resulting in a disturbance of the electric balance and the bacterium explodes.

Long cationic polymers disrupt bacterial cell membranes, akin to a needle bursting balloons, thus proving effective against dental biofilms. In 1994, Imazato et al. first incorporated a QAM into dental composite resin materials.[35] QAMs such as 12-methacryloyloxydo-decyl pyridinium bromide (MDPB), methacryloxyethyl-cetyl ammonium chloride, quaternary ammonium dimethacrylate[36], and quaternary ammonium polyethylenimine have been integrated into dental materials, such as etching-adhesive system, glass ionomer cement (GIC), and composites.[37,38]

Others therapies

Replacement therapy. Replacement therapy involves the implantation of relatively innocuous "effector" bacteria that can competitively exclude or outgrow potential disease-causing bacteria without significantly disrupting the balance of the existing microbial system. Many studies have reported the challenge of successfully introducing effector strains into the human mouth.[39,40]

Gene therapy. In the early 1980s, the "genetic replacement therapy" was introduced to protocols involving an element of gene transfer. Gene therapy is a method of insertion of therapeutic genes into an individual's cells and tissues to treat a disease, such as a hereditary disease in which deleterious mutant allele is replaced with a functional one. *Ex vivo* and *in vivo* are the two approaches for delivering genes into the cells of the body. In *ex vivo* gene transfer, the tissue is removed and cells are genetically modified extracorporeally; then, the modified cells are reimplanted. For *in vivo* gene delivery, the vectors are administered directly to the recipient and gene transfer occurs *in situ*.[6,41,42]

Gene transfer strategy requires three essential elements: a vector (gene delivery system), a gene to be delivered (therapeutic gene), and a relevant target cell to which the DNA or RNA is delivered. Generally, the vectors proposed for gene delivery fall into two categories: viral, which is assembled in a cell, and nonviral, which is constructed in a test tube. Viral vectors are difficult to produce and expensive, which include retrovirus, adenovirus, lentivirus, adenovirus, and herpes simplex virus, whereas nonviral vectors are considered to be less toxic, less pathogenic, and immunogenic and can be produced on a large scale. Natural and synthetic nonviral gene vectors include lipid-based vectors, polymeric vectors (polyethyleneimine, poly-L-lysine, polymethacrylate, carbohydrate-based polymers, linear poly (amidoamine), chitosan, dextran, β-cyclodextrin, polyphosphoester, poly (amino ester)), dendrimer-based vectors (PAMAM dendrimer and polyporpyleneimine), polypeptide vectors, and nanoparticles. *In vivo* gene therapy helps in enhancing the healing of the dento-pulp complex.[43-45]

(b). Bioactive agents/materials for dental caries prevention

The bioactivity approaches used to prevent caries are as follows:

a. Reduction/modulation of biofilm formation [discussed in section (a)].

b. Control/prevention of tooth-mineral loss.

Bioactive substances to Control/prevention of tooth-mineral loss: Dynamic of demineralization and remineralization

Initial mineral loss can be assessed only by an electron microscope. Demineralization is the process of removing mineral ions from hydroxyapatite (HAp) crystals in the hard tissues. The process of restoring this mineral loss by adding HAp crystals is called remineralization. Chemical demineralization on the enamel surface occurs in two phases: at the atomic level, when the bacteria metabolize fermentable carbohydrates and produce organic acids, which diffuse through water among the crystals in the tooth, and when the acid in the susceptible crystal site dissolves the calcium (Ca^{2+}) and phosphate (PO_4^{3-}) ions into the surrounding aqueous phase between the crystals. If the critical pH continues to remain at 5.5, it eventually leads to cavitation. A sufficient concentration of fluoride ions on the crystal surface before or during demineralization can increase the adsorption of the surface of the crystals and remarkably inhibit acid demineralization. During remineralization (natural repair of the initial carious lesion) process, Ca^{2+} and PO_4^{3-} ions from the saliva (enhanced by Statherian salivary protein) and topical sources diffuse into the tooth along with F^- to form a fluorapatite (FAP) acid-resistant remineralized layer.[46-49]

Nanoparticles based

Nanoparticles of Amorphous calcium phosphate (ACP).

