REVIEW PAPER

Management of Periodontal Disease Using Green Synthesized Nanomaterial: An Overview

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ABSTRACT

Background

Periodontal disease is a chronic inflammatory condition affecting supporting tissues that can result in tooth loss. Traditional therapies, such as scaling, flap surgery, and antibiotics, have limitations. Green nanoparticles from plants have been studied as a potential solution using nanotechnology.

Main body

This study explores the classification, method of synthesis, mechanisms of action, characterization techniques, and application of nanoparticles. Nanoparticles are microscopic particles with dimensions typically less than 100 nm. Nanoparticles are created using both top-down and bottom-up techniques. Nanoparticles can be organic (liposomes, dendrimers, solid lipid nanoparticles), inorganic (metal, metal oxide, magnetic, calcium phosphate nanoparticles), or carbon-based (carbon nanotubes, graphene, fullerenes). Nanoparticles break down bacterial cell membranes, stop biofilm formation, and improve drug absorption. The nanoparticles are evaluated using various characterization techniques, including dynamic light scattering, electron microscopy, drug loading measurements, in vitro drug release studies, and spectroscopic and diffraction methods. Nanoparticles are effective in treating periodontal disease owing to their antibacterial, anti-inflammatory, targeted drug delivery, tissue regeneration, and immune system alteration properties.

Conclusion

Green nanotechnology offers eco-friendly, biocompatible, and efficient alternative therapies for periodontal therapy, addressing drug retention and its side effects. However, further investigation is needed to improve the composition and clinical applications of these products.

Keywords: Targeted Medication Delivery, Biogenic Nanoparticles, Periodontal Disease, Periodontal Pockets, Green Nanotechnology, biosynthesis of nanoparticle

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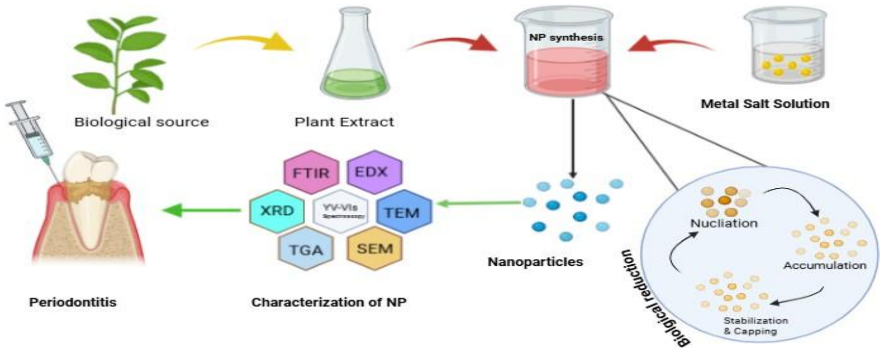

Graphical abstract of management of periodontal disease using green synthesized nanomaterial: An overview

1. Introduction:

Nanotechnology has emerged as a revolutionary field in pharmaceutical sciences, offering potential for targeted drug delivery and enhanced bioavailability of active compounds(1). In recent years, its application in dentistry has gained attention due to its ability to improve oral health outcomes and address the persistent challenges in the management of oral diseases (1).

Periodontal disease is chronic inflammatory disorder involving the gums, gingiva, periodontal ligament, and alveolar bones which support and protect the teeth within its socket(2,3).

The WHO report 2022 on Global Oral Health Status shows that 3.5 billion peoples are affected by oral diseases(4).This health burden is mostly caused by edentulism, periodontal disease, dental caries, and oral cancers(5).American Academy of Periodontology categorize periodontal disorders as gingivitis and periodontitis(6).In preliminary phase, gingivitis manifests as gum inflammation, haemorrhage, and irritation(7).If left untreated, this site can lead to infection, tar, calculus deposition, tooth destruction, and tooth loss(8). Periodontitis can result in systemic disorders such as cardiovascular, diabetes, and pulmonary issues(9,10). The main risk factor includes consumption of alcohol and tobacco, alongside unhealthy dietary habits, particularly those high in sugar(7).

The pathogenesis of periodontal disease is primarily driven by the formation of dental biofilms, which trigger local inflammatory responses and damage the host's supporting tissues (8,9).

Periodontal disease is characterized by formation periodontal pocket having a depth up to 5mm caused due to enzymatic activity of bacteria and collagen degradation which leads to break down of tissue (10,11). The periodontal pocket creates an ideal site for growth of anaerobic microbial proliferation (10,11). In oral cavity more than 700 species are identified, with around 400 species isolated from subgingival microenvironments(11).The figure No.1 indicated the most commonly found species in oral cavity.

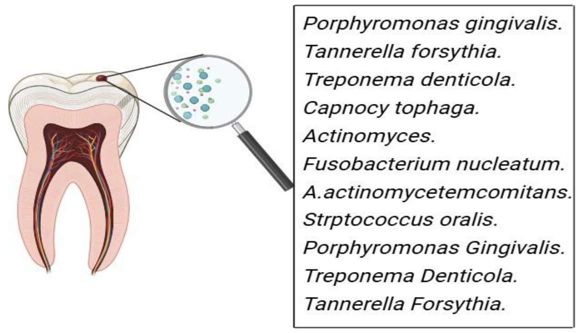

Figure No.1: The most common oral infection (19)

Conventional periodontal therapies include regular brushing, flossing, mechanical debridement and adjunctive antimicrobial therapy are effetely used to reduce plaque accumulation and disease progression but often fail to provide sustained therapeutic benefits (4, 9,14,15).

Professional intervention such as scaling, antibiotics, air polishing, root planning, and, if necessary, surgery are also employed for advanced cases(12). Existing therapy fails to overcome the challenges posed by the anatomical and microbiological complexity of the periodontal environment resulting in poor drug penetration, retention, and bioavailability (13).

Limitations of existing periodontal treatment strategies is inadequate drug retention at the infection site, rapid drug clearance from periodontal pockets, systemic side effects, and increasing incidence of antimicrobial resistance (10). These challenges necessitate the development of advanced, localized, and sustained drug delivery systems that can enhance therapeutic efficacy while minimizing adverse effects (11).

Therefore, integrating nanotechnology into periodontal disease management presents a novel approach to improve treatment efficacy and clinical outcomes. The development of a targeted, sustained, and ecofriendly nanotechnology-based drug delivery system addresses the limitations of current periodontal therapies (14). The synthesis of green nanoparticles is both economical and environmentally friendly(3,4).Nanoparticle possess unique physicochemical properties, such as high surface area, tunable size, and enhanced bio adhesion, which enable improved drug retention, controlled release, and targeted delivery at the diseased site.

