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Review Article

Plant Extracts Mediated Synthesis of Nanoparticles: A Review of Innovations for Dentistry

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Abstract

Lately, nanotechnology has made significant advancements in various scientific and medical fields, including dentistry, by developing nanoparticles with distinct chemical and physical properties. Green synthesis is considered an eco-friendly alternative and a safe and sustainable method compared to conventional chemical and physical synthesis methods, which often contain toxic and environmentally harmful materials. This method is also cost-effective, biocompatible, and consumes less energy, thereby reducing pollution and environmental hazards, and making it suitable for various biomedical applications. Many nanoparticles have been employed in dentistry to enhance preventive treatments, including dental implants, orthodontics, the treatment of tooth decay bacteria, and endodontics. Despite their numerous benefits in the dental field, nanoparticles can exhibit toxicity risks, long-term impacts, and limited stability that require further investigation before their use in clinical applications. This review analyzes and classifies over 70 studies from the past 10 years based on plant extract source, nanoparticle types, and dental applications. We offer a new classification framework that organizes nanoparticles synthesized using green methods according to their manufacturing process and functional applications in dentistry. Comparative analysis reveals that, for instance, zinc oxide and silver nanoparticles synthesized through a green process exhibit the highest antibacterial activity with low toxicity. This review highlights current research gaps in biostability and toxicity, and provides insights into potential clinical applications and future research directions. It focuses on the role and benefits of the green method in improving the properties of nanoparticles, as well as its impact and effectiveness in developing dental materials and mitigating biological risks, opening up broad and new horizons in advanced dental treatments.

Keywords: *Nanoparticles, Green Synthesis, Plant Extract, Dentistry, Nanocomposite*

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1. Introduction

Nanotechnology is a pioneering discovery in the field of science. Its diverse applications have led to innovative approaches to producing higher-quality nanomaterials [1]. Nanotechnology involves the scientific manipulation of materials on the molecular level, typically ranging in size from 1 to 100 nm. Rapid advances in this field have opened up new fundamental and applied opportunities in science and engineering [2]. These include nanobiotechnology, bionanotechnology, quantum dots, surface-enhanced Raman scattering, and applied microbiology [3-6]. It is increasingly important in diverse fields such as mechanics, optics, chemical industry, biomedical sciences, electronics, aerospace, catalysis, energy science, photoelectrochemical applications, optoelectronics, and nonlinear optical devices [2]. Nanotechnology is an interdisciplinary field that enables the development of novel materials with unique and valuable characteristics. These materials, known as nanomaterials, are composed of nanoparticles [7].

Nanomaterials are materials with dimensions ranging from 1 to 100 nm. Nanoparticles have a higher surface-to-volume ratio due to their small size, compared to bulk materials. This larger surface area indicates a greater number of active sites, resulting in improved chemical interactions and more rapid adsorption and absorption processes. Metal nanoparticles (e.g., nano-alumina, titanium, and nano-silica show unique optical and physical properties that vary depending on their particle size and shape. In contrast, bulk materials have particle sizes larger than 100 nm and have a smaller surface-to-volume ratio. As a result, their chemical and physical properties remain stable, regardless of size and shape. Absorption and adsorption of molecules in bulk materials are slower and less efficient. Bulk materials involve salts, cement, and alumina [8]. Nanoparticles are tiny particles. They can involve metal oxides, carbon, metals, and organic matter [9]. Compared to larger particles, these particles display unique chemical, biological, and physical properties at the nanoscale. This phenomenon is attributed to a relatively large surface area-to-volume ratio, which enhances reactivity and stability in chemical processes, as well as mechanical strength. These distinctive properties of nanoparticles led to their use in several applications [10]. Nanoparticles vary in dimensions, shapes, sizes, and materials. They can be classified based on their dimensionality: zero-, one-, two-, and three-dimensional. Zero-dimensional nanoparticles, such as nanodots, are characterized by having fixed dimensions (height, length, and breadth) at a singular point. One-dimensional nanoparticles, like nanotubes, possess only one measurable parameter. Two-dimensional nanoparticles, such as nanosheets, have both length and breadth. Like gold nanoparticles, three-dimensional nanoparticles encompass all three parameters (length, breadth, and height) [11]. Nanoparticles can take on various shapes, including cylindrical, spherical, tubular, hollow-core, conical, flat, and spiral forms. Their surfaces can be irregular or uniform. Additionally, nanoparticles are amorphous or crystalline, consisting of a single or multiple crystalline solids that can be either loose or agglomerated [12].

Nanostructures or nano-sized materials can be synthesized through various methods, generally categorized into two main approaches: top-down, which involves breaking down larger molecules or bulk matter into smaller molecules, and then transforming them into nanoparticles. Examples of top-down synthesis techniques include grinding, physical vapor deposition, and laser ablation [1, 12]. Bottom-up syntheses are created from simpler materials (atoms or molecules). This method involves synthesizing materials from atoms to clusters, thereby forming nanoparticles. Chemical methods involve chemical vapor deposition, spinning, pyrolysis, and sol-gel processing, whereas biological methods include bacteria, plants, and other organisms (Fig. 1) [13, 14]. Conventional nanoparticle synthesis methods are not preferred because they depend on carcinogenic chemicals and high-energy inputs to produce nanomaterials. The contamination generated by these

traditional methods highlight the urgent need for more environmentally sustainable synthesis techniques.

Like plant-based green synthesis, Pulse Laser Ablation in Liquid (PLAL) is also considered a clean or chemical-free method in the synthesis of nanoparticles. Both methods eliminate the use of toxic chemical materials and resulting nanoparticles, resulting in lower surface pollution. PLAL relies on laser ablation, a physical process rather than a biological agent, which provides greater purity and better size control. In contrast, green synthesis is a cost-effective, eco-friendly, and scalable method that utilizes natural plant extracts [15].

Green synthesis is one such technique and is a highly efficient method. It provides an eco-friendly approach to manufacturing nanomaterials by utilizing raw materials from natural sources and employing low-energy processes [1]. This technique integrates biological methods, such as those using fungi, bacteria, plants, and yeast, making it a more eco-friendly and safer alternative to traditional methods. Plant extracts have been widely utilized due to their large and readily available reserves, safe use, availability of various metabolites with high reduction potential, low energy costs, and low waste [16]. Current green synthesis methods utilize plants or plant parts to reduce metal ions into their corresponding nanomaterials biologically. These methods are cost-effective and free from chemical contaminants, which is of great significance in the biomedical domain due to concerns about the purity of nanomaterials [17, 18].