ACP ($Ca_3(PO_4)_2$), a precursor of the final crystalline HAp is a suitable remineralizing agent and has an average diameter of 0.95 nm with a spherical cluster of ions (Ibrahim et al., 2018). It has a thermodynamically stable calcium phosphate (CaP) phase, i.e., HAp and octacalcium phosphate in a dry or wet state by reacting with atmospheric water. Enamel remineralization occurs according to two principles: (a) gradual release of Ca^{2+} and PO_4^{3-} ions resulting in a local supersaturation that triggers the remineralization of hard tissues and (b) attachment to the hard tissue surface, from where it is transformed to Hap[50,51] to stabilize the crystalline phase of ACP. Several additives and ions, such as adenosine triphosphate, casein phosphopeptides (CPP), polyethene glycol (PEG), carboxymethyl chitosan, polyaspartic acid, magnesium ions, and poly (ethylene glycol)-block-polylactide have been studied. A systematic review suggests that for remarkable enamel remineralization to occur CPP-stabilized ACP (CPP-ACP) should be directly applied on the tooth surface (i.e., marketed as GC tooth mousse).[51] Inpatient with lactose intolerance, CPP is contraindicated as it is a milk-derived protein. The trade names of this compound are "GC tooth mousse, MI Paste, and MI Paste plus," and "Topical C-5".[52,53]

Calcium glycerophosphate. It is a fine white, slightly hygroscopic powder of Ca salt of gylcerophophate and commercially available as a mixture of Ca beta-, D-, and L- alpha-glycerophosphate. On direct interaction with hydroxyapatite, a combination of calcium glycerophosphate and sodium monofluorophosphate has been found to decrease the acid formation and enhance remineralization of the enamel due to increased uptake of fluoride in the non-alkaline-soluble form at the expense of a fraction remaining in the alkaline-soluble form (CaF); moreover, calcium glycerophosphate buffers the pH of the plaque and increases plaque Ca^{2+} and PO_4^{3-} levels, thus providing cariostatic effect.[54]

Dicalcium phosphate dihydrate. Dicalcium phosphate dihydrate (DCPD) has a stable CaP phase under acidic conditions and helps in the remineralization of carious lesions by forming FAP. DCPD has high solubility and is resorbable compared to HAp in the oral environment.[4]

Hydroxyapatite-tricalcium phosphate. This is a biphasic material, and its resorption ability and biological behaviour depend on the hydroxyapatite-tricalcium phosphate (HAp/TCP) ratio.[55] A constitutive proportion of 2:8 has the most significant effect on mesenchymal stem-cell-induced bone formation. Furthermore, beta-tricalcium phosphates[56] can induce hard tissue formation, although HAp alone has no dentinogenetic impact on pulp tissue as a pulp capping agent. Dentinal tubule-like structures observed in most of the hard tissue and columnar cells showed positive immunoreactions for dentin sialoprotein and heat shock protein 25 and were aligned beneath the hard tissues.[57] Some examples of TCP include Clinpro™ 5000 with 5000 ppm fluoride (USA), Clinpro Tooth Crème with 850-950 ppm fluoride (Asia/Australia), and Clinpro™ White Varnish with 26,000 ppm fluoride (USA/Asia/Australia).

Relatively, the specific area of ACP nanoparticles (17.76 m^2/g) is high compared to that of CaP particles (about 0.5 m^2/g) in dental resins.[58] Owing to the increased release of Ca^{2+} and PO_4^{3-} ions by the nanostructured compound, it has led to new possibilities for combating enamel demineralization. It has exemplary osteoconductivity, bioactivity, high cell adhesion, and modified biodegradation. Other applications of this compound include the production of hybrid composites when mixed with polymers, coatings on metallic prostheses, and chemical-setting injectable cement.

