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Nano-Based Platforms for Antimicrobial Photodynamic Therapy -A Review

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Abstract :
Objective: This review enhances recent advances in the field of nano-based platforms for antimicrobial photodynamic therapy (aPDT) targeting pathogenic oral biofilms.
Background data: It is challenging to disinfect dental tissues in a clinically appropriate manner using aPDT alone. Limited penetration into both soft and hard oral tissues, photosensitizer diffusion, and the low light absorption coefficient have all been determined to be contributory factors. As a result, aPDT's efficacy in in vivo applications is diminished. Nanotechnology has been suggested to improve the penetration and delivery of photosensitizers to target bacteria and increase the bactericidal action in order to overcome constraints.
Materials and methods: The current literature was screened for the various platforms composed of photosensitizers functionalized with nanoparticles and their enhanced performance against oral pathogenic biofilms
Results: The evidence-based findings from the up-to-date literature were promising to control the onset and the progression of periodontal diseases.
Conclusions: The promise of nano-based platforms to treat pathogenic oral biofilms, which are currently out of reach, has generated excitement. These nano-based platforms' novel modes of action, which enable us to get beyond the difficulties of intra-oral and hard-tissue disinfection, account for a large portion of their potential.
Key words : Nano-based platforms ,Photosensitizer, Photodynamic therapy

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INTRODUCTION

Photodynamic therapy (light-induced inactivation of cells, microorganisms, or molecules) was first used in medical therapy in 1904.(2) In the early twentieth century, Oskar Raab and Hermann von Tappeiner "noticed that Paramecium spp. protozoans stained with acridine orange killed upon exposure to intense light," which led to the development of aPDT procedures. Although aPDT treatments have long been utilised in medicine (particularly for the treatment of various types of tumors), John Toth coined the term "photodynamic therapy" in 1981 after observing the "photodynamic chemical effect .With an increase in the treatment modalities in the progression of periodontal disease , in recent years the use of photodynamic therapy (PDT) as a non-invasive remedy for viral, bacterial, and fungal diseases have been explored. In PDT the photosensitizing agent is activated by light, initiating a photochemical reaction that is oxygen-dependent, producing cytotoxic reactive oxygen species, primarily singlet oxygen. PDT can be applied topically to a periodontal pocket to prevent systemic overuse and negative side effects of antibiotics. It also lowers the likelihood of bacterial resistance.(1) PDT, also refer to as photoradiation treatment, phototherapy, or photochemotherapy,." To evaluate and assess the effectiveness of nanophotosensitizers in periodontics, various nanoscale platforms that aids in periodontal disease treatment practise are the focus of this literature review

What is photodynamic therapy

It is a therapy which receives a nontoxic medication or dye known as a photosensitizer systemically, locally, or topically, in a period of time, wherein the targeted site is illuminated with visible light (typically long wavelength red light), which, in the presence of oxygen, causes the generation of cytotoxic species, which in turn causes cell death and tissue destruction.(3)

Need for photodynamic **therapy**

There are a number of limitations in other treatment modalities especially in the use of antibiotics which has paved the way for PDT

The Drawbacks in Antibacterial Drug Treatment in Periodontal Disease include

- increased resistance to antibiotics used in periodontics
- increase in the number of immune-suppressed patients and

periodontal infections related to many many diverse pathogens requiring different antibiotics and risks of adverse reactions(4)

Mechanism of action

PDT requires the use of oxygen inside the cells, a photosensitizing agent, and light with a wavelength between 635 and 690 nm. A photosensitizer changes from its ground state to a higher energy level to a certain wavelength. The excited state can then either dissolve back to its ground state or produce the triplet state with higher energy. Type I and Type II interactions between the photosensitizer and the biomolecules are both possible when it is in the triplet state.(5)