The green synthesis process usually yields between 80% and 85%, depending on the natural source and optimizing parameters such as extract concentration and pH. Green synthesis efficiency also drops from 80–90%; for example, an efficiency of approximately 85% was achieved in silver nanoparticles synthesized employing citrus limon extract after 48 hours. On the contrary, traditional methods show significant improvements, producing yields over 90%, like 92–95% when utilizing gold chloride reduced by sodium citrate. This method exhibits 95–98% interaction efficiencies, with interaction times ranging from ten minutes to one hour, depending on specific synthesis conditions [19].

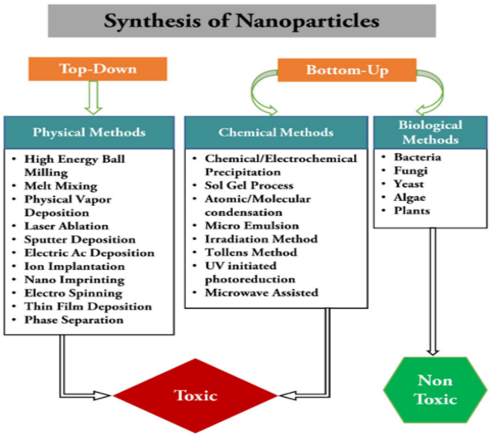

Figure 1. Illustrates the synthesis methods of NPs [14]

Nanotechnology has contributed significantly to the progression of the healthcare sector. The applications of nanotechnology are a fundamental pillar of newfangled medicine and dentistry. Nanoparticles (NPs) are now widely employed in dental prosthetics, where they are combined into Polymethyl Methacrylate denture bases to improve their poor mechanical properties, such as impact resistance [20]. Their use has increased in multiple areas of dentistry, including dental diagnostics, cosmetic dentistry, dental materials, preventive dentistry, dentures, endodontics, periodontics, and dental implants [21]. Nanotechnology also contributes to the tools employed by dentists, such as light-emitting diode (LED) light-curing units [22], the protection of dental hard tissues from acidic foods [23], and the characterization of dental hard tissues and dental materials [24], among other applications. Nanoparticles have a variety of essential applications in different branches of dentistry, illustrated in Fig. 2 [25].

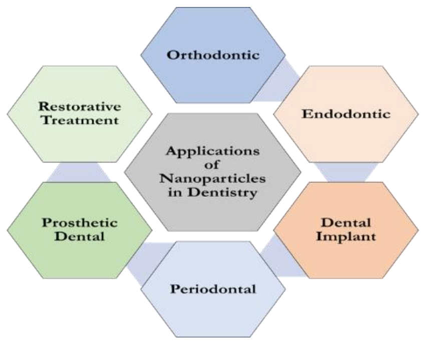

Figure 2. Illustrates the applications of NPs for dentistry [25]

In restorative dentistry, nanoparticles are incorporated into dental composites to enhance mechanical properties, improve aesthetic appearance, and reduce shrinkage [26]. Antimicrobial nanoparticles like silver and zinc oxide inhibit bacterial growth, thereby reducing the infection hazard [27]. In addition,

nanoparticles play a vital role in endodontics, where they are utilized in drug delivery, tissue regeneration,
and removing bacteria and biofilms, thereby contributing to enhanced oral health [28].
In preventive dentistry, nanoparticles, such as calcium phosphate and hydroxyapatite, play a significant role in remineralizing tooth enamel and preventing tooth decay. Additionally, in dental implants, nanoparticles enhance osseointegration and surface adhesion, improving treatment outcomes. Modern advances have enabled the utilization of nanoparticles in developing adhesives that help reduce biofilm buildup and improve oral health [29]. This review aims to highlight innovations in NP synthesis utilizing plants, focusing on their possible advantages and applications in the dental field.

2. Eco-Friendly Synthesis of Nanoparticles

Conventional methods include physical and chemical techniques. Physical methods are top-down and include milling, physical vapor deposition, and laser ablation. These methods require high energy and bulky equipment, and one drawback is the difficulty of producing nanoparticles of complex sizes and shapes. Chemical methods are bottom-up, including chemical vapor deposition, spinning, pyrolysis, and sol-gel processing. These methods often employ harmful reducing agents and toxic solvents. These conventional methods have significant health and environmental hazards due to high temperatures and the release of poisonous substances. Therefore, environmentally friendly and safe methods, including biological methods, have been adopted [12]. Biological synthesis is an eco-friendly alternative that reduces environmental and human toxicity. Microorganisms, such as yeast, fungi, bacteria, viruses, and algae, have been utilized to synthesize nanoparticles because of their adaptability, ease of growth in artificial conditions, and enzymatic ability to reduce metal ions. Plant extracts are a branch of the biological approach. It is of broad interest due to its eco-friendly capability to produce stable NPs without toxic materials, and cost-effectiveness [30, 31]. Green synthesis is a cutting-edge branch of green chemistry, as it employs sustainable processes. Green chemistry aims to evolve safer products and decrease the use and manufacture of hazardous components [32]. One of the major disadvantages of traditional methods for synthesizing nanoparticles is the production of heterogeneous mixtures with irregular shapes, which may be harmful to the environment due to the utilization of toxic chemical materials and high temperatures [33]. Consequently, the biological method has been suggested as an eco-friendly alternative to traditional methods for manufacturing nanoparticles. This approach does not require expensive, harmful, or toxic
chemical materials. Recently, biological methods have been widely used to manufacture nanoparticles with various shapes, sizes, compositions, and physical and chemical properties [34]. Nanoparticles produced using plant extracts and microorganisms are stable and may be monodispersed by controlling synthetic parameters like pH, temperature, incubation period, and mixing proportion. Among the existing biological alternatives, plants and their extracts are a promising option due to plants' ability to produce various chemical compounds naturally [35]. The advantages of green or biological synthesis include energy efficiency, reduced waste, environmental friendliness, economic benefits, low-cost production, safe products, and Protection of human health and communities [36]. In conventional methods, the reducing agents used to reduce mineral ions and the stabilizers utilized to prevent unwanted agglomeration of the resulting nanoparticles pose toxic hazards to the cells and environment. Further, the contents of the resulting nanoparticles are believed to be harmful in terms of size, shape, and surface chemistry. Nanoparticles from green synthesis are biocompatible, and the agents used in this method are naturally present in living organisms [17]. Significant advantages and disadvantages exist between green synthesis and conventional techniques, which are illustrated in Fig. 3 [37].