The nanoparticulate system has a number of advantages, such as superior stability, controlled release rate, and great dispersibility in an aqueous medium(15).The figure No.2 indicates the merits and demerits of nanoparticle. Nanoparticles are used in medicine for targeted administration, contrast imaging, combination therapy, tissue engineering, bone and tooth healing because of their small size, shape, and surface qualities(16).

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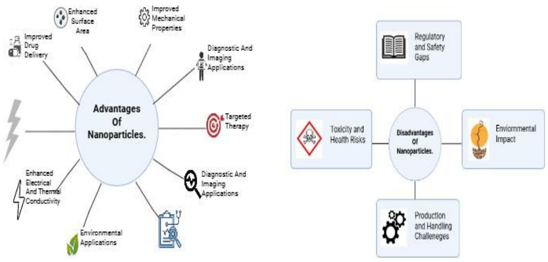

Figure 2: Merit and Demerits of nanoparticles (15)

2. Literature Review:

The article examines potential integration of Ayurveda with nanotechnology as a strategy to address infectious diseases, emphasizing holistic principles inherent in Ayurveda and its innovative antimicrobial properties(17).The review examines application of traditional medicine and herbal product in treatment of oral disorders as it is easily accessible, cost-effective, safe and culturally familiar. It is categorized into eight groups: compounds, vegetation, flavonoids, microorganisms, proteins, complex products, phytohormones, and phytonutrients(4,18).

Various herbs, including *Curcuma longa* (turmeric), *Punica granatum* (pomegranate), *Azadiracta indica* (neem), *Aloe indica* Royle (Indian aloe), *Acacia catechu* (cutch tree), *Eucalyptus globulus, Glycyrrhiza glabra, Plantago major, Melaleuca alternifolia, Scutellaria baicalensis,* honey, and *Camellia sinensis* have been effectively investigated in the context of periodontal infection because of antibacterial, immunomodulatory, and anti-inflammatory properties (3,19,20). The plant-derived phytochemicals like alkaloids, tannins, polyphenols, terpenoids, flavonoids, and polyphenols suppresses periodontal infections and modulate inflammatory responses through receptor interactions(21).

It has been studied by Amina Fouad Farag et al. (2025) that a 2% curcumin concentration enhanced the viability, proliferation, and adhesion of PDL fibroblasts to root surfaces damaged by periodontitis, necessitating randomized clinical trials(22).

It has been demonstrated by Anahita Javad Khani et al. (2023) that catechin nanoparticles were used as a potent antibacterial agent to treat periodontal diseases(23).It has been reveal by Swati Goyal (2020), silver nanoparticles were made using an extract from Ocimum sanctum demonstrated strong antibacterial activity against pathogen(24).It has been studied by Shi-Yuan Yang et al. (2024) that a nano-delivery method based on quercetin can effectively repair alveolar bone abnormalities associated with periodontitis(25).It has been studied by Krishnappan et al. (2024) that neem extract-loaded silver nanoparticles (99%) exhibit greater antibacterial activity against *T. forsythia*, *P. gingivalis*, and *T. denticola* compared to chlorhexidine, the clinical reference drug. It has been studied by Krishnappan et al. (2024) reveals that neem-loaded silver nanoparticles (99%) ethanolic neem extract had better antibacterial action against *T. forsythia, P. gingivalis,* and *T. denticola* than chlorhexidine (Clinical reference drug)(26).

Medicinal plants used in drug delivery systems for periodontal disease can be classified based on their origin, active phytochemicals, mechanism of action, and type of delivery system utilized, as follows**:**

Medicinal Plant	**Active Phytochemicals**	**Mechanism of Action**	**Therapeutic Benefits**	**Formulation Type in PDDS**
Curcuma longa (Turmeric) (21)	Curcumin(21)	Inhibits NF-κB, scavenges ROS, inhibits bacterial growth	Anti-inflammatory, antimicrobial, antioxidant	Nanoparticles, gels, films
Azadiracta indica (Neem) (21)	Nimbin, Nimbidin, Azadirachtin	Disrupts bacterial cell walls, inhibits prostaglandin synthesis	Antibacterial, anti-inflammatory, promotes healing	Mouthwash, nanoparticles, gel
Camellia sinens	EGCG (Epigallocatechi	Inhibits MMPs, reduces	Antioxidant, anti-	Nanoparticles

is (Green Tea)(27–29)	n gallate) (7,30)	oxidative stress and inflammation	inflammatory, antimicrobial	, strips, irrigant
Aloe vera(21)	Aloin, Aloemannan, Saponins	Promotes fibroblast activity and collagen synthesis	Wound healing, anti-inflammatory, soothing effect	Herbal gel, nanoparticle-loaded hydrogels
Ocimum sanctum (Tulsi)(21)	Eugenol, Ursolic acid, Rosmarinic acid	Inhibits bacterial adhesion, reduces inflammation	Antimicrobial, antioxidant, mild analgesic	Herbal paste, nano emulsion
Glycyrrhiza glabra (Liquorice)	Glycyrrhizin, Glabridin	Inhibits glucosyltransferase and bacterial growth	Antimicrobial, anti-inflammatory, anticaries	Sustained release films, gels
Terminalia chebula (Haritaki)	Chebulagic acid, Gallic acid	Inhibits oxidative damage and promotes healing	Antioxidant, antibacterial, anti-inflammatory	Herbal rinses, nanoparticle coating
Salvadora persica (Miswak)	Salvadorine, Trimethylamine	Disrupts plaque biofilm, natural abrasiveness	Antiplaque, antimicrobial, promotes gingival health	Herbal stick extract, nanoparticle gel
Triphala	Gallic acid, Chebulinic acid	Inhibits MMPs, collagenase, promotes fibroblast function	Antioxidant, gingival healing, anti-inflammatory	Mucoadhesive gel, mouth wash

Table No.1. Medicinal Plants in Drug Delivery Systems for Periodontal Disease (3,19,20).