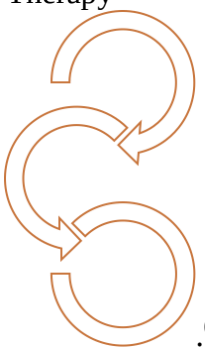
Type I

Ions are produced directly through the photosensitizer's charged particle transfer, or free radicals that are produced when an electron or hydrogen is removed from a substrate molecule. These radicals form highly reactive oxygen species when they come into contact with oxygen producing these unstable ion(superoxide, hydroxyl radicals, and hydrogen peroxide).[6]

Type II

Singlet oxygen (1 O2) is created when the triplet state photosensitizer combines with oxygen. This excited electron and reactive phase of oxygen can interact with a variety of biological substrates and cause radical damage to the cell membrane and cell wall. Singlet oxygen is one which is seen to have detrimental effect on viruses, bacteria, and fungi. It has a narrow area of action and a brief lifespan in biological systems (0.02 mm). It is ideal for its usage in localised areas. As a result, many experts believe that the type II response is the most significant mechanism in microbial cell damage.[6]

Principles of Photodynamic Therapy



.[7]

(flow chart :1)

PDT selectivity

The described photocytotoxic reactions occur only within the pathological tissues in the area of photosensitizer distribution, enabling selective destruction .Photosensitizers accumulate in significantly higher concentrations in diseased cells than in regular cells. This due to the biodistribution of photosensitizers to combine preferentially with low density lipoproteins (LDL). The role of LDL is to provide tissues with the necessary lipids to create protective membrane during cell division. Vehemently dividing cells show an increased uptake of LDL lipoproteins, which act as a "transporter" of the photosensitizer to the diseased tissues . The affinity of photosensitizers for serum lipoproteins, in particular for LDL, plays an important role in the delivery of these drugs to the affected tissue . Photodynamic therapy affects the vascular system of the targeted tissue and stimulates the immune system. The process of destruction of an unwarranted tissue is complemented by the activation of coagulation processes (occlusion of targeted vessels) and local accumulation of inflammatory cells[8]

Photosensitizers

Photosensitizers in addition to light and oxygen, are one of the three essential components of PDT. According to its definition, these dyes are compounds that may absorb light of a certain wavelength and cause photochemical or photophysical processes.[9]

Ideal properties of photosensitizer[10]

- High degree of chemical purity.
- Stability at room temperature.

- Photosensitive effect only in the presence of a specific wavelength.
- High photochemical reactivity; the maximum absorption of light should be at wavelengths from 600 nm to 800 nm. Absorbance of light at a wavelength above 800 nm does not provide enough energy to stimulate singlet oxygen and production of other reactive oxygen species.
- Absorption is minimum in ranges between 400 nm to 600 nm,thereby preventing excessive photosensitive reaction caused by sunlight.
- The absorption bands should not overlap each other substances in the body, including endogenous dyes such as melatonin, hemoglobin or oxyhemoglobin.
- Minimal cytotoxicity in the dark.
- Easy solubility in the tissues of the body.

- Inexpensive and simple synthesis and easy availability

Generations of photosensitizer [(12)](Table 1)

Table1: Generations of photosensitizer

GENERATIONS	photosensitizers	Limitation of the generation	wavelength
First generations hematoporphyrin derivative" (HpD). HpD was obtained by purification and chemical modification of the first porphyrin used as PS - hematoporphyrin (Hp) HpD was available under the trade name "Photofrin	hematoporphyrin	low chemical purity (it is a mixture of over 60 molecules) or poor tissue penetration due to maximum absorption at a relatively short wavelength - 630 nm. In addition, after PDT, skin hypersensitivity to light for several weeks because of long half-life of PS and its high accumulation in the skin occurs.	630nm
Second generations The second-generation photosensitizers are characterized by a higher chemical purity, higher yield of singlet oxygen formation and better penetration to deeply located tissues due to their maximum absorption in the wavelength	• ALA (5-aminolevulinic acid) • Chlorins • Methylene blue	• poor solubility in water, which is a significantly limiting factor in their intravenous administration	650–800 nm.
Third generations	With external carrier	• Complex elimination	630nm to