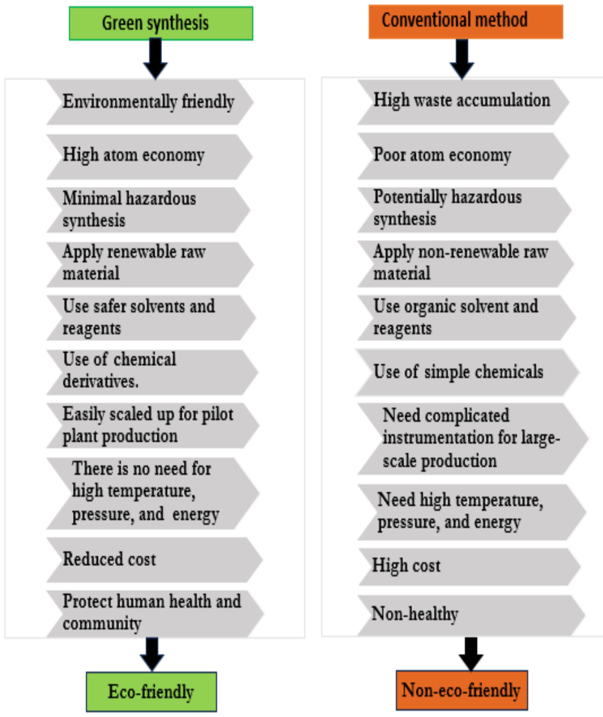

Figure 3. The differences between green synthesis and the conventional method [37]

2.1. Eco-Friendly Synthesis of Nanoparticles Using Plant Extract

Green synthesis method using plants for nanoparticles is considered the most efficient compared to other green synthesis methods because it produces a larger quantity of nanoparticles due to the ability of plants to maintain the stability of the synthesized nanoparticles inside them. This stability is due to the metabolites and biochemical compounds present in plants. Therefore, this method is considered economical and environmentally friendly [38]. One of the critical reasons for searching for plants to create nanoparticles is their ease of access. Metallic nanoparticles can be prepared utilizing an extract of a specific plant part, a powder resulting from the plant, or the entire plant [39]. The synthesis of nanoparticles (NPs) involves mixing plant biomass or plant extract with a metal salt solution at a specific pH level and temperature. A color change in the solution is A primary indication of successful synthesis of nanoparticles [31].

The nanoparticle synthesis procedure involves several steps. First, plant collection and preparation involve collecting and washing the leaves of the plants required for nanoparticle preparation thoroughly with distilled water to remove any impurities. Air drying it at room temperature (25 °C) for 48 hours, and then grinding to produce a powder substance. Second is the production of Plant Extract, where a specific amount of plant powder is dissolved in a particular volume of distilled water and boiled for approximately 30 minutes. The solution is then filtered using filter paper (Whatman), thus obtaining the plant extract. Third, to form nanoparticles, a specific volume of a metal salt solution, such as silver nitrate, is added to a particular volume of the plant extract at approximately 70°C under continuous stirring using a magnetic stir bar. When the color of the solution changes, this indicates successful nanoparticle formation. Lastly, the nanoparticles are separated using a centrifuge for 15 minutes, then washed with ethanol and distilled water. They are then placed in an oven at 400–600°C to produce powdered nanoparticles. The resulting nanoparticles' optical properties, shape, size, and crystal structure are determined using XRD, UV-visible, SEM, and TEM [40-42]. The main procedures for synthesizing NPs (e.g., Ag NPs) using plant extracts are shown in Fig. 4 [43].

The advantages of employing plant extracts in the manufacture of nanoparticles are that it uses natural aqueous solvents, it is an easy process that does not require pressure, high temperatures, or the utilize of toxic chemical materials, it relies on natural stabilizing and reducing agents like proteins, enzymes, alkaloids, polyphenols, saponins, phenols, essential oils, flavonoids, and polyols, it is pollution-free, and has a high reducing potential [39]. These natural stabilizing and reducing agents contain various functional groups, including aldehydes (-CHO), carboxylic acids (-COOH), nitriles (-CN), amines (-NH2), and hydroxyl groups (-OH). These functional groups reduce metal ions into free metals like Cu+2 to Cu0, Ag+ to Ag0, Pt+ to Pt0, Au+ to Au0, and Zn+2 to Zn0 (Fig. 5) [44].

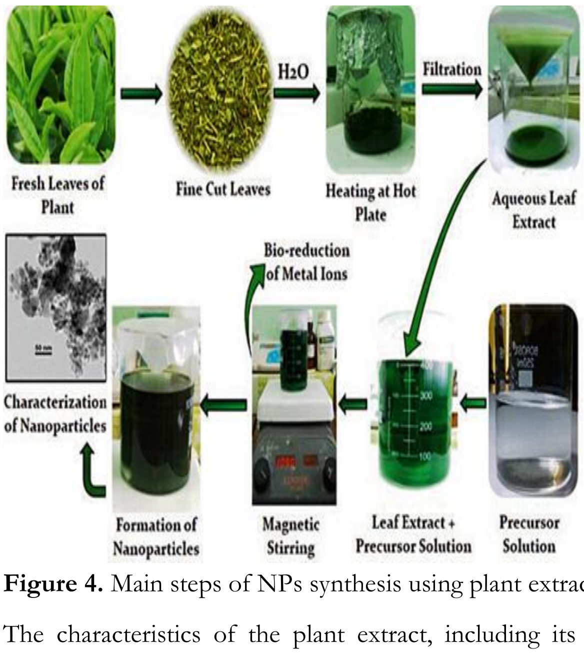

Figure 4. Main steps of NPs synthesis using plant extracts [43]

The characteristics of the plant extract, including its type and concentration, as well as the concentration of the mineral salt, temperature, pH level, and contact time, all impact nanoparticle production, their quantity, and other characteristics [44]. The mechanism of producing metallic and metallic oxide nanoparticles utilizing plants includes three stages. The activation phase is the first and most crucial step in the nanoparticle synthesis process. It involves reducing metal ions in solution to metal atoms (such as Ag+ to Ag0) using active compounds in plant extracts that act as reducing agents, such as terpenoids, phenols, and flavonoids. After the reduction process is complete, the reduced atoms initiate nucleation, accumulating to form small, cluster-like nuclei that serve as the primary sites for nanoparticle growth. In the growth phase, the small nuclei formed during the nucleation process will grow and develop into larger nanoparticles. This process is known as Ostwald ripening, where smaller nanoparticles melt and then reprecipitate onto larger nanoparticles, thereby decreasing surface energy while continuing to reduce metal ions, which in turn increases the formation of new nanoparticles. This stage plays a crucial role in determining the shape and size of the resulting nanoparticles, while also enhancing their thermodynamic stability. The termination Phase is when the nanoparticles complete their growth or formation and reach their final shape and size. The capping agents in the plant extracts stabilize the shape and size of NPs. For mineral oxide nanoparticles, the ultimate product is usually air-dried or roasted in air to produce the required metal oxide nanoparticles. The mechanism of these three stages is illustrated in Fig. 6 [45]. Table 1 summarizes different types of nanoparticles manufactured using plants and used in various dental applications.