3. Literature Gaps

Typical nanoparticle synthesis processes, including chemical reduction, electrochemical deposition, and thermal decomposition, have caused environmental and health issues as the demand for nanomaterials has increased(31).These include safety concerns, historical misalignment, complex formulations, regulatory barriers, research gaps, costs, lack of established procedures, insufficient clinical confirmation of efficacy, limited understanding of molecular pathways, and accessibility, all of which call for careful investigation and ethical considerations (17).This review discusses the synthesis, characterization, and application of green nanoparticles (31).

4. Principles for local intra-pocket delivery of antimicrobial drugs(14)

Early diagnosis and management of periodontal disease, including surgical and non-surgical methods, are crucial to prevent further deterioration(32).The equilibrium between subgingival bacteria and host's immune system is maintained by GCF's interaction with well-vascularized tooth tissues; nevertheless, disturbance can lead to periodontal disease(7).GCF is a naturally formed reservoir that facilitates the leaching of drugs from the periodontal pocket(33).

Systemically administered antimicrobial agents stop bacterial growth and eradicate gingival germs invading the GCF(34).However, the systemic approach is not recommended due to potential adverse effect such as fever, nausea, diarrhoea, stomach pain, and bacterial resistance(14,18,35).Local administration of conventional dosage forms like films, fibres, gels, and strips in periodontal pockets offers improved drug delivery and reduced systemic exposure (33).Long-term use of this medication can cause adverse effects like tongue numbness, dry mouth, tooth discoloration, altered taste perception, frequent administration of dose and drug resistance(36).Achieving drug concentration level in pockets has proven challenging for many proposed local drug delivery systems (18).

An intrapacket device's goal is to deliver and sustain therapeutic dosages of medication for the necessary amount of time in order to suppress or kill microorganisms without any injury to the tissues. Controlled delivery methods release drugs gradually, ensuring long-term effectiveness and availability. The periodontal pocket is the ideal location for LDD placement and the most effective technique.

Administration of nanoparticulate sustained-release drug delivery maintain therapeutic medication levels for the required duration, reduces frequency of drug administration, reduces salivary secretion, dose while maximizing antibacterial therapeutic efficacy(37).Nano-drug delivery systems, effective against resistant microbes, are used in periodontitis treatment because of small size and antibacterial properties by breaking down the membranes of bacteria, which eliminates the pathogen(38).Inorganic nanoparticles (NPs) are perfect for dental applications because of their numerous structural flaws, diverse shapes, and high surface-to-volume ratios(38).Drugs can be delivered to particular locations of action after they are encapsulated, particularly by using polymers and they can be released gradually and under control into organs or tissues(16).Nanotechnology innovations are increasingly suitable for dental disorders(39).Specially designed nanoparticles, with sizes measured in nanometers, can target the periodontium and other oral tissues(40).For ex, AgNPs, specifically designed for periodontal disease, combine silver's antibacterial properties with neem's anti-inflammatory and antioxidant flavonoids. Their effectiveness against key bacteria is confirmed through UV-Vis, TEM, FTIR, and in silico docking studies(41).

Main text

Methodology for data collection

The primary databases consulted were Web of Science, Research Gate, PubMed/MEDLINE, The Scopus, The Scientific Web, and The Library of Cochrane. A comprehensive search was conducted of the literature about the use of nanoparticles in dentistry. The electronic database search approach combines keywords and boolean operators.

Key concepts include "antimicrobial," "periodontal disease," "oral surgery," "drug delivery," "nanoparticles," "nanomaterials," "nano dentistry," and "dental material," along with various suitable combinations of these terms.

5. Nanotechnology in Periodontal Drug Delivery Systems (PDDS):

Professor Keric E. Denler, a well-known author and researcher in the field, is credited with creating the word "nanotechnology," while Richard Feynman used it initially in 1959 (42,43).The word "nano" comes from Greek word "dwarf"(42–44).Nanotechnology is described as "the creation and use of materials, tools, and systems" (43,45–47).Nanomedicine is the result of recent developments in the use of nanotechnology in medicine(48,49) .

5.1. Nanoparticles in Periodontitis:

Nanoparticles represent a primary subfield of nanotechnology that enables the creation of numerous innovative solutions(50).A particle described as having at least one dimension between 1 and 100 nanometres is called a nanoparticle(1nm $=10^{-9}$ m)(16,51).Nanoparticles can be hollow, conical, cylindrical, tubular, spherical, core, spiral, flat, or irregular in shape(51).The distinctive physicochemical properties of nanoparticles include high surface area, adjustable size, particle size distribution, agglomeration or aggregation, porosity/roughness, water solubility, dispersibility, hydrophobicity, enhanced reactivity, hydrophilicity, surface charge or zeta potential, and photocatalytic and catalytic activity(1,47,52).Nanoparticles encompass a variety of forms, including nanopores, nanorods, nanotubes, quantum dots, nanocaps, nano shells, liposomes, dendrimers, nanospheres, nanowires, nanobelts, nanoring's, and fullerene(43,49,53,54).Nanoparticles, composed of single or combined materials, are utilized in clinical applications for enhanced durability, aesthetics, and patient safety (55).

5.2. Classification of Nanoparticle for treating periodontal disease:(39,51)

Nanoparticles are divided into 3 types: organic, inorganic, and carbon-based. (39,51)

The classification of nanoparticle are indicated in figure No.3.

Figure No.3. Classification of nanoparticle- Organic, inorganic nanoparticle

1. **Organic nanoparticle/ nano capsules:**(16)

This category comprises organic molecules with dimensions of at least 100 nm characterized by their non-toxic and environmentally friendly properties(16).Organic nanoparticles or polymers such as ferritin, liposomes, micelles, and dendrimers exhibit heightened sensitivity to heat or light(38,56). The composition, mechanism of action,drug used in periodontal disease, advantages, and application of organic nanoparticles are listed in Table No.2 below:

Type of Nano	Composition	Mechanism of Action	Drugs/Ag	benefit	Applications for

particle			**ent Used**		**Periodontal Disease**
Liposomes (57)	An aqueous core in a phospholipid bilayer	Deliver hydrophilic/lipophilic medications into tissues; integrate with cell membranes (16,58)	Minocycline and Doxycycline	biodegradable, have low toxicity, provide prolonged release and have dual drug loading (lipophilic and hydrophilic) (58)	Local administration of antibiotics and anti-inflammatory therapy, (35,38)
Solid Lipid Nanoparticles (SLNs) (59)	Solid lipids + surfactants	Drug entrapment in a solid lipid matrix, gradual release, and gingival attachment (59)	Chlorhexidine, metronidazole	enhanced tissue penetration, controlled release, and medication stability	Periodontal infection treatment and local drug delivery methods (59)
NLCs, or nanostructured lipid carriers	Lipids, both liquid and solid	An imperfect lipid matrix improves retention in gingival pockets and permits better drug entrapment.	NSAIDs, curcumin, and coenzyme Q10	Improved bioavailability, prolonged retention, and higher drug loading	Long-term administration of anti-inflammatory and antioxidant compounds
Polymeric TNanoparticle(39)	Natural (chitosan, alginate) or synthetic polymers (PLGA) (39)	Drugs are released by biodegradable polymers, which can be surface-modified for specific purposes. (39)	Growth factors, statins, and tetracycline(39)	Site-specific delivery, biocompatible, and tunable degradation(39)	Delivery of antibiotics with guided tissue regeneration (GTR(39))
Chitosan Nanoparticle (60)	Chitosan, a cationic polymer (60)	Antimicrobial and mucoadhesive effects of electrostatic interaction with bacteria and	Antimicrobial peptides and chlorhexidine (60)	Antimicrobial, healing-promoting, biocompatible, and bio adhe	Local antibacterial activity, bone regeneration, and wound healing (60)

		mucosa (60)		sive (60)	
Dendrimer (49,61)	Polymers with many branches, like PAMAM (49,61)	High drug loading, controlled release, and functional groups that enable targeting (49,61)	Antimicrobial agents and NSAIDs (49,61)	High stability, adjustable surface, and controlled drug distribution (49,61)	Anti-inflammatory therapy, targeting inflamed periodontal tissues (49,61)
Micelles	Amphiphilic copolymers of blocks	For drug loading, create a hydrophobic core; release the drug in reaction to enzymes or pH.	Ibuprofen and curcumin	Improve hydrophobic medication solubility and tissue penetration.	Anti-inflammatory drug delivery in deep periodontal pockets
Protein/Peptide Nano particles	Self-assembled proteins or peptides	ligand-receptor interaction to target bacteria or host cells; enzym	Growth factors, antimicrobial peptides,	Targeting specific tissues, biodegradable, and low	Antimicrobial activity and growth factor delivery for
		e-degradable		in toxicity.	regeneration.
Carbon-based Nano particle(62) (Graphene Oxide, for example)	Carbon Nanotubes, carbon nanofibers, graphene, fullerenes, nanodiamonds, nanohorns, onions, and graphite (63).	break down the cell walls of bacteria, produce ROS, and serve as regenerative scaffolds and drug transporters (63).	Antimicrobials and anti-inflammatory drugs	Promotes osteogenesis, has a large surface area for drug attachment, and is antibacterial.	Carbon nanotube is suitable for dental filling and other applications(64) Graphene is beneficial for applications in biosensing(64).(65)

Table No.2: Organic Nanoparticle (16)

2. Inorganic nanoparticle:(16)

Metal and Metal oxides nanoparticle includes silver, gold, silicon, copper oxide, zinc oxide, magnesium oxide, and titanium dioxide (66). Nanoparticles made up of metals and metal oxides, have strong antimicrobial activity against various periodontal pathogens, disrupting bacterial cell walls, metabolic activities, and producing reactive oxygen species(1). Metal oxide nanoparticles' having antibacterial qualities make them useful in biosensors, bio nanotechnology, and nanomedicine because of their larger surface area and smaller size (11). The figure No.4 shows various types of metal and metal oxide nanoparticle. Table No. 3 lists the composition, mode of action, advantages, and applications of inorganic nanoparticles for periodontal drug delivery.

Figure No.4: Metal and Metal Oxide Nanoparticles in Periodontal Therapy

Type of Nanoparticle	**Composition**	**Mechanism of Action**	**Benefits**	**Uses in Periodontal Disease**
Metal Nanoparticles(66)	copper, zinc, cadmium, iron, lead, silver, cobalt, gold, platinum, palladium, nickel, zirconium, titanium, chromium, beryllium, boron and aluminium.(67)	Antibacterial by breaking down membranes, producing ROS, and deactivating enzymes (1)	Long-lasting, broad-spectrum, potent antibacterial low- or non-toxic ingredients(68)· biocompatible.(69)	Eliminating periodontal pathogens (*A. Actinomycetemcomitans, P. gingivalis*)
Silver nanoparticle (Ag-NPs)(70)·(62)	Silver salts or elemental silver	Attach to the membranes of bacteria → breach the cell wall → prevent enzymes and DNA replication (63)	effective at low doses, strong antibacterial (63)	Green manufacturing of Ag NPs with biomolecules offers simple, cost-effective, and eco-friendly dental solution.(71)
AuNPs, or gold nanoparticles (72)	Frequently functionalized, elemental gold (71)	Excellent for photothermal therapy and drug administration, non-toxic (16,39)	Easy surface modification, optical qualities, and biocompatibility (16,39)	used in photothermal therapy as antibacterial agents for dental treatment.(71)
Zinc Oxide Nanoparticle(70)	Nano-sized zinc oxide particles	Zinc oxide nanoparticles exert antibacterial activity by interacting with bacterial membranes, generating reactive oxygen species (ROS), releasing Zn^{2+} ions, and causing oxidative damage that leads to cell death, they have antibacterial qualities. (63,72)	Antibacterial by producing ROS and affecting protein activities. biocompatible, osteogenic, and anti-inflammatory	wound healing, and biomedical applications. (72,73).