Mussel-inspired polydopamine and polydopamine-assisted hydroxyapatite. Mussels are fouling organism that can adhere to assorted aqueous conditions ranging from natural organic and inorganic materials to synthetic materials; they are rich in 3,4-dihydroxy-l-phenylalanine (DOPA) and lysine amino acids.[59] Mussels have a unique robust adhesive property under wet conditions because the oxidative polymerization of dopamine in aqueous solutions spontaneously forms polydopamine (PDA), mimicking DOPA. Zhou et al. (2012)[60] investigated the formation of polydopamine-assisted hydroxyapatite, an influential novel approach in creating HAp-based organic-inorganic hybrid biomaterials, regardless of the type, size, and shape of the hybridized correspondent materials (noble metals, ceramics, semiconductors, and synthetic polymers). They concluded that it remarkably promoted the remineralization of demineralized dentin and dentin tubule occlusion with densely packed HAp crystals. Thus, the coating on the dentin surface with polydopamine may induce enamel and dentin remineralization in the presence of a metastable Ca^{2+} and PO_4^{3-} solution.

Fluoride. Fluoride is an essential mineral for hard tissues (bone and teeth) and appropriate exposure and method of usage are beneficial for both bone and tooth integrity. Fluorohydroxyapatite (FAP) are generally present along with HAp in the outermost layer of the healthy human enamel, and the OH groups (<5%) in HAp are replaced by fluoride (depth, 50 μm).[61] Fluoride helps in reducing the demineralization of the enamel, increasing remineralization in early enamel caries, and inhibiting

bacterial activity. Overwhelming proven literature is available on various modes and forms of application, and the adverse effects of fluorides.[62,63] The tolerable upper intake limit is 0.10 mg/kg/d daily over an extended period in infants, toddlers, and children up to 8 years of age. Studies have shown that CaF^2 and NaF have a similar effect on caries-like enamel lesions.[64] Under an acidic pH, the F- ions are released from CaF^2 deposits due to the reduced hydrogen phosphate ($HPO4_{2-}$) ions, which help stabilize the CaF^2 and make a solubility-inhibiting protective film on the tooth surface. Hence, CaF^2 functions as a pH-driven F– ion reservoir, which releases F– at low pH conditions during an acid attack and remains stable for a longer period on the enamel surface at a neutral pH.

Arginine technology. Arginine amino acid (1.5%) was recently incorporated into toothpaste containing 1450 ppm fluoride in the form of sodium monoflurophosphate and insoluble calcium carbonate. The toothpaste was customized for the prevention of development of new lesion and remineralization of early caries lesions. The amino acids are deaminated by the arginine deaminase (enzyme) system in saliva producing ammonia, which is highly alkaline, and induce a pH increase within the oral environment. Thus, an ideal condition for the reduction in the pathogenicity of the cariogenic plaque as well as for remineralization is created.[65] Some of the examples of toothpaste with this addition include Colgate Sensitive Pro-Relief™ Toothpaste with Pro-Argin and Tom's of Maine Rapid Relief Sensitive Natural Toothpaste.

Silver diamine fluoride (SDF) (fluoride compound) functions to arrest the inner dental caries and prevent secondary caries formation after treatment. The American Academy of Pediatric Dentistry recommends the use of SDF (38%) to arrest the active cavitated caries lesion in primary dentition as part of a comprehensive caries management program. Although SDF is not advised for use for primary (active) caries prevention, Studies have demonstrated signs of initial prevention when applied to other sites in the oral cavity. This product should be handled by specifically trained professionals during the application, as there is persistent black staining of the carious tooth, soft tissues (lips, buccal, and lingual mucosa, and tongue) and operator's fingers and clothing.[66] Amine fluorides have a slightly acidic pH and are biannually applied intra-orally Studies have suggested that acidified fluoride-containing dentifrices may have a specific effect on enamel remineralization.[67]

Silver nitrate. Ammoniacal silver nitrate or Howe's solution is used to reduce pain due to aphthous stomatitis, disinfect the root canals, and treat deep carious lesions; moreover, it can be used for indirect pulp capping because silver particles can diffuse into the affected dentin and demineralize dentin. Silver nitrate hinders cell division; positive silver ions bind to the negatively-charged peptidoglycans on the bacterial cell wall. Additionally, the bacterial cell wall system facilitates binding between proteins and DNA, wherein the silver ions bind to sulfhydryl groups on enzymes and inactive them, eventually stabilizing the DNA and its replication. Enhanced antibacterial effects of monodispersed Ag-doped silica (Si) particles are obtained by the incorporation of silver nitrate.[68]