The development of the third generation photosensitizers is based on the synthesis of substances with higher affinity to the tumor tissue, which reduces damage to surrounding, healthy tissues.	• Metal based nanoplatforms • Liposomes • Nanoemulsions • Antibody conjugate	route • More cost	700nm

Overcoming PDT limitations with nanoparticles

The photosensitizer must overcome the biocompatibility and selectivity restrictions of aPDT in order to bind to pathogens instead of host cells and the microbiota, especially in situations where the photosensitizer must accumulate at the infection site, such as after systemic administration in clinical aPDT . In order to overcome these constraints, researchers have either employed nanoparticles as photosensitizer delivery systems or directly chemically modified photosensitizer qualities (such as adding cationic charge).[13] All nanoparticles have the benefit of having a large surface area to volume ratio, which enables high drug (photosensitizer) loading. Their dimensions can be tailored to produce unique electrical and optical characteristics and to enhance uptake through cell membranes and the blood-brain barrier. The bioavailability, biocompatibility, and selectivity of a medicine can all be improved by altering the nanoparticle composition and/or surface. These surface changes may entail several ligand types with various features, such as tailored delivery of photosensitizers.[14]

Both "passive" and "active" methods can be utilised for nanoparticle-based targeting in aPDT. Passive targeting depends on the drug circulating in the body for a long time and accumulating there preferentially over other parts of the body. Selective ligand-receptor interaction to the target bacterial cell is necessary for active targeting. (Fig 1)

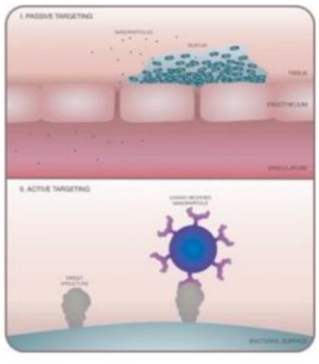
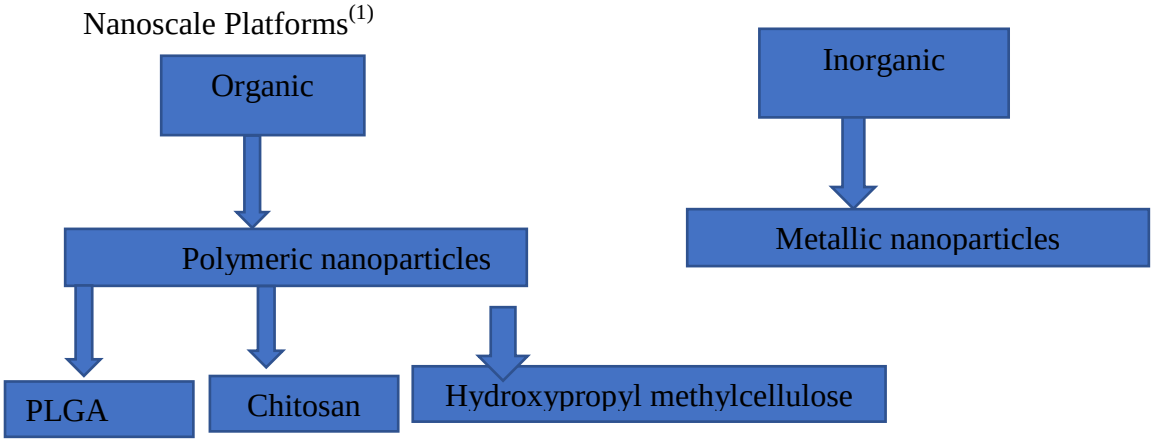


Fig 1:Paasive and active targeting

Regarding passive targeting, nanoparticles with the proper size, shape, composition, and surface modification are well-documented for their capacity to pierce leaky vasculature linked to disease and inflammation (known as the "enhanced permeation and retention (EPR) effect") and for their potential to increase the time that drugs spend in the bloodstream during circulation .An efficient barrier is formed by healthy vasculature, but when there is inflammation, the vasculature around the infection site becomes more porous.[15] Due to the

size and poor clearance of nanoparticles, this enhanced permeability allows immune cells to enter the area as well as access the infection site. For anti-cancer PDT, the EPR effect has been effectively utilised in nanoparticle-based systems, but less so in aPDT. Made that the vasculature loses permeability at later stages of infection, the EPR impact is restricted to early phases of acute infection, consideration should be given to the timing of drug application in passive targeting approaches for aPDT .Passive targeting lacks selectivity for the bacterial cell, which limits the timing of therapeutic application and increases the risk of host toxicity and microbiota damage.[16]