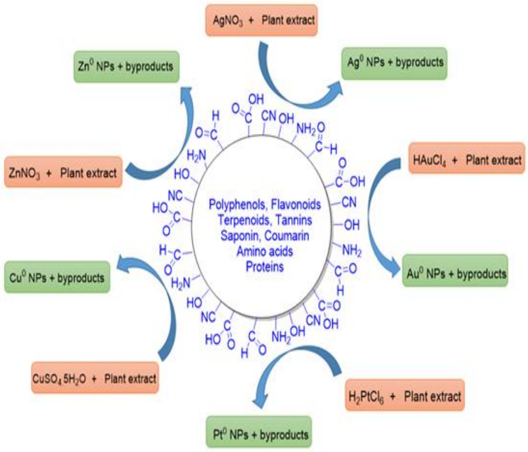

Figure 5. Shows the reducing mechanism for functional groups [44]

Plant extracts that produce smaller NPs are more efficient in antibacterial applications, which is attributed to the larger surface area-to-volume ratio associated with smaller particles [46]. For instance, as shown in Table 1, green tea extract generated the smallest silver nanoparticles of 11 nm compared to other extracts like cinnamon, Allium sativum, and Alocasia indica. Thus, it can be considered a promising choice for the green synthesis of antibacterial nanoparticles.

3. Nanoparticles in Dentistry

Norio Taniguchi introduced the term nanotechnology in 1974 [47] to dentistry, providing an excellent opportunity to develop dental products that can be used in dental implants, restorative dentistry, oral cancers, biomineralization, periodontics, adhesive dentistry, and endodontics [48]. The development of nano-dentistry began in 2000, when nanotechnology had a significant impact on various fields of dentistry.

Nano-dentistry aims to provide overall oral care, enabling the early detection and treatment of dental diseases through diagnostics and therapies that are based on nanotechnology. Many nanoparticles have an effective role in dentistry as antibacterial and antifungal materials, including: nHA, TiO_2, ZnO, and Ag NPs [49].

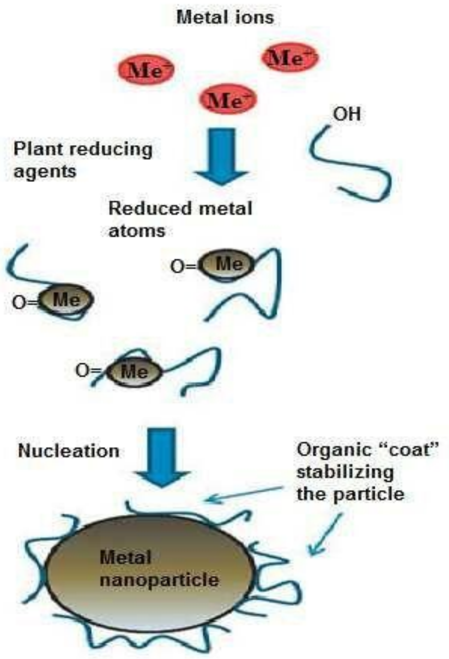

Figure 6. The mechanism of synthesis of NPs by plants [45]

Nanomaterials that have applications in dentistry are classified, based on their shapes, into nano capsules, nanocomposites, solid lipid nanoparticles, nanobubbles, metal nanoparticles, nanospheres, nanotubes, nanofibers, and nanocrystals. Due to their multiple properties, Nanoparticles have many benefits in dental applications. They have antiviral, antifungal, and antimicrobial characteristics and can, therefore, prevent the formation of biofilms when combined with antimicrobial agents in resin composites. They also have a large surface area, which enhances their effectiveness. Additionally, nanoparticles improve the mechanistic characteristics of dental materials, particularly in restorative dentistry. They help prohibit crack diffusion and the development of white stain lesions. Nanoparticles also improve the bond force between biomaterials and dentin and the fracture toughness of porcelain restorations [50]. Nanomedicines employed as dental materials possess unique biological, chemical, and physical characteristics that can be utilized to conquer complications connected with conventional dental medications [51].

Destroyed dental tissues may lead to tooth decay, gum disease, tooth allergy, and pre-cancerous conditions in the mouth. These cases may be treated with therapeutic intervention and biocompatible composite materials. Various types of nanoparticles and nanocomposites have been demonstrated to exhibit characteristics similar to those of host tissues [52]. Despite these developments, challenges such as long-term biocompatibility and toxicity remain active research fields. Regulatory bodies confirm the significance of standardized testing protocols and risk evaluation models to guarantee patient safety.

For example, the use of nHA in toothpaste at up to 10% was recently approved in the European Union after careful assessment of genotoxicity [26, 53, 54]. Safety assessments and regulatory compliance remain vital for the incorporation of nanotechnology in dental practice. An overall comprehension of nanoparticles' physical and chemical characteristics and their interactions in the oral medium is primary for improving their utilization in dentistry [55]. The incorporation of nanomaterials into the drug delivery of dental implants has shown promising clinical results. Afflicted drug delivery methods can alleviate complications with dental implants, decrease inflammation, and improve osseointegration [56]. Furthermore, nanorobots have been suggested as a novel solution to implement several tasks, like dental plaque removal and guided anesthesia [57]. Some advanced nanoparticles that play a significant role in dentistry shall be discussed.

Table 1. Plant-mediated nanoparticles for various dental applications

Plant extract	Nanoparticles	Particle Size (nm)	Shape	Applications	Zone of Inhibition (mm)	Ref.
Alocasia indica	Silver	13.8, 19.6, 24.0	circular	Dental implant, antibacterial	_	[58]
Green tea	Silver	11	Spherical	Antibacterial	_	[59]
Allium sativum Mentha piperita	Silver	78.06 100	Spherical Quasi-spherical	Antibacterial Antibacterial activity of glass ionomer cements	17, 19 11.67±0.29	[60] [61]
cinnamon	Silver	50	Spherical	Antimicrobial	20 ± 0.11, 13 ± 0.07, 14 ± 0.08	[62]
Salvadora persica	Titanium dioxide	8-47	Spherical	Orthodontic	_	[63]
Azadirachta indica, Ficus benghalensis, Syzygium aromaticum	Titanium dioxide	10 – 35	Tetragonal	Antibacterial	8.0, 10.0, 14.0	[64]
Salvadora persica	Nickel	18.20 -45.12	Spherical	Oral microbes	31 ± 0.50	[65]
Fioria vitifolia	Nickel oxide	17–168	Spherical	Antibacterial	21.1 ± 0.2 24.6 ± 0.5	[66]