Silver, gold nanoparticles, platinum, and diamond nanoparticles. Nano-Ag particles adhere specifically to the bacterial cell wall and evoke and bind to the released substance from the microorganisms.[69] Nano-Pt disintegrates the bacterial cell walls and causes the release of substance leaking from the cells. Nano-Au particles act in "noncontact" manner by stimulating biofilm production and aggregating within the biofilm. Nano-D binds closely to the microbial cell wall surface without causing visible damage to the cells, indicating good self-assembling ability. Taken together, these findings suggest that nanoparticles can be used as antimicrobial agents against caries activity.[70]

Zinc compounds (zinc chloride, zinc oxide). Generally, low concentrations of zinc can reduce enamel demineralization and modify remineralization. The addition of zinc to fluoride toothpaste has not affected their ability to reduce caries. Zinc is readily desorbed from HAp by Ca^{2+}, which is abundant in plaque and saliva. In instances where the crystal-growth sites remain occluded by zinc, they may simply be "overgrown" by remineralization initiated at unoccupied sites. Zinc chloride (2.0%) is effective in reducing calculus accumulation, whereas zinc oxide is effective in preventing root caries.[71]

Vitamin K. Vitamin K2 has been tested as a possible anticaries agent by virtue of its enzyme-inhibiting activity in the carbohydrate degradation cycle. A healthy tooth is nourished by centrifugal fluid (dentinal fluid) in the dentin, which is moderated by the hypothalamus/parotid axis, signalling the endocrine portion of the parotid glands. High sugar intake induces increase reactive oxygen species and oxidative stress in the hypothalamus. When this signalling mechanism stops or reverses the dentinal fluid flow, it renders the tooth vulnerable to the oral bacteria, leading to enamel surface dissolution and dentin disintegration. Vitamin K2 has antioxidant potential in the brain and can preserve the endocrine-controlled centrifugal dentinal fluid flow.[72,73]

Platelet-rich fibrin (PRF) and concentrated growth factors (CGF). PRF belong to second-generation platelet concentrate and are easily prepared with no added biological agents with increased osteogenic ability. CGF is obtained from autologous blood using a centrifuge device. Various centrifugation speeds permit the isolation of a fibrin matrix that is remarkably larger, denser, and richer in growth factors as compared to previous-generation platelet concentrate products. The effect of PRF and CGF on exposed dental pulp tissue is to act as scaffolding material and also as a reservoir to deliver certain growth factors and proinflammatory cytokines at the implantation sites. As PRF and CGF are collected from autologous blood, no hypersensitivity reactions are expected.[74]

Polymer-based bioactive materials

P***olyamidoamine polymethylmethacrylate***. Amino-terminated polyamidoamine (PAMAM) dendrimers are highly branched polymers with internal cavities and numerous reactive terminal groups and are used as nucleation templating analogues for biomineralization. PAMAM polymethylmethacrylate has been referred to as an "artificial protein" due to its biomimetic property.[36] They have three generations: the first and second generations are linear molecules, while the third generation comprises spherical molecules with a large number of functional groups. The terminal groups comprise amine-terminated PAMAM (PAMAM-NH_2), carboxyl-terminated PAMAM (PAMAN-COOH), hydroxy-terminated PAMAM (PAMAM-OH), and phosphorylated PAMAM (PAMAM-PO_3H_2). A study by Liang et al. shown that PAMAM-COOH acts as an organic nucleation template and absorbs Ca^{2+} and PO_4^{3-} ions within collagen fibrils to induce intrafibrillar remineralization. PAMAM-PO_3H_2 produces enamel prism-like structures and binds to dentin collagen to stimulate the regeneration of a demineralized dentine surface. PAMAM-OH helps in occluding the dentinal tubules, whereas PAMAM-NH_2 macromolecules adhere to dentin collagen fibrils by electrostatic interactions.[75] Overall, PAMAM has dual effects of mineralization and antibacterial properties.