Iron oxide nanoparticles (16)	Magnetite or Maghemite	magnetic fields produce heat, killing bacteria and reducing inflammation.(74,75)	Magnetic guiding, imaging (MRI) and antimicrobial agent.	magnetic nanoparticles can be used for hyperthermia therapy and targeted medication administration (16,74)
Calcium Phosphate Nanoparticles(62)	Nano-hydroxyapatite ($Ca_{10}(PO_4)_6(OH)_2$)	Mimic bone mineral to encourage remineralization and bone repair (1)	Bioactive, promotes osteoblast adhesion, and integrates with bone (63)	Nanoparticles can be utilized a carrier to transfer growth factors and other osteogenic agents to the periodontal tissues or as alternatives to bone grafts(16)
Titanium dioxide nanoparticle(62,66)	Nano-TiO_2 (used in coatings)	antibacterial and photocatalytic activity under UV/visible light (1)	Strong adhesion, antimicrobial, and high mechanical strength. (62,70)	Surface coatings for dental implants to prevent peri-implantitis.
Magnesium oxide nanoparticles (16)	Nano-MgO	Antibacterial by alkaline pH and ROS release (1)	Biocompatible, promotes osteogenesis.	Bone regeneration and antibacterial dental pastes.
Copper Nanoparticle(70)		It has strong antimicrobial activity against various periodontal pathogens, disrupting bacterial cell walls, metabolic activities, and producing reactive oxygen species(1)	antibacterial properties.(73)	treatments for periodontitis is due to their enhanced photothermal properties and anti-inflammatory effects.(76)

Table No.3. Inorganic nanoparticle (16)

5.3. Traditional methods for synthesis nanoparticle(63)**:**

To control particle size, traditional techniques like thermal breakdown, microwave irradiation, and ultrasonication need specialized equipment and high energy inputs (47). Traditional nanoparticle creation methods have drawbacks like environmental impact, chemical hazards, energy-intensive procedures, shape control, cost, equipment, labour, and time (77,78)**.**

Techniques for producing nanoparticles using classical methods are as follows:

Method	Principle/Process	Features
Chemical Reduction	It involves reducing metal ions in solution with RA such as sodium borohydride or trisodium citrate, and then stabilizing the result with a capping agent	Common for metal nanoparticles like gold and silver.

Co-precipitation	Synthesis involves combining metal ion-containing solutions, causing precipitation and producing nanoparticles by the process of mixing liquids.	Simple, fast, often used for magnetic nanoparticles.
Sol-gel	The process involves combining a metal salt with a solvent and gelling agent, evaporated, and heated to solidify and form nanoparticles	Produces oxides like silica, titania; good chemical control.
Micro-emulsion	It involves reducing metal ions in solution with RA such as sodium borohydride or trisodium citrate, and then stabilizing the result with a capping agent.	Offers narrow size distribution; surfactants are necessary.

Table No.4. Techniques for creating nanoparticle by traditional method (16)

5.4. Methods/approaches /synthesis for producing nanoparticles-(79)

Nanoparticles are synthesized by two method such as top-down method and bottom-up method. The various Synthesis Methods and approaches for synthesis nanoparticles are mentioned in Figure No.6 and Figure No.7.

1. **Top-Down approach/Physical Approach** (78,80)

The top-down strategy employs strategies to convert bigger bulk materials to microscopic nanoparticles by using techniques such as electrospinning, laser ablation, sputtering, electron explosion, sonication, microwave (MW) irradiation lithography or milling(1,63,66,81). Evaporation and condensation are widely recognized physical processes that enable the creation of nanoparticles by vaporizing material (82).

2. **Bottom-up approach**(80,83)

Bottom-up techniques combine tiny atoms and molecules to produce nanostructured particles(81,82).In order to create more complicated assemblies, nanoparticles are created from "building blocks" of atoms or molecules(78). The "bottom-up" strategy is better to the "top-down" method since it requires less specialized equipment and generates nanoparticles faster(47,78).The various technique for producing nanoparticle is mentioned in Figure No.5.

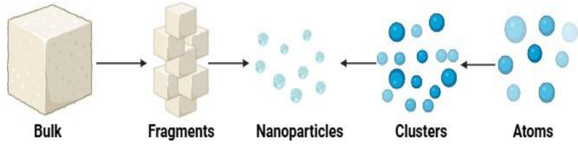

Figure No. 5.: Techniques for producing nanoparticles(84)

a) Chemical Approach:(63)

In the bottom-up approach, NPs are assembled using a chemical process from atomic or molecular components like self-assembly, spinning, sol-gel synthesis, hydrothermal, laser ablation, ion sputtering and Chemical Vapor Deposition (CVD) (63).The primary elements of chemical method are the Reducing Agents (RA) (both organic and inorganic), Stabilizing Agents SA, and Metallic Agent(MA) (66,82).NPs are available in various forms such as colloidal solutions, gels, and powders; their properties influence their applicability for specific applications.(1,81) These methods have several drawbacks, including high equipment costs, need skilled labour, and their environmental impact(66).

b) Green Approach:(66)

Green synthesis offers the potential to revolutionize a number of scientific disciplines and industrial processes by adopting a more sustainable and ecologically friendly paradigm(77) .Green synthesis has been designed to overcome disadvantages of conventional approaches(63,78) .Biomolecules like flavonoids, terpenoids, alkaloids, and polysaccharides that are present in bacteria, yeast, fungi, algae, plant materials, and biowastes are used for production of green nanoparticles(47,54,83,85,86).The features of green-synthesised nanoparticles include high porosity, dispersibility, hydrophobicity, hydrophilicity, nanosized, robust mechanical capabilities, and enhanced surface area(47,85).

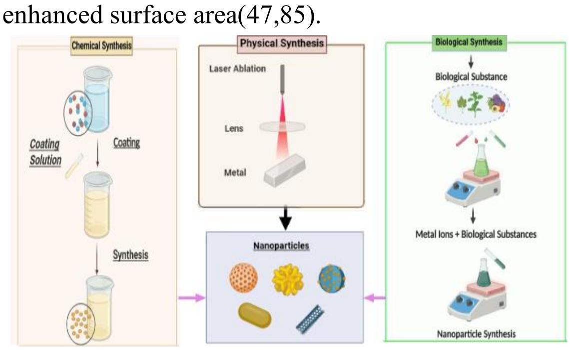

Figure No.6.: Synthesis Methods for Nanoparticles: (a) Chemical Synthesis method (b)Physical Synthesis method (c) Biological Synthesis method(87)

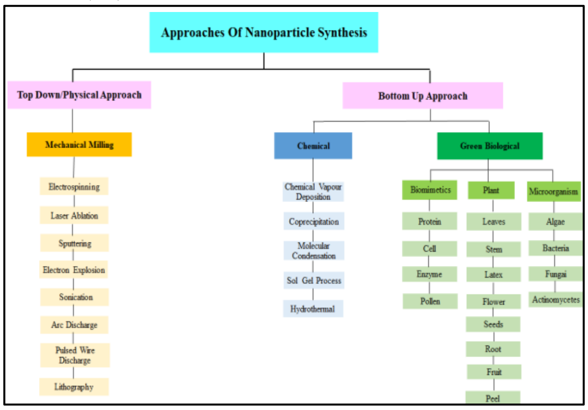

Figure No.7.: Approaches of nanoparticle synthesis(87)

5.5. Mechanism of metal nanoparticle synthesis: (78)

The article provides an overview of principles for environmentally friendly nanoparticle production using plant extracts(88).The quantity(concentration) of phytochemicals in plant leaf extract is crucial for producing nanoparticles(89).Nanoparticle have a huge impact on the medical field, however how much of an impact they have depends on dosage. If not, they might have a negative impact on the body. For sustainable development, the right technique for creating nanoparticles is essential(31). Since plants are special sources of ingredients with a variety of properties, choosing the perfect sample will yield the greatest results(90).The process involves four stages: Nucleation, activation, growth, and termination(72).