Nanoscale Platforms[1]



Flow chart3:Nanoscale platforms

Polymeric nanoparticles

Therapeutic chemicals can now be delivered to malignant tissues and bacterial biofilms with the help of polymeric nanocarriers, which have shown promising results. [17]

They can operate as drug delivery systems for long-lasting therapeutic medicines with a controlled-release profile and exhibit low cytotoxicity and good permeability through the cellular membrane

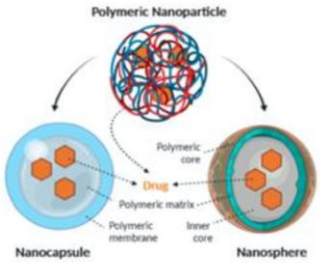


Fig 2:Polymeric Nanoparticle

Polymeric carriers have received a lot of attention in the field of aPDT due to a number of benefits, including an increase in charge density and the photosensitizers' bioavailability to target live cells.[18] (Table :2)

Table 2: Studies on Applications of Polymeric Nanoparticles as Carriers of Photosensitizers in Antimicrobial Photodynamic Therapy

Various polymeric carrier	Carried photosensitizer	Outcomes
Chitosan[19]	indocyanine green-loaded nanospheres coated with chitosan	The positive charge that the chitosan with ICG might provide could boost the material's ability to interact with the bacterial membrane. To improve the bactericidal action, these positively charged nanospheres might stick to the P. gingivalis and other periodontal infections' cell walls. When compared to ICG alone, ICGchitosan considerably increased the antibacterial action against P. gingivalis.
Chitosan hydrogels containing hydroxypropyl methylcellulose (HPMC) [20]	toluidine blue O (TBO)	Strong antibacterial activities against periodontal infections were produced as a result of the HPMC-enhanced TBO's adhesion to the gingival model by *7 to 10-fold. When 2-h incubation and 108 J/cm2 irradiation were obtained, P. gingivalis and A. actinomycetemcomitans were completely eradicated.
Cationic poly (lactic-co-glycolic acid) (PLGA)[21]	methylene blue	The photodestructive action of MB (PLGA-MB) carried by cationic poly (lactic-co-glycolic acid) nanoparticles against oral biofilms was effective.

Metallic nanoparticles

High surface-to-volume ratios of metallic nanoparticles influence their capacity to interact with bacterial membranes and provide bactericidal effect.[22] (Table :3)

Table 3: Studies Using Elemental Nanoparticles to Enhance the Antimicrobial Action of Photosensitizers

Agent	Delivery approach	Outcomes
Zinc oxide nanoparticles[	Crystal violet-coated polyurethane with oleic acid[34]	4 and 1-log reductions of S. aureus and E. coli colonies, P.gingivalis respectively.
Gold nanoparticles	Vancomycin Combination of TBO and gold nanoparticles[35]	Inhibition of >99% of gram-positive and gram-negative bacteria
Silver nanoparticles	Combination of methylene blue and silver nanoparticles[36]	4-log reduction of Streptococcus mutans biofilm was observed