Synthetic polymers. Synthetic polymers such as polylactic acid (PLA), ploy glycol acid (PGA), and PEG hydrogels offer the advantages of non-toxicity, low immunogenicity, biocompatibility, and ability to undergo *in vivo* degradation. PLA and PGA scaffolds help in the seeding of stem cells like SHED, DPSCs, and dental pulp fibroblasts. PEGs are hydrophilic oligomers synthesized from ethylene oxide and consist of a repeating unit of -(O-CH_2-CH_2)-. PGE is used in tissue regeneration, cell culture, cancer diagnostics and for drug delivery, surface modifications, wound healing, and tissue scaffolds. Synthesized hydrogel are included in peptidic substrates to induce the secretion of the matrix metalloproteinase (MMP) enzyme form tissue cells during migration.[76-79]

Polytetrafluoroethylene(PTFE). PTFE is a linear polymer of tetrafluoroethylene that resembles polyethene (PE) chemically, except that fluorine atoms are completely replaced by the hydrogen atoms. The characteristics of PTFE are as follows: chemically inert nature, very low coefficient of friction (resulting in high surface smoothness), resistance to high temperatures without degradation between 260°C to 400°C, insoluble in water and any organic solvents, non-stick, low dielectric constant (excellent electric insulator), and malleability. The disadvantages are low creep resistance, poor weldability, high microviod content, and low radiation resistance. The application of this agent in dentistry includes the following: Teflon tape, surgical sutures, dental floss, a membrane for guided bone regeneration, and the coating of accessories and dental instruments.[80]

Biopolymer composites. Composite restorations play a vital role in restorative dentistry, changes in composition are done by adding spherical silicon dioxide nanofiller (average size of 540 nm or 0.00050.04 μm), amorphous $CaPO_4$ nanostructures (obtained from calcium chloride (30 mM) and sodium acid phosphate (20 mM) in the presence of buffer, anticaries CaF^2 nanoparticles, recombinant amelogenins to develop biomimetic composites, and variety of CaPs (HAp ACP, tetracalcium phosphate, and dicalcium phosphate anhydrous) to produce mineral-releasing dental composite.[81] In case of smart composite, ACP is converted into HAp and precipitated into gel form within seconds when the pH level in the oral cavity drops to below 5.8, which then forms into amorphous crystals in less than 2 min, resulting in Ca^{2+} and PO_4^{3-} production.[82]

Recently, the inclusion of zirconia-hybridized pyrophosphate-stabilized ACP (Zr-ACP), and tetraethoxysilane or $ZrOCl_2$ to ACP was considered to improve the mechanical properties (biaxial flexural strength and marginal adaptability). Zr-ACP is more soluble than HAp and allows controlled release of Ca^{2+} and PO_4^{3-}.[83] Bioactive composites have enhanced adhesion to the tooth surface and antibacterial activities, thereby reducing biofilm formation and increasing the reliability and longevity of the adhesive restoration compared to conventional composite.

It constitutes resin-filled epoxy microcapsules. The self-repairing mechanism is based on microcapsules, a crack in the epoxy composite material will destroy the microcapsules located nearby the crack and release the

resin, which will subsequently fill the crack and react with a Grubbs catalyst (dispersed in epoxy composite) resulting in resin polymerization and crack repair. Clinical performance of such material is better as compared to the conventional macroscopic repair approach.[82]

These materials can be categorized based on the composition: polyethyl or butyl methacrylate, polymethyl methacrylate, micro filled bisphenol A-glycidyl dimethacrylate, polymethyl methacrylate, and urethane dimethacrylate (light-polymerizing resins). Clinical performance of methyl methacrylates and bis-acryl resins are superior as compared to ethyl methacrylate which has poor aesthetics and wears resistance.[84]

3.3.1.c. Other bioactive components

Peptide derivatives. The DGEA (aspartic acid-glycine-glutamine-alanine) peptide, derived from the αβ1 integrin-binding domain of collagen I, is a potential target ligand for the stimulation of osteogenesis. In one study, DGEA peptide-mediated cell adhesion utilized peptides adsorbed on the HAp crystals in the presence of fetal bovine serum. Leucine-rich amelogenin peptide is a product of alternative splicing of the *amelogenin* gene, regulates HAp crystal formation depending on its phosphorylation status, and is potentially used for the treatment of enamel lesions or defects.[85,86]