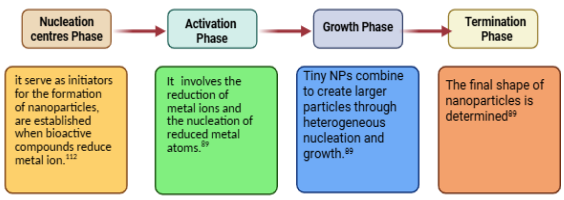

Figure No.8. Mechanism for synthesis of metal nanoparticle

5.6. Green synthesis mechanism: General overview

The green synthesis process involves 4 steps: selecting biological agent, preparing extract, reducing metal ions and characterizing nanoparticle(31).

a) Selection of Green plant for treatment of periodontal drug delivery system:(86)

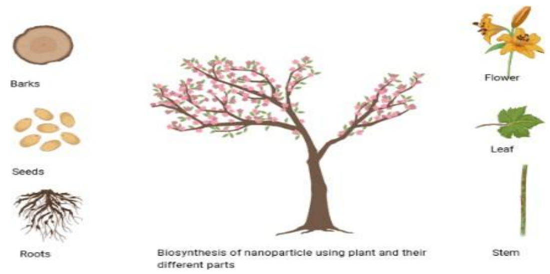

Figure No.9: Nanoparticle production mediated by plants.(87)

Plant parts like leaves, fruits, roots, stems, and seeds contain bioactive compound that act as capping and reducing agent can be utilized(47,69,71).The origin of plant extract can affect the properties of nanoparticles (81). Plants produce a chemical compound known as phytochemical. (86).These are the products of primary or secondary plant metabolism(86).The synthesis of nanoparticles with different sizes, shapes, and surface characteristics is made possible by the chemical variety(88).Biological agents are chosen based on the desired nanoparticle type (90).For ex. fungus can be used to create gold nanoparticles, and plant extracts high in flavonoids and phenols are best suited to create silver nanoparticles(90).The nanoparticles production depends on plant extract and type of nanoparticles produced(86). These plants are selected for their bioactive compounds that exhibit properties beneficial for managing periodontal diseases such as reducing microbial infection, inflammation, and oxidative damage. The synthesis of therapeutic agents based on these phytochemicals can offer natural, effective adjuncts or alternatives to conventional periodontal treatments. Figure no. 10 indicates the merits and demerits of utilization of plant extract for nanoparticle synthesis.

The classification of phytochemicals is mentioned in figure No.11. A summary of various types of nanoparticles produced by using phytochemicals present in plants for periodontal therapy is provided in table No.5.

Plant Source	**Phytochemical**	**Nanoparticle Type**	**Target Pathogens**	**Effects**
Curcuma longa	Curcumin	Chitosan nanoparticles	*P. gingivalis, A. actinomycetemcomitans*	Antibacterial, anti-inflammatory

Camellia sinensis	EGCG	Gold nanoparticles	Periodontal biofilm species[111]	Biofilm disruption, cytokine suppression
Ocimum sanctum	Terpenoid, Flavonoids	Silver nanoparticles	*F. nucleatum, P. intermedia*	Antimicrobial Against gram positive & gram-negative bacteria
Azadirachta indica	Flavonoids Quercetin	Silver nanoparticles	gram-negative bacteria	Synergistic antimicrobial, immunomodulation
Allium cepa	Quercetin	Lipid nanoparticles	Gingival fibroblasts (oxidative stress)	Antioxidant, anti-MMP

Table 5: Overview of Selected Nanoparticles Based on Phytochemicals for Periodontal Treatment

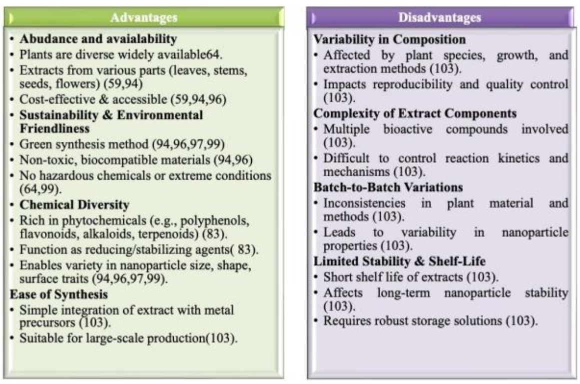

Figure No.13: Technique for producing nanoparticles from plant extract(71)

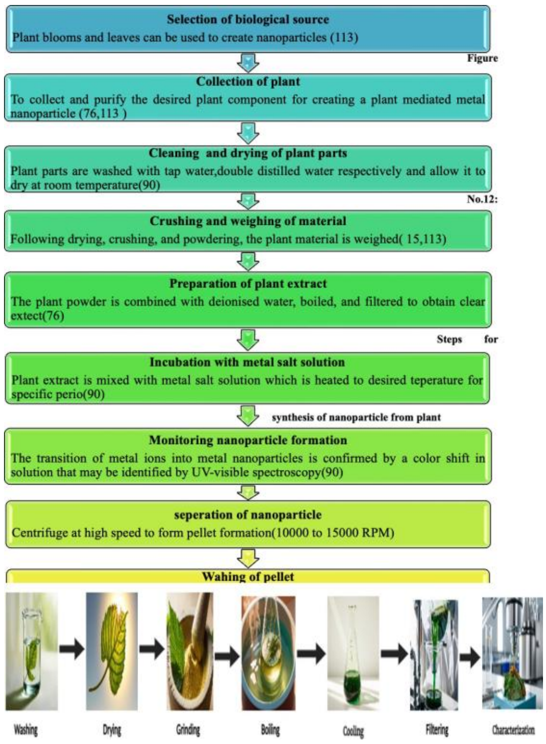

Figure No.12: Steps for synthesis of nanoparticle from plant

b) Reduction of metal ion:

Phytochemical ingredients are used in the manufacture of eco-friendly nanoparticles to lower and stabilize metal ions(73).Phytochemical enables the plant to fight off many viral or bacterial diseases (86).These phytochemical substances can actively chelate metal ions and transform them into nanoparticles(73). Phenolic compounds in plant extracts are antioxidants due to their redox properties, neutralizing free radicals and reducing metallic ions to nanoparticles. Phyto nanofabrication does not require cell cultures, extended incubation periods, or high temperatures as like bacteria and fungi(89).