	Combination of methylene blue and silver nitrate nanoparticles[37]	multispecies periodontal biofilm containing Aggregatibacter actinomycetemcomitans, P. gingivalis, and Prevotella intermedia microorganisms
Titanuim dioxide	5,10,15-tris(1-methyl pyridinium-4-yl)-20-(pentafluorophenyl)porphyrin(38) tri-iodide photosensitizer combined with titanium dioxide nanoparticles([39]	Approx. 4-log reduction was observed against Streptococcus sanguinis, P. gingivalis, and Fusobacterium nucleatum
Lanthanidedope nanoparticles	Lanthanide-doped nanoparticles combined with b-carboxyphthalocyanine zinc and polyvinylpyrrolidone polymer(40)	4- to 5-log reduction of S. sanguinis, Prevotella gingivalis, and F. nucleatum
Iron oxide magnetic nanoparticles	Combination of chlorine e6, coumarin 6, and Fe3O4 magnetic nanoparticles[41]	magnetic nanoparticles was attempted to increase the killing efficiency against periodontal pathogens. Ce6 is a highly efficient photosensitizer with low toxicity
Graphene quantum dots/graphene oxide	Graphene quantum dots combined with toluidine blue[42]	Around 1-log reduction against a multispecies periodontal biofilm containing Aggregatibacter actinomycetemcomitans, P. gingivalis, and Prevotella intermedia microorganisms
Fullerenes (C60 and C70)	Fullerenes combined with carbon nitride[43]	Around 2-log reduction was observed against S. mutans biofilm. Also, gtfB gene expression was reduced by 7.9-fold

Zinc oxide nanoparticles

Due to their intriguing physical characteristics and antibacterial activity, zinc oxide (ZnO) nanoparticles are widely used in dentistry. Our skin, muscles, bones, and brain all contain zinc, a necessary mineral. ZnO nanoparticles have the ability to produce ROS when used as an antibacterial agent, which increases ZnO's membrane permeability and causes cell wall destruction in a variety of pathogens.[23]

Gold nanoparticles

Gold nanoparticles are simple to functionalize and may be made in a variety of geometrical sizes and forms, making it easier to control their optic, plasmonic, and photothermal properties. This led to the creation of various gold nanoparticles, including nanoclusters, nanospheres, nanoprisms, nanorods, nanoflowers, and core shells.[24]

Silver nanoparticles

Silver (Ag) has been used for many years to target a variety of microbes, including bacterial types that are resistant to some drugs. In order to explain the mechanism of Ag's antibacterial effect, various theories have been established. The two most widely accepted explanations are protein deactivation brought on by the release of Ag ions and direct contact killing induced by cell membrane damage.[25]

Titanium dioxide.
The primary mechanism to cause biological reactions against live cells by the formation of ROS has been recognised as the oxidative stress of titanium dioxide (TiO2) [26]

Lanthanide-dope nanoparticles.
By incorporating incompatible dopants into the nanoscale level of lanthanide-doped nanoparticles, multicolor tuning is a possibility. Different methods, including surface polymerization, thermal annealing, and chemical bonding, have been proposed to incorporate lanthanide-doped nanoparticles into various dye atoms.[27]

Magnetic nanoparticles.
In the past few years, there has been an increase in the usage of magnetic nanoparticles to improve the delivery of anticancer medicines. Other investigations showed that magnetic nanoparticles might be used to specifically target and kill particular microbes.[28]

Graphene quantum dots/graphene oxide
As an alternative to producing ROS, quantum dots, such as those made from graphene, have been used for photodynamic treatment. When quantum dots are exposed to radiation with a higher energy than their band gap, radicals are produced in the valence band that have the potential to damage bacterial membranes.[29]

Graphene quantum dots showed antibacterial activity after light activation at the blue range (465–475 nm)

Fullerenes.
Fullerenes have a prolonged lifespan of the triplet excited state throughout irradiation, indicating that these substances can cause ROS.Fullerenes' primary drawbacks are connected to their hydrophobicity and antioxidant activity. Specific methods, such as surface modifications with anionic and cationic functional groups and supramolecular methods with PEGylation and encapsulation, could be used to overcome these drawbacks.[30]

Nanodiamonds.
Nanodiamonds were employed as fillers in dental materials to enhance the mechanical qualities of autopolymerized polymethyl methacrylate, such as flexural strength and impact strength. However, investigations evaluating the antibacterial efficacy of nanodiamonds against oral biofilm utilising a photodynamic treatment technique have not yet been conducted.[31]