Chitosan. It is a natural carbohydrate biopolymer; its grafted hydrophobic chains make chitosan molecule amphiphilic and enhance the antimicrobial activity by increasing its electrostatic interactions with the bacterial cell wall. Studies have suggested that chitosan-based chewing gum and mouthwash have antibacterial effects and can reduce the mucoadhesion of cariogenic bacteria. The addition of nano-chitosan to GIC could develop anti-cariogenic properties and improve mechanical properties. The addition of chitosan to adhesives reduced collagen destruction starting with the endogenous MMP and prevented water permeation in hybrid layers, thus suggesting its role in eliminating bacteria from the dentin surfaces.[87,88] Amelogenin-chitosan (CS-AMEL) hydrogel and chitosan+collagen have been reported as promising materials for *in situ* enamel growth. During enamel remineralization with CS-AMEL hydrogel, microstructure formation with an organization similar to that of enamel is promoted, thus resulting in a successful reconstruction.[87,89,90] Addition of chitosan in the nano-diamond-based form to of methyl methacrylates and bis-acryl resins is suitable for functional temporary restorative applications.[91] Chitosan in combination with nanohydroxyapatite is used as a chemo-chemical solution in removal of caries.

Collagen. A popular biomaterial found as an abundant collagen protein in ECM; it is used as a coating material. Due to its natural origin, collagen has a wide range of applications, such as being a suitable binding site for cellular attachment and an appropriate bone substitute material in combination with bioactive inorganic phases. Moreover, bone morphogenetic proteins and collagen I and IV have been commercialized as dermal substitutes.[93] Collagens are refined and produced in sponges, sheets, films, or injectable scaffolds. Collagen films are in practice for corneal replacement and infection treatment along with anti-inflammatory drug delivery system.

Fibrin glue. Fibrin is a biocompatible, biodegradable, natural scaffold that provides initial stability to the grafted stem cells, which is commonly used for tissue engineering. The growth factor in fibrin glue stimulates and promotes proliferation, cell migration, tissue repair, matrix production by accelerating angiogenesis, and enhances the healing of the exposed pulp tissue (pulp capping agents). The advantages of autologous fibrin scaffolds are easily manufactured in large quantities, cost-effective, easy handling, and reduced probability of viral or prion transmission. Therefore, they are excellent for tissue engineering and appear to be a promising scaffold in regenerative endodontics and maxillofacial surgery.[94]

Hyaluronic acid hydrogel. Hyaluronic acid (HA) is a natural, biocompatible, biodegradable glycosaminoglycans and is found as a tissue component in ECM. It is widely distributed in the mammalian body, especially in the synovial fluid of the joints, umbilical cord, and vitreous body of the eyes. It is a linear polysaccharide with a repeating unit of disaccharide of glucuronic acid and N-acetyl-D-glucosamine and a molecular weight ranging from 10^4 to 10^7 g/mol. It has anti-inflammatory, antibacterial, and tissue-healing properties.[6,83]

(c). Bioactive agents/materials as a restorative material for dental caries management:

This section discusses replacement dentistry and cavitated lesion management with no chance of initial remineralization; the tooth defect has to be restored with restorative materials. The cost of restorative/replacement dentistry can vary worldwide; for example, in the USA, the annual cost is $5 billion.[95] Currently, the concept of minimally invasive dentistry (MID) has emerged due to the increased understanding of the caries process and advancement of the adhesive system. According to Ericson, "MID is the application of systemic respect for the original tissue"; the concept of remineralization and restoring (small filling) incipient lesions.[81]

Briefly, restorative dental elements comprise synthetic

constituents such as primers, bonding agents, liners, cement bases, amalgam, resin-based composites, hybrid ionomers, compomers, cast metals, metal ceramics, ceramics, and denture polymers, which can be used to mend or replace the missing structure of the teeth. Certain materials are created to be controlled-delivery devices for the release of agents for treatment or diagnosis. The use of restorative material is temporary, short-term (temporary cement, crowns, and resin bridges), or long-term (dentin bonding, indirect inlays, crowns, onlays, overlays, removable dentures, fixed multiple unit, and orthodontic appliances). Materialistic advantages have been executed with aid of nanotechnology; it is possible to facilitate interaction with cell components, control cell proliferation and differentiation, and produce an organized ECM. Nanobiomaterials include nanoparticles, nanocrystals, nanoclusters, nono-wires, nanofilms, and nanofibers.[81]