Cupressus macrocarpa	Copper	11.3-22.4	Spherical to oblong	Periodontal disease-causing microorganisms	_	[67]
Ocimum sanctum	Copper oxide	100	_	Antimicrobial	_	[68]
Licorice root	Sio2	46-77	Spherical	Antibacterial	_	[69]
Clove and Cinnamon	Zinc Oxide	8-12	_	Antimicrobial efficacy against oral pathogens	13, 15	[70]
Chamomile and Ginger Echinacea	Zinc Oxide	20-40	Spherical	Anticariogenic	14 12, 14, 16, 18	[71] [72]
Cissus quadrangularis	Gold	10-50	Spherical	Orthodontic	17, 20	[73]
Curcumin	Gold	20	Spherical	Antimicrobial, anti-inflammatory, and antioxidant activity against oral pathogens	12, 14, 18	[74]
Magnolia champaca Avicennia marina Ficus racemosa	Magnesium Oxide	100 120-150 24-28	Irregular Spherical Nanoflakes	Antibacterial	21 ± 0.22 11 23 ± 0.30	[75] [76] [77]

3.1. Hydroxyapatite Nanoparticles (nHA)

Hydroxyapatite nanoparticles can remineralize carious enamel surfaces due to their surface bioactivity and chemical and physical characteristics that are similar to those of normal tooth enamel. It was found that nHA continuously stimulated the remineralization of enamel caries by forming a homogeneous apatite layer on demineralized enamel surfaces through chemical binding with normal apatite crystals. The elastic modulus and hardness of the restored enamel were identical to those of natural enamel. The surface of the initial enamel lesion had high porosity, allowing excellent penetration of nHA. The surface of nHA helps attract and accumulate phosphate (PO_4^{3-}), calcium (Ca^{2+}), and hydrogen phosphate (HPO_4^{2-}) ions from saliva. These ions are precipitated on the nHA surface, forming a layer that combines with the existing enamel. The structural and chemical resemblance between natural enamel and nHA promotes the mechanical characteristics of enamel, bonding force, and toughness of the restored layer. This process is illustrated in Fig. 7 [78].

A study by Sultan et al. aimed to evaluate the impact of a toothpaste containing hydroxyapatite nanoparticles compared with fluoride toothpaste on the remineralization of carious enamel. The results demonstrated that the toothpaste containing hydroxyapatite nanoparticles and the fluoride toothpaste were equally effective in remineralizing tooth enamel [79].

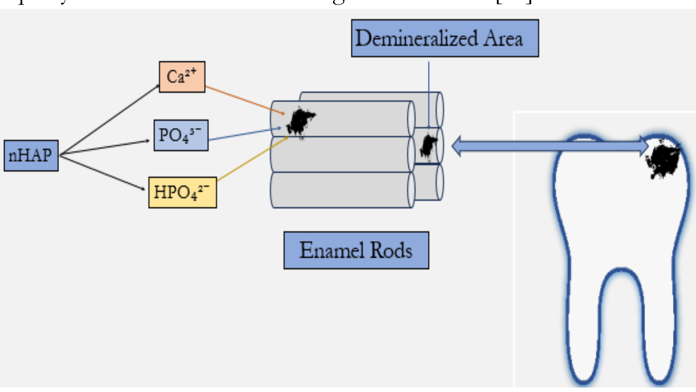

Figure 7: Mechanism of work of Nanohydroxyapatite on primary Enamel Caries [78]

Aliyyu et al. compared toothpaste containing nanohydroxyapatite extracted from rice snail shells and mixed with basil leaf extract, with a fluoride herbal toothpaste, regarding their effectiveness as remineralizing and antibacterial agents. The results showed that the nanohydroxyapatite toothpaste demonstrated antibacterial and remineralizing efficacy similar to the fluoridated herbal toothpaste [80]. An in vitro study showed that toothpaste containing nanohydroxyapatite crystals significantly increased the hardness values of tooth enamel after exposure to a corrosion challenge, compared to the same toothpaste without nanohydroxyapatite [81].

One of the most essential uses of nanohydroxyapatite is as a coating for implants made of titanium and stainless steel, which helps improve the contact between the implant and the bone, as well as enhances the bonding of bones with each other and the formation of new bone. A study conducted by Abdelkarim et al. utilized nanohydroxyapatite as a coating material for dental implants. Titanium discs were plated with hydroxyapatite nanoparticles and zinc oxide nanoparticles. The outcome showed that surfaces coated with nanoparticles (nZnO, nHA) were more effective in reducing bacterial biofilm accumulation than uncoated surfaces, indicating that these particles exhibited antibacterial activity, which contributes to the success of dental implants [82].

Using nanohydroxyapatite to reduce tooth sensitivity resulting from bleaching. Mohamed et al. conducted a study to evaluate the influence of utilizing nanohydroxyapatite on hypersensitivity after bleaching utilizing different bleaching mechanisms. The results showed that nanohydroxyapatite reduced hypersensitivity after tooth bleaching [83].

Recently, nanohydroxyapatite has been utilized as an effective alternative in autologous bone grafting for alveolar and periodontal tissue regeneration because of its biocompatibility features, lack of toxicity, and low morbidity. When combined with other biological materials or active molecules, it promotes periodontal tissue regeneration more than when utilized alone. Studies have confirmed that nanohydroxyapatite is beneficial in treating periodontitis by promoting alveolar bone regeneration. Tanongpitchayes et al. conducted a study on dogs with periodontitis. They used a nanohydroxyapatite-based hydrogel that preserved dental cavities after extraction in dogs with periodontitis. The results showed that it significantly enhanced the regeneration of these cavities; thus, nHA could be considered a bone substitute for protecting dental cavities after extraction, which helps in planning for future dental implant placement [84]. Another study, conducted by Al-Ahmady et al., aimed to evaluate the efficiency of employing platelet-rich fibrin (PRF) with autologous bone marrow mononuclear cells (BMMNCs) and nanohydroxyapatite in bone restoration and the repair of alveolar clefts.

The study was conducted on 20 patients and split into two sets. The first set received treatment using a regenerative technique that involved PRF, BMMNCs, and nanohydroxyapatite. The second set received classic treatment, including the use of alveolar bone grafts from the iliac crest bone. After twelve months, the results exhibited that the first set yielded better outcomes in terms of tissue healing speed, reduced pain, and fewer complications after surgery. The proportion of whole bone fusion in this set was 90%, compared to 70% in the second set. Therefore, the regenerative technique can be considered a favourable and active choice and an alternative to conventional treatment for alveolar clefts [85].

3.2. Silver Nanoparticles (Ag NPs)

Silver nanoparticles exhibit antibacterial properties against oral pathogens and have various applications in dentistry, including the treatment of endodontic diseases, periodontal diseases, and the prevention of tooth decay, as illustrated in Fig. 8 [86]. A study has been conducted on the manufacture of removable dentures, where acrylic resin is a commonly used material. However, this material can be a hotbed for opportunistic oral pathogens, leading to dental infections. This condition can be treated by incorporating silver nanoparticles into the acrylic resin to inhibit the growth of bacteria such as Staphylococcus aureus (S. aureus), Streptococcus mutans (S. mutans), and Escherichia coli (E. coli) [87]. In addition to their antibacterial characteristics, silver nanoparticles integrated into acrylic resin exhibited antifungal characteristics against the adhesion of Candida albicans (C. albicans) denture resin, a significant cause of opportunistic infections on denture bases [88].