5.7. Mechanism of Action of Nanoparticle in Periodontal Treatment

Antimicrobial Activity:

Antimicrobial nanoparticles such as metal and metal oxide nanoparticle are used in dentistry to prevent microbial diseases(91).Nanoparticles damage microbial cells by breaking cell walls, disrupting metabolic processes, and producing reactive oxygen species, effectively reducing bacterial load in periodontal pockets(37,92).Herbal extracts and essential oils offer antibacterial qualities, which help inhibit bacterial development and reduce the risk of disease progression in periodontal pathogens(93).

Anti-inflammatory and immunomodulatory Activity:

Green tea and curcumin have immunomodulatory and anti-inflammatory qualities that can help lower periodontal inflammation by blocking pro-inflammatory enzymes and mediators(58).

Antioxidant Activity:

It has been discovered that medicinal plants and herbs can scavenge free radicals and lessen oxidative damage, suggesting their potential in periodontal therapy to mitigate tissue destruction and promote healing(93).

Drug Delivery:

Nanoparticles are effective carrier for the direct administration of antibiotics, anti-inflammatory agents, and growth factors to periodontal tissues(45).It enhance the bioavailability and therapeutic efficacy of drugs by preventing degradation, prolonging release, and improving penetration into periodontal pockets(45).

Example-Thermosensitive gels with fluconazole-loaded solid lipid nanoparticles and clindamycin-loaded noisome have shown efficacy against periodontitis-causing bacteria and fungi(94).

Tissue Regeneration:

Plant-based PELNs are naturally occurring nanocarriers that are packed with lipids, proteins, RNAs, and other active substances(19).Nanoparticles help damaged periodontal tissue to regenerate by offering a scaffold for cell adhesion, proliferation, and differentiation(95).Their ability to enter mammalian cell and control cellular activity suggests that they may be able to control inflammation, immunological responses, microbiome, and tissue regeneration—all of which are important processes that are addressed during the therapy of periodontitis(19).They can also promote bone formation and accelerate tissue regeneration by delivering growth factors and other osteogenic agents to periodontal tissues(62).

Ex. It have been shown to facilitate the development and specialization of critical cell types essential for effective disease treatment and tissue regeneration (62).

5.8. Factors affecting nanoparticle production:

A variety of physiochemical parameters, including metal ion concentration, pH, incubation temperature, and the concentration of reducing agent, stabilizing agent, and biosurfactant, can be changed to create stable NPs(47,69,72).The Figure No.14 indicates the enlist of factors affecting nanoparticle synthesis.

Reducing Agents:

Bioactive compounds such polyphenols, flavonoids, and terpenoids are present in plant extracts act as stabilizing and reducing agents during the creation of nanoparticles(88).Among several natural substances, polysaccharide is an excellent scaffold for NP production(88).In the precursor solution, electrons are provided to metal ions, enabling their reduction and subsequent production into nanoparticles(72,88).

Stabilization and Capping:

Capping agents are bind directly to nanoparticle surface while stabilizing agent prevent aggregation of particle(88).

Biosurfactant:

The biosurfactants' surface binding inhibits the clustering process to varying degrees, resulting in the generation of NPs of variable sizes(69).NPs with high biosurfactant activity shrink in size, whereas those with low biosurfactant activity enlarge and contract(69).

pH(72)**:**

pH significantly influences nanoparticle synthesis by affecting nucleation rate, particle size, shape, stability, and overall morphology(78).Low pH tends to produce large particle or agglomeration due to reduced stability and slower nucleation(78).High pH tends to produce smaller and uniform nanoparticles due to faster nucleation and better stabilization(78).Certain nanoparticles require acidic or alkaline conditions for synthesis(96).Magnetic nanoparticles are created at alkaline pH, whereas metal oxide nanoparticles are typically synthesized at acidic or neutral pH(78).

Temperature(72)**:**

Temperature significantly impacts synthesis, size, and shape of various materials like spherical, prismatic, flakes, triangular, and octahedral(78).Rising temperatures increase reaction rate and nucleation centre formation, leading to higher yields(78).Temperature affect size and morphology of nanoparticles by influencing reaction kinetics, with an increase in size reported at higher temperatures(88).

Time:(72)

The parameter significantly influences nanoparticle size, with longer reaction periods resulting in larger nanoparticles and higher yields due to increased reactant interaction(78).

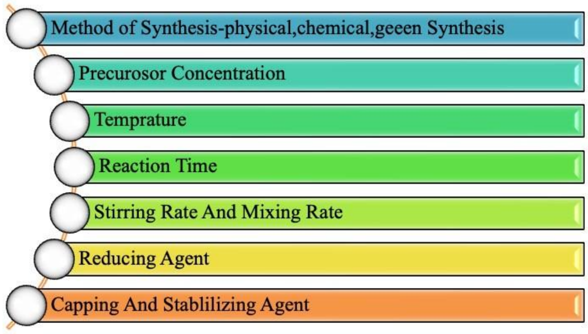

Figure No.14. Factors affecting nanoparticle production

Mechanism based on microorganisms

Different bacteria produce metal nanoparticles (NPs) through various mechanisms, but the bio reduction mechanisms underlying their production remain poorly understood (89).

5.9. Characterization of nanoparticle(1)

Several ways to assess the form of NPs are mentioned in following Table No.6.