Bioactive Glass based material

Bioactive glass. In 1969, the first bioactive glass (BAG) was introduced as Na, Ca, and PO_4 silicate glass. The two classes of BAG are silicate-based and phosphate-based glasses. The increase in pH promotes the precipitation of HAp from the tooth surface. The Ca^{2+} and PO_4^{3-} ions from BAG and mineralizing agents in saliva may promote the remineralization process. A commonly available noncrystalline amorphous BAG (Bioglass 45S5; NovaMin; GlaxoSmithKline, UK) is used in toothpaste for dentin hypersensitivity (96). Various combinations of bioglass are discussed below:

Silicate-based glasses: The particles or granules of Bioglass 45S5 (Si-based) comprise 45 wt% of SiO_2, 24.5 wt% of CaO, 24.5 wt% of Na_2O, and 6.0 wt% of P_2O_5.[4] Based on the amount of free oxygen available for the branching and interconnection of the glass, four types of silicate-based glasses structures are available: Q0, with no free oxygen; Q1 or end unit, with one free oxygen; Q2 or middle unit, with two free oxygens; and Q3 or branching units, with three free oxygens. The common network modifiers can be oxides of Na, K, Ca, Mg, Ti, and Ca. In general, as the Ca/PO_4 ratio decreases, the ability to bond also decreases. The addition of specific atom substitutions (like fluoride) induces some changes in glass properties, which reduces the dissolution rate. The increase in pH promotes network dissolution by breaking the Si–O–Si bonds and is followed by the formation of silanol groups (SiOH). The polymerization of the SiO_2-rich layer occurs through the condensation of the SiOH groups. The migration of the Ca^{2+} and PO^{4+} groups to the surface of the Si-rich layer results in the formation of CaO-P_2O_5-rich film.[81]

Phosphate-based glasses. They have wide biomedical applications, as they rapidly dissolve when exposed to an aqueous environment, wherein the Na^+ ions are exchanged with hydrogen ions (H^+). Meanwhile, Ca^{2+} and PO_4^{3-} ions are released from the biomaterial, which increases the localized pH and induces the precipitate to form CaP-rich layer on the lesion surface. The Si network from BAG can react with hydroxyl ions from the aqueous solution and form soluble silanol compounds. The increase in Ca^{2+} and PO_4^{3} contents is inversely proportional to Si content. Ultimately, the newly formed layer that is structurally similar to the enamel and dentin has excellent abrasion resistance and transforms into HAp layer.[97,98]

Hydroxyapatite and bioglass. The combination of HAp and bioglass (BG) favours bone formation but has potential as a restorative material for cavitated carious lesions. The intrinsic osteoinductivity property of BG induces degradation process whereby growth factors remain captured within the gel phase formed during material degradation and are consequently released into the cells upon complete material dissolution. Furthermore, fibronectin (ECM) structural proteins form strong bonds with particles of the degrading material. The silicon ions of BG stimulate osteoblast (progenitor cell) differentiation and subsequently form a new bone.[93]

Mesoporous bioactive glasses. Mesoporous bioactive glasses are synthesized into particles, spheres, fibres, three-dimensional (3D) scaffolds, and composites with organized mesoporous channel structures, have excellent bioactivity and used for drug delivery and bone regeneration.[6]

Ag-doped bioactive glass nanoparticles (Ag-BGNs). The addition of silver oxide (0.2–0.5 mol%) to SiO_2-CaO-P_2O_5-Na_2O glass composition at the expense of Si did not allow the glasses to crystallize by melt-quench firing method.[99] Studies have investigated the antimicrobial property of silver and its effect on remineralization. The drawback of this agent is the staining due to the silver content.