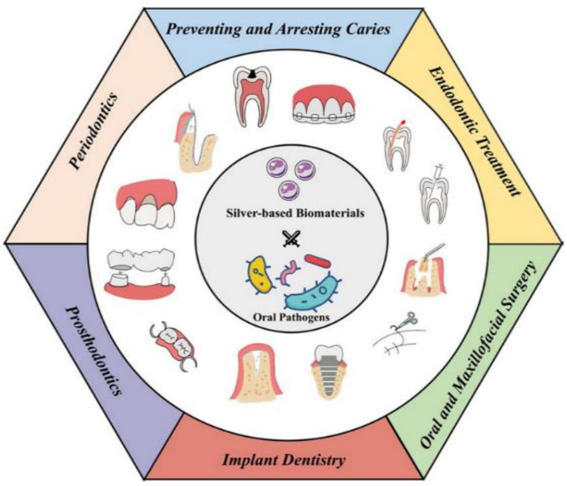

Figure 8. Shows most applications of Ag NPs used in dentistry [86]

Silver nanoparticles increased the modulus of elasticity and flexural force of the acrylic resin while enhancing compressive strength and thermal conductivity of the acrylic base [89]. Silver nanoparticles have antibacterial characteristics, especially against bacteria that cause tooth decay, such as S. mutans. A study by Jiménez-Ramírez et al. evaluated the effectiveness and inhibitory impact of Ag NPs on dental biofilms from individuals with decay-free and decayed teeth. Two specimens of Ag NPs with various sizes were prepared, and plaque specimens were collected from 30 decay-free and 30 decay-affected individuals. The results showed that Ag NPs have an antibacterial impact and can be employed as a therapeutic agent to prevent dental decay [90]. Another study by Al-Ansari et al. utilized Ag NPs in the treatment of S. mutans bacteria. These particles were prepared using gum arabic, which protects and caps the particles. Several techniques, including SEM, UV-visible spectroscopy, TEM, and XRD, were employed to analyze the physical characteristics of the particles. The results demonstrated the effectiveness of Ag NPs in eliminating S. mutans [91]. Enamel decay is a common issue affecting individuals undergoing orthodontic treatment. To solve this problem, silver nanoparticles have been integrated into adhesive materials, such as composite adhesives, to prevent the growth of biofilms. They can also be incorporated into orthodontic elastomeric modules, such as ligatures, which reduces the incidence of enamel decay [92]. The development of a nano-toothbrush by Raval et al., integrating colloidal gold or silver nanoparticles between toothbrush bristles. Further to their ability to enhance plaque removal, the researchers noted the antibacterial activity of the added gold and silver nanoparticles, considerably reducing gum illness [93].

Silver nanoparticles prepared using the leaf extract of Alocasia indica showed 99% inhibition against S. aureus bacteria [58]. An innovative nano-toothpaste (D-nP) has been advanced utilizing calcium sulfate hemihydrate, silver nanoparticles, curcumin nanoparticles, and demineralized bone matrix. The results showed that D-nP performs fantastically for dental tissues in bone repair [94]. Marsala et al. evaluated the effect of silver nanoparticles synthesized from tea extract and silver coated with silica, Ag@SiO2, against S. mutans bacteria. These particles show a substantial antibacterial impact, helping to prevent tooth decay [59].

In a study aimed at evaluating the mechanistic and antibacterial characteristics of dental restorative materials (GIC) modulated with various ratios of graphene and Ag NPs (R-GNs/Ag). R-GNs/Ag nanocomposites demonstrated good antibacterial action, making them a promising choice for enhancing the antibacterial characteristics of dental restorative materials (GIC) [95]. Another study assessed the antibacterial impact of AgNPs incorporated into dental porcelain and their influence on surface hardness and flexural strength. These particles demonstrated significant efficacy in inhibiting bacterial growth and enhancing the flexural force of the ceramics, but they did not affect the surface hardness of porcelain [96].

3.3. Titanium Dioxide Nanoparticles (TiO2)

TiO2 NPs have numerous applications in dentistry, including the surface modification of dental implants, the addition to dental materials, and diagnosis and therapy of oral tumors, as illustrated in Fig. 9. [97]. Two key issues in orthodontics are bond failure and plaque collection. To address this problem, titanium dioxide nanoparticles have been used due to their antimicrobial characteristics. Sudhagar et al. conducted a study to evaluate the antimicrobial and mechanical features of orthodontic composite resins modulated with Titanium dioxide nanoparticles. The results confirmed that Titanium dioxide nanoparticles integrated in the composite resins improve the antibacterial characteristics of the adhesives. At the same time, the bond strength remains within an acceptable range, i.e., Titanium dioxide nanoparticles do not affect the shear bond strength [98]. An in vitro study investigated the shear bond strength (SBS) and antibacterial activity of titanium dioxide nanoparticles when incorporated into orthodontic adhesives, comparing their performance with that of chitosan- and hydroxyapatite-modified adhesives. The results showed that integrating titanium dioxide nanoparticles into orthodontic adhesives optimized their antibacterial effects without negatively impacting the shear bond strength (SBS) [63].

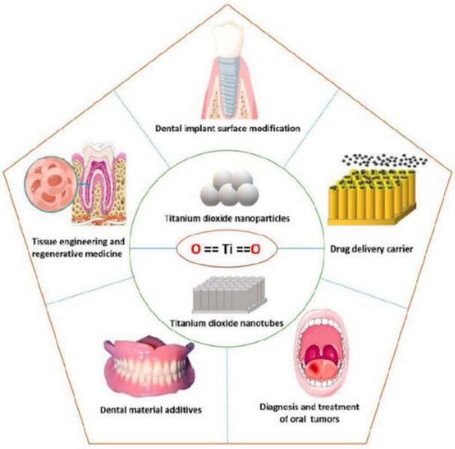

Figure 9. Shows most applications of TiO_2 used in dentistry [97]

Mahmood et al. conducted a study to improve the surface properties of orthodontic wires made of Nickel-Titanium (NiTi) alloy and improve the biocompatibility of this alloy by using a coating consisting of two materials, TiO2 and Ta2O5. These materials were deposited on NiTi alloy substrates using the DC reactive sputtering technique under various power statuses. The results demonstrated that the coating consisting of TiO2 and Ta2O5 improved the biocompatibility of NiTi wires employed in orthodontic treatment, enhancing the cellular behavior and action of orthodontic devices made of NiTi [99].