Other nano-carriers
A solid sphere with an amorphous, lipophilic negative charge surface makes up a nanoemulsion. Oil and water droplets between 20 and 200 nm in size, coupled with a surfactant that organises the oil/water interface, make up the majority of nanoemulsions. It is possible to employ nanoemulsion to improve the distribution of hydrophobic medicines

which makes nanoemulsions excellent candidates to enhance the delivery of photosensitizers.[32]
Nanospheres

Nanospheres are utilised to carry or regulate the release of medicinal or antibacterial chemicals inside a colloidal matrix. As a photodynamic antibacterial agent, the inclusion of ICG photosensitizer into nanospheres was tried. The broad-spectrum absorption of ICG shows a peak around 805 nm.

Due to the usage of ICG-loaded nanospheres and the 3-5 minute diode laser treatment, the CFUs of P. gingivalis were decreased. Increasing the irradiation time was associated with more inhibition because 5 min irradiation demonstrated 3-log reduction for the CFUs of P. gingivalis
The findings of this study may point to the advantages of employing nano-carriers to deliver antibacterial drugs to target periodontal pathogens in places where mechanical debridement may be difficult, such as deep periodontal pockets and furcation areas. [33]

Recent advances in nanoparticle- based active targeting approaches in aPDT
Active targeting necessitates 'targeting ligands' that recognise pathogen structures specifically. Because nanoparticle surfaces may be changed with a variety of ligands, they provide a convenient way to combine targeting ligands and photosensitisers for an active targeting aPDT strategy . These targeting ligands can take several forms, ranging from low selectivity (such as charge) to high selectivity (such as antibodies, peptides and glycans).[44](Table: 4)

Table 4:Studies Using Recent advances in nanoparticle- based active targeting approaches in aPDT

Targeting agent	Reference	Targeting species	In vitro -vivo	Nanoparticle	photosensitiser
Charge	(51)	E.coli,S.aureus	In vitro	Polymer	Chlorin e6
	(52)	S.aureus	In vivo ,mouse thighs	Magnese oxide coated with BSA	Indocyanine green
Antibiotic	(53)	MRSA, methicillin-sensitive S. aureus	In vitro, planktonic; in vivo, rats	Gold	Plasmon gold nanopart
	(54)	Vancomycin-resistant *E. faecium* and *E. faecalis*	In vitro, planktonic; in vivo, mouse wounds	Gold, silver, silica	2,3-naphthalocyanine

Glycans	(55)	Drug-resistant *P. aeruginosa*	Gadofullerene-based	Indocyanine green	Galactose and/or fucose	
	(56)	*S. aureus*	In vitro, planktonic	Hyperbranched polyglyceroL	Methylene blue	
Antibodies	(57)	MRSA and methicillin-sensitive *S. aureus*	In vitro, planktonic in rabbit blood	Iron core, gold shell	Methylene blue	
	(58)	MRSA	In vitro, planktonic; in vivo, mouse wounds	Iron oxide	Hematoporphyrin	

Charge

Charge has been thoroughly investigated as a targeting approach in aPDT. As previously indicated, many of the photosensitisers utilised in aPDT have cationic charges that allow them to bind to bacterial cells rather than human cells . The cationic photosensitiser preferentially binds to anionic groups on the bacterial surface (such as teichoic acids and lipopolysaccharides) .While adding a cationic charge to free photosensitisers can improve localisation to a bacterial cell, employing nanoparticles can enhance photosensitiser uptake while decreasing clearance from bacterial cells and biofilms (through pumps) compared to free photosensitisers. [(45)]While cationic nanoparticles have showed great promise in enhancing aPDT efficacy, charge generally relies on extensive and non-specific binding interactions with the bacterial surface, with the potential to bind a wide range of microbial cells. As a result, as previously stated, cationic nanoparticles may bind to and harm non-target bacteria such as microbiota members.[(46)]