Tri-Calcium Silicate Based Materials

Mineral trioxide aggregate. During the last decade of the 20th century, a bioactive material MTA was developed as a root-end filling material at Loma Linda University.[99] It consists of Portland cement (75%), gypsum (5%), bismuth oxide (20%), and traces of Sio_2, CaO, MgO, K_2SO_4, and Na_2SO_4. Portland cement comprises tricalcium aluminate, dicalcium silicate, tricalcium silicate, and tetracalcium aluminoferrite. The removal of tetracalcium aluminoferrite removes the grey colour resulting in the production of the white MTA. It is used for pulp capping, root perforation, retrograde root-end filling, and the obturation.[74]

Biodentine. comprises tricalcium silicate, dicalcium silicate, calcium carbonate, calcium oxide, and zirconium oxide (radiopaque). The liquid consists of calcium chloride and hydro-soluble polymer based on polycarboxylates (responsible for low water content and consistency of the mixture). Biodentine was used as a bioactive build-up material in large areas where the tooth structure is missing and for treating pulp exposures and root perforations. It sets in 10–12 minutes.[81]

Smart materials

Bioceramic-based and smart ceramics. The physical, chemical and biological properties of bioceramic (third-generation orthopaedic biomaterials) are similar to the natural bone.[100] Some of the most commonly investigated bioactive ceramics are β-tricalcium phosphate (β-TCP), HAp (HA), and BAG 4 5S5. These materials are osteoconductive and biocompatible but differ considerably in the rate of resorption. Resorption rate of HA is very slow compared to β-TCP and BAG. Bioceramic-based materials are used as a permanent restorative material.

Smart ceramics are polycrystalline ceramic containing zirconia instead of glass. High-tech ceramic zirconia is used in space shuttles, the brake disks of sports cars, and spherical heads of artificial hip joints. Zirconia is monoclinic at room temperature and tetragonal at firing temperature, with a monoclinic unit cell occupying about 4.4% more volume than when tetragonal. This transformation resulted in crumbling of material on cooling; therefore, in the late 1980s, ceramic engineers suggested to add small amounts of Ca and later, yttrium or cerium (approximately 3–8 mass%) to stabilize the tetragonal form at room temperature. But this form is only "metastable," as trapped energy still exists within the material to convert back to the monoclinic state. CAD-CAM (computer-aided system) technology is implemented using 3D data set of either the prepared tooth or a wax model of the desired substructure. The ceramic powder (Procera, Nobel Biocare, Gothenburg, Sweden) is packed and fired on the enlarged die and in some cases, it is used to machine an oversized part for firing (ZirCAD, Ivoclar Vivadent; Cercon Zirconia, Dentsply Prosthetics, York, Pa.; Lava Zirconia, 3M ESPE, St. Paul, Minn.; Vita In-Ceram YZ, Vita Zahnfabrik). In both procedures, the firing shrinkage can be managed or predicted accurately if well-characterized ceramic powder (i.e., tight control over particle size and packing density) are packed. The highly localized stress ahead of a propagating crack can trigger grains of ceramic to transform around the crack tip. In this case, 4.4% more volume becomes beneficial by altering the material conditions around the crack tip and protecting it.[82]

Graphene-based restorative material. In restorative dentistry, graphene family of nanomaterials (GFNs) includes reduced GO, ultrathin graphite, graphene sheets, few-layer graphene, graphene oxide (GO; from a monolayer to a few layers). Studies have suggested that GFNs have the potential to improve the mechanical properties of antimicrobial and antibiofilm fillers when reinforced with resin polymer matrices and glass ionomer (polyacrylic acid). Additionally, a combination of graphene gold nanoparticles filler and GFNs showed remarkable improvement in the degree of conversation and surface properties, thus providing a stable solution in improving physicochemical properties of dental nanocomposites.[81,101,102]

CONCLUSION

Currently, materials with excellent biocompatibility and regenerative properties have been utilized by clinicians to save teeth that were under various therapeutic modalities and condemned to extraction. However, the compiled data presented will help the clinicians to have complete knowledge and periodic updates regarding these materials and their clinical applications. As to conclude for prevention of dental caries still fluoride therapy is followed; nanohydroxyapatite, bioactive glass, and natural bioactive based materials are used for restorative materials. Researchers are emphasising in tissue engineering and regeneration for enamel and dentin. The path to overcoming any challenges regarding will require active collaboration among clinicians, a material scientist and pulp biologist.

ACKNOWLEDGEMENT

None

Disclosure Statement

The authors have no conflicts of interest to declare.

Funding Sources

Have no such funding sources involved.

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