Mouthwashes containing titanium dioxide nanoparticles help prevent the appearance of unfavorable white spots on teeth after orthodontic treatment [100]. Titanium dioxide nanoparticles have been employed for dentures to improve their antimicrobial features. A study conducted by Ragheb, N., and H. Borg aimed to assess the influence of adding various concentrations of Titanium nanoparticles to acrylic resin polymethyl methacrylate (PMMA). The study was conducted on 24 tooth losses split into three sets. In the first set, eight patients were rehabilitated with complete dentures without the use of nanoparticles. In the second set, eight patients were rehabilitated with dentures containing 1% of Titanium nanoparticles. As for the third group, eight patients were rehabilitated with dentures containing 3% Titanium nanoparticles. After a period of using the dentures, a microbiological examination of the denture surfaces was conducted. The results demonstrate an antimicrobial impact when adding Titanium dioxide nanoparticles at 1% and 3% concentrations to PMMA, which decreases the colonization of Staphylococcus epidermidis (S. epidermidis), S. aureus, and C. albicans compared to traditional dentures [101]. Another study included adding 10% and 20% concentrations of TiO2 NPs to PMMA, where the results showed that these ratios decreased biofilm formation of S.mutans [102].

In a study by Chambers et al., dental resin was produced using Ag-TiO2 nanoparticles to evaluate their antimicrobial properties. The results showed that the Ag-TiO2-filled resin has promising antimicrobial properties [103]. Titanium dioxide nanoparticles have been employed as cosmetic substances in dentistry and have proven to be efficient in teeth whitening. Monteiro et al. conducted a study that involved adding titanium dioxide nanoparticles to a tooth whitening material containing 3.5% hydrogen peroxide (H2O2), which improved the aesthetics of the teeth and enamel color compared to a traditional whitening material containing only 3.5% hydrogen peroxide without Titanium dioxide nanoparticles [104]. A study evaluated the effect of titanium dioxide nanoparticles on the activity of the peroxidase enzyme in the saliva of patients with gingivitis. The study involved 44 persons with gum disease and 31 healthy persons. The results revealed that individuals with gingivitis showed higher activity of the enzyme than healthy individuals, and that Titanium dioxide nanoparticles increased the activity of the peroxidase enzyme in the saliva [105].

A study was carried out to assess the anti-inflammatory characteristics of a dental varnish embedded with rosemary and Zingiber officinale extracts intermediated by titanium dioxide nanoparticles. The results indicated that the antioxidant and anti-inflammatory properties of the varnish are attributed to the bioactive components found in Zingiber officinale and rosemary, including terpenes and phenolic components. Additionally, this formulation demonstrated the therapeutic possibility of titanium dioxide nanoparticles in treating inflammatory conditions [106].

3.4. Silicon Dioxide Nanoparticles (SiO2)

Nanoparticles have been integrated into denture base substances at varying ratios to improve mechanical characteristics. The integration of SiO2 nanoparticles at low ratios has shown favourable results. One study investigated the effect of SiO2 nanoparticles on the flexural strength of thermoset denture base materials. [107]. Another study assessed the impact of adding SiO2 nanoparticles to denture soft lining materials on contact corner, surface roughness, and C. albicans adherence. The results exhibited that adding various proportions of SiO2 nanoparticles to a self-polymerizing soft acrylic liner decreased the contact corner, C. albicans adherence, and surface roughness [108]. The effect of TiO2 and SiO2 nanoparticles was evaluated in one study, and the trauma strength of two commercially available thermosetting acrylic resins was compared. The results demonstrated that the incorporation of SiO2 and TiO2 nanoparticles reduced the durability of commercially obtainable and heat-cured denture base resins [20].

Gingivitis can occur because biofilm is present on acrylic resin dentures. A study assessed the action of SiO2 incrustation applied to acrylic resin on the adherence of microorganisms. The results indicated that the SiO2 plating reduced the activity of polymicrobial biofilms created on acrylic resin. This plating can benefit patients with traditional dentures or acrylic resin implants who experience mobility difficulties that prohibit them from properly purifying their dentures [109].

Dental alloys are commonly exposed to a diversity of oral states, including complicated erosion, which can compromise the structural integrity of dental implants, leading to issues like fracture, implant loosening, toxicity, allergic reactions, and possible osseointegration. Composite nanomaterials can modify the surfaces of alloys to improve their biocompatibility and erosion resistance. These materials provide a protective layer for the alloy and act as a partition to prohibit corrosive materials from reaching the base material. A study was conducted involving surface amendment of a dental Ti-13Nb-13Zr alloy employing fluoroapatite (FAP)/SiO2 -modified zirconia (ZrO2) nanocomposites. The modified surfaces were treated with artificial saliva solutions and simulated body fluids, utilizing in vitro techniques. The material demonstrated good corrosion resistance and is considered excellent for dental implant applications [110].

Bacterial collection on the edges of dental resin Composites is the primary cause of secondary caries. Antibacterial nanocomposites, including regular-shaped SiO2–ZnO complex clusters (CCs), addressed this problem. These clusters demonstrated antibacterial action while preserving the mechanical and aesthetic characteristics of dental resin composites [111]. In one study, the antibacterial activity of SiO2 nanoparticles was evaluated. They demonstrated excellent efficacy against S. mutans [69].

The nanoparticles discussed in this review are summarized in Table 2, along with their disadvantages, advantages, and applications in dentistry.

4. Cytotoxicity and Environmental Impact of NPs

The cytotoxicity of NPs indicates their ability to destroy living cells through destruction of cellular structures, the creation of oxidative stress, and the stimulation of programmed cell death. Due to their large surface area and small size, NPs can breach cell membranes and alter biological functions. The cytotoxicity of metal NPs is affected by their chemical structure, shape, size, and surface charge. Inflammation and oxidative stress are significant elements contributing to cytotoxicity, in addition to the processes of autophagy and apoptosis. Oxidative stress is distinguished by the production of reactive oxygen species (ROS), which alters the oxidation and reduction conditions. In contrast, inflammation is a protective mechanism against infection; however, it can be harmful if not properly regulated [112-114].

Reactive oxygen species (ROS) can trigger an inflammatory response and their amplification, producing a feedback loop that aggravates oxidative stress. This cycle can destroy mitochondria and, consequently, lead to cell death. Cytotoxicity stimulated by metallic nanoparticles often involves the activation of numerous intracellular signaling pathways. For instance, zinc oxide NPs have been demonstrated to stimulate neurotoxicity through activating nuclear factor kappa B (NF-κB), mitogen-activated protein kinases (MAPKs), and extracellular signal-regulated kinases (ERK). Several studies have been conducted in vivo and in vitro to test the toxicity of nanoparticles and their effects. In vitro, a survey of the reaction of TiO2 NPs in mice revealed that after prolonged exposure to TiO2 NPs, superoxide (O2 -) is produced in conjunction with hydrogen peroxide, which leads to lipid peroxidation. In vivo, A study by Guan et al. indicates that TiO2 NPs cause acute neurotoxicity in oysters' blood by increasing the neurotransmitter GABA [114, 115].