Antibiotics

Although their potency is diminishing, attaching broad- or narrow-spectrum antibiotics (defined by the number of bacterial species they target) to nanoparticles improves therapeutic efficacy by enhancing transport to the target bacteria .As a result, antibiotic-nanoparticle combinations provide a promising method for selective aPDT against bacteria. For aPDT, antibiotic-nanoparticle systems can specifically kill antibiotic-resistant bacteria. [(47)]However, the manner of antibiotic resistance used by a specific bacteria should be considered, as this strategy is limited by bacteria that have adapted their antibiotic-binding sites. Furthermore, conventional antibiotic concerns persist, such as antibiotic exposure to non-target bacteria in the microbiota, which can harm commensal bacteria and raise the likelihood of antibiotic resistance forming and spreading among the microbial population.

Highly selectivity nanparticle- based active targeting PDT

Recent advances in nanoparticle delivery systems for aPDT have led to the highly selective targeting of bacterial cells using glycans, antibodies, and molecularly imprinted polymers. As glyconanoparticles mimic glycans (‘glycomimetics’) found on the surfaces of human cells, glycans offer biocompatibility and aqueous solubility to drug delivery systems

Glycans

By recognising lectins on target cells, glycans (sugars) provide a highly selective targeting approach. Lectins rely on multivalent glycan structures for high-affinity binding. Surface lectins are used by bacteria to recognise glycan structures on host cell surfaces in order to adhere and invade .These 'glyconanoparticles' can imitate the natural glycan presentation found on host cells and provide high affinity and selective bacterial attachment due to nanoparticles' capacity to display numerous glycan patterns on their surfaces.(48)

Molecular imprinting

Molecular imprinting typically entails combining target structures with polymers and then removing the target structures, leaving a 'imprint' (or binding cavity) of the target structure in the polymer .This method provides highly stable and selective high-affinity bacterial binding. The method is often less expensive because only a modest amount of targeted ligands are required as a template molecule. Molecular imprinting is a promising targeting strategy for aPDT. However, the technique currently relies on relatively small molecule templates that can be isolated or synthesised. Nonetheless, molecular imprinting offers a highly selective targeting technique for aPDT.(49)(Fig: 3)

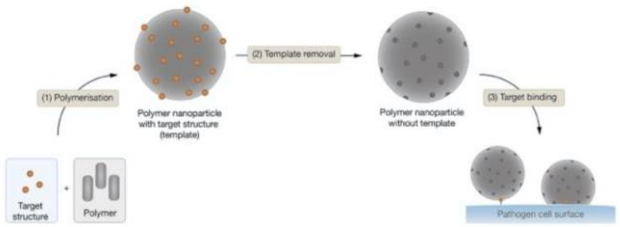


Fig 3:Molecular imprinting

Antibodies

The high specificity and affinity of antibody-antigen interactions suggest that they have tremendous potential as a highly selective targeting agent for aPDT. These antibody-targeting systems illustrate antibody recognition's great specificity and selectivity. However, antibody manufacturing can be a time-consuming and costly procedure . Furthermore, for therapeutic applications, the possible immunogenicity of antibody constructions and the loss of efficient targeting if bacteria modify their antibody-binding structure should be taken into account.(50)

Limitations and Future trends

Together, studies have uncovered a number of factors that must be considered in upcoming research. The stability, pharmacokinetics, biodistribution, toxicity, size, dispersion, and motion of the nanobased platforms are frequently taken into account in many of these investigations in addition to design principles affecting the photosensitizer. Although the antibacterial activity and therapeutic efficacy of these compounds remain limited in evidence,

the exploration of the unique properties of nanomaterials is promising for the design of platforms for oral disinfection[(1)]

Conclusion

The promise of nano-based platforms to treat pathogenic oral biofilms, which are currently out of reach, has generated excitement. These nano-based platforms' novel modes of action, which enable us to get beyond the difficulties of intra-oral and hard-tissue disinfection, account for a large portion of their potential. Although they are still in the early stages of research, nano-based platforms have a lot of promise. The information that is now available focuses primarily on in vitro preclinical studies that highlight the capabilities of various nanotechnologies to enhance the penetration and distribution of photosensitizers.

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