Category	Parameter	Techniques	Purpose
Physical	Particle size (97,98)	DLS (99),TEM (99),SEM (71,97)	Determine size and polydispersity (97)
	Shape and Morphology (97,98)	TEM (99),SEM (71,97)	Reveals geometry (rod, cubic, spherical) (71,97)
	Surface area	BET Analysis (97)	Important for adsorption (97)
	Pore size	BJH Method (97)	Relevant for porous nanoparticle (97)
Structural	Crystallinity (97)	X ray Diffraction (97)	Identify structure (97)
	Lattice arrangement	TEM (99)	Confirm crystalline order (99)
Surface and Chemical	Surface Functional Group	FTIR (71,100) Raman Spectroscopy (71,100)	Detects capping/stabilizing agents (71,100)
	Elemental composition	XPS	Determines elements and their oxidation
	Surface charge	Zeta Potential Analysis	Assesses colloidal stability
Optical and Electronic	Optical Absorption	UV Vis Spectroscopy	Surface plasma resonance, band gap
Thermal and stability	Thermal stability (97)	TGA, DSC (97)	Evaluate decomposition, thermal behaviour (97)
	Suspension stability	Zeta Potential (97), DLS	Monitor aggregation (97)
	Drug Release Profile (98)	HPLC, invitro drug release (98)	Studies drug release kinetics (98)

Table No.6. Characterization of Nanoparticle

5.10. Application:

Local drug delivery:

Nanoparticles have been employed as local drug delivery methods for periodontitis therapy, allowing therapeutic drugs to be released in controlled and sustained doses directly into periodontal pockets(35). Local delivery systems include fibres, films, strips, compacts, injectables, microparticles, gels, and nanoparticles(101).P. Kadam et al. (2020) found that subgingival local medication delivery of silver nanoparticles was just as effective as tetracycline in treating chronic periodontitis patients(37).

Guided Tissue Regeneration (GTR)

GTR membranes have been enhanced with nanoparticles to improve biocompatibility, mechanical characteristics, and regenerative potential(2).These barriers can inhibit epithelial cells from migrating into the periodontal defect, allowing for selective repopulation with bone-forming cell(2).It has been stated by Wang et al., 2024 that nanomaterials have the ability to promote osteogenic repair and tissue regeneration, creating a favourable microenvironment for healing(102) .

For example, membranes incorporating nanoparticles mixed with metronidazole have been found to increase medication penetration and promote periodontal tissue regeneration.

Antibacterial Therapy:

To eradicate periodontal infections, nanoparticles with built-in antibacterial properties, including AgNPs and ZnO NPs, have been employed as supplements to mechanical debridement(91).Nanoparticles can improve periodontal therapy results by effectively eliminating bacteria, stopping biofilm formation, and reducing inflammation(74).It has been stated by Wang et al., 2024 that the excellent antibacterial properties are exhibited by nanoparticles, which are essential in the fight against bacterial infections linked to periodontitis(102).It has been studied by Ton et al.,2023 that in a rat model, linked ferromagnetic nanoparticles effectively eliminated periodontal biofilm(74).

Photodynamic therapy:

Nanoparticles can improve the efficacy of Photodynamic Therapy (PDT) for treating periodontal disease(32,103).Nanoparticles can improve PDT selectivity and efficiency by delivering photosensitizers directly to the site of infection, resulting in bacterial cell killing and reduced periodontal inflammation(103).

Novel administration Systems:

It has been revealed by Agrawal et al., 2023 that by controlling medication administration, nanoparticles can improve therapeutic agents' effectiveness and lessen systemic negative effects(104).

5.9. Conclusion

Nanotechnology has shown promise in predicting, detecting, and treating oral disorders such tooth caries and periodontal disease(60).Nanomaterial advancements are crucial for commercial applications in detecting and treating periodontal disorders, highlighting the importance of tailored nanomaterial development. (105).

Advancements in nanotechnology and understanding of periodontitis pathogenesis suggest nanoparticles could transform periodontal care, improve long-term outcomes, and develop effective intra-pocket drug delivery systems.

Green synthesis is a sustainable, eco-friendly method that utilizes plants, fungi, bacteria, and algae to create non-toxic, antibacterial, antioxidant nanoparticles due to their abundance, chemical diversity, and ease of synthesis(88).

Plant extracts can hinder nanoparticle production due to composition heterogeneity, complexity, and instability. To lessen the harmful effects of physical and chemical processes, metal nanoparticles for green synthesis have been successfully created utilizing microorganisms and plant extracts. These nanoparticles contain active biological molecules that function as chelating, stabilizing, or reducing agents to convert ionic metal into a metal.

The phytochemicals in plants influence reaction rates, making metallic nanoparticles crucial for various applications like medication transportation, periodontal treatment, cancer treatment, and biosensor development. Additional research and development are necessary to fully harness the promise and overcome the limitations of plant extracts(88).Nanoparticles are extensively studied for their extraordinary qualities, with a future emphasis on developing toxicity-free, antimicrobial effects. The controlled LDDS delivery system is regarded as the most promising for rapid treatment, pain relief, faster recovery, and comfort.

Future Scope:

Looking ahead, this study has a lot of interesting potential. Plant-based formulations can improve treatment outcomes while minimizing unwanted adverse effects(93).Nanoparticles are one type of targeted drug delivery technology that can enhance local release of natural chemicals, leading to greater bioavailability and efficacy (93).It may be possible to create potent formulations with enhanced therapeutic advantages through ongoing synthesis process development and optimization techniques. Novel treatments for periodontal diseases could result from examining possible synergistic effects with other medicinal medications. Establishing guidelines, rules, and quality standards for the effectiveness and safety of new periodontal medications should be the main goal of future initiatives.(93).

List of abbreviation

- Periodontal Drug Delivery Systems (PDDS)
- Periodontal Ligament (PDL)
- Gingival Cervical Fluid (GCF)
- Reducing Agents (RA)
- Stabilizing Agents (SA)
- Metallic Agent (MA)
- Reactive Oxygen Species (ROS)
- Plant-Derived Extracellular-Like Nanoparticles (PELNs)
- Nanoparticle (NP)
- Guided Tissue Regeneration (GTR)
- Photodynamic Therapy (PDT)
- Local Drug Delivery System LDDS
- Matrix Metallo Proteinases (MMPs)
- Dynamic Light Scattering (DLS)
- Barrett-Joyner-Halenda (BJH)
- Nanoparticle Tracking Analysis (NTA)
- Brunauer-Emmett-Teller (BET)
- Transmission Electron Microscopy (TEM)
- Scanning Electron Microscope (SEM)
- Fourier Transform Infrared Spectroscopy (FTIR)
- X-Ray Diffraction (XRD)
- X-Ray Photoelectron Spectroscopy (XPS)
- Differential Scanning Calorimetry (DSC)

List of Diagram:

List of Tables:

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