The widespread use and disposal of nanoparticles (NPs) in various medical, industrial, and consumer products have raised growing concerns about their environmental impact. NPs are released into the environment during manufacturing, usage, and disposal, reaching aqueous systems, soil, and the atmosphere. Due to their small size, ranging from 1 to 100 nm, and high surface reactivity, NPs can remain in the environment and interact with inorganic and organic compounds. Studies indicate that some NPs can negatively impact aquatic organisms like fish and algae by damaging growth, reproduction, and metabolic activity[116].

NPs interfere with microbial diversity and enzymatic functions in soil ecosystems, potentially disrupting nutrient cycling and soil fertility. TiO_2 and cerium oxide (CeO_2) NPs have shown toxicity to earthworms and nitrogen-fixing bacteria, which are essential for soil health. NPs may also bioaccumulate in organisms and biomagnify through the food chain, posing long-term ecological risks. In plants, NPs can penetrate root systems, alter photosynthetic activity, and inhibit seed germination, ultimately affecting crop productivity and food safety [117].

5. Limitations of the Green Synthesis of Nanoparticles

Despite the green synthesis of NPs providing an eco-friendly alternative to traditional methods, it faces many limitations that prohibit its expansion and industrial application. These limitations may be summarized as follows:

5.1 Materials:

Different plant materials have been utilized for the green synthesis of NPs, with numerous studies focusing on locally plentiful and easily accessible plant types. While this method promotes the utilization of territorial resources, it poses challenges for the universal scalability of green-synthesized metal NPs. For instance, Pd NPs were synthesized employing Lithodora hispidula (Sm.) Griseb., a plant local to specific zones like Cyprus, Cyrenaica, southern Turkey, and the south of the Aegean Sea [118]. Another study, the Andean blackberry (Rubus glaucus Benth.), found in Colombia and Ecuador, has been employed to synthesis Cu NPs [119], indicating the potential of scouting the utilization of regionally obtainable plant types for the widespread production of metals at the nanoscale. Time handcuffs essentially limit the practical utilization of raw materials in production. For example, the materials employed in synthesizing Ag NPs should be obtained from cotton leaves during the flowering season only [120] or from Sargassum fusiforme, a seaweed that grows seasonally and exhibits significant variations between regions. Hence, the time required to obtain the papers is more critical [121].

5.2 Synthesis Process:

One of the significant challenges in NPs synthesis is the long reaction periods, high energy exhaustion, and dependence on chemical reagents. Many green synthesis methods require high temperatures for extended periods, which increases energy consumption and contradicts the principles of environmental sustainability. Additionally, numerous plant extracts employed in green synthesis must be stored at low temperatures, which requires energy-intensive cooling and contributes to economic and ecological costs. Thus, preparing metal NPs at room temperature is advised, which will decrease energy consumption. Extracting effective compounds from plants can be energy- and time-consuming, including freeze drying over several days and prolonged boiling periods, which makes the green synthesis operation less effective and complex [121].

5.3 Nanoparticles Quality

Nanoparticles created using different plant extracts exhibit a range of shapes and sizes. Present studies exhibit considerable variation in particle size, making the green method unsuitable for large-scale production. For example, the size of Au NPs synthesized from Nigella arvensis leaf, Galaxaura elongata, and aqueous Elaise guineensis varies significantly, with particle sizes ranging from 5 to 100 nm, 13 to 97 nm, and 2 to 100 nm, respectively [122-124].

Table 2. Summary of the nanoparticles discussed in this review along with their disadvantages, advantages, and applications in dentistry

Name of NPs	Advantages	Disadvantages	Applications	Ref.
Hydroxyapatite NPs	Biocompatibility, remineralization, enhances bone regeneration, and exhibits antibacterial properties.	Potential inflammation at high concentrations, low mechanical strength	Toothpaste, dental implants, desensitizing agents, periodontal regeneration, and alveolar cleft repair.	[78-85]
Silver NPs	Improves mechanical properties, exhibiting strong antibacterial and antifungal properties.	Can be cytotoxic at higher levels	Dentures, adhesives, composites, toothbrushes, toothpaste, restorative materials	[86-96]
TiO_2 NPs	Biocompatibility, improves aesthetics, antibacterial.	Unknown long-term biocompatibility, potential cytotoxicity	Orthodontic adhesives, wires, dentures, mouthwash, whitening products, and anti-inflammatory varnish	[97-106]
SiO_2 NPs	Reduces biofilm, exhibits antibacterial properties, and improves mechanical strength.	Can reduce durability at higher concentrations	Denture bases and liners, coatings for alloys, resin composites, and anti-biofilm surface modifications	[107-111]

6. Standardized Guidelines of the Green Synthesis Process

The green synthesis protocols for NPs vary significantly across studies, as parameters such as pH, temperature, concentration of plant extract, and reaction time directly influence the stability, shape, and size of NPs. This variability is one of the challenges to the comparability and reproducibility of results across varying studies. Therefore, there is an imperative need to standardize guidelines for green synthesis protocols. These could include maintaining a reaction temperature below 100°C, adjusting the pH to 5–8, and employing standardized characterization techniques such as XRD, UV-Visible spectroscopy, and SEM. Standardizing these factors can promote reproducibility and enhance the reliability of green synthesized NPs for biomedical applications [125, 126].

7. Conclusion

This review concludes that green nanoparticle synthesis employing plant extracts has significantly progressed in nanotechnology and dentistry. The utilization of nanoparticles synthesized through a green process has led to significant potential in various fields of dentistry, including their ability to prevent the growth of biofilms, enhance remineralization, and provide antimicrobial coatings. However, the dangers related to stability and cytotoxicity should be carefully considered to ensure safe and effective utilization. Optimizing the choice of plant extracts is crucial for enhancing the synthesis of nanoparticles. Recent research indicates that combining several extracts can synergistically promote the stability of nanoparticles and their biological activity. Scout these combinations might lead to more efficient and adapted nanoparticles for applications in dentistry. Future research could treat specified gaps, like the evolution of hybrid NPs, which collect various materials to improve their functionality, and the exploration of compound therapies incorporating nanoparticles with conventional dental treatments to enhance therapeutic activity. Further in vivo studies are necessary to evaluate the clinical integrity and long-term effects of nanoparticles. Based on the studies, this work provides a comprehensive review of the most efficient plant-based nanoparticles in dental applications. These insights support an obvious orientation for development and research, confirming the need for clinical trials, improved synthesis protocols, and the extension of these treatments into preventive and restorative dental care. As progress continues, incorporating nanoparticles into clinical practice will likely revolutionize dental care and treatment approaches.

8. References

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