



Plant-Derived Nanobiomaterials as a Potential Next Generation Dental Implant Surface Modifier

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Dental implants resemble synthetic materials, mainly designed as teeth-mimics to replace the damaged or irregular teeth. Specifically, they are demarcated as a surgical fixture of artificial implant materials, which are placed into the jawbone, and are allowed to be fused with the bone, similar to natural teeth. Dental implants may be categorized into endosteal, subperiosteal, and zygomatic classes, based on the placement of the implant “in the bone” or on top of the jawbone, under the gum tissue. In general, titanium and its alloys have found everyday applications as common, successful dental implant materials. However, these materials may also undergo corrosion and wear, which can lead to degradation into their ionic states, deposition in the surrounding tissues, as well as inflammation. Consequently, nanomaterials are recently introduced as a potential alternative to replace the conventional titanium-based dental implants. However, nanomaterials synthesized *via* physical and chemical approaches are either costly, non/less biocompatible, or toxic to the bone cells. Hence, biosynthesized nanomaterials, or bionanomaterials, are proposed in recent studies as potential non-toxic dental implant candidates. Further, nanobiomaterials with plant origins, such as nanocelluloses, nanometals, nanopolymers, and nanocarbon materials, are identified to possess enhanced biocompatibility, bioavailability and no/less cytotoxicity with antimicrobial efficacy at low costs and ease of fabrication. In this minireview, we present an outline of recent nanobiomaterials that are extensively investigated for dental implant applications. Additionally, we discuss their action mechanisms, applicability, and significance as dental implants, shortcomings, and future perspectives.

Keywords: dental implants, nanobiomaterials, biocompatibility, endosteal, titanium alloys, zygomatic implants

INTRODUCTION

In general, implants are synthetic components that are placed in a living organism as a replacement for a damaged part and eventually supports the normal activity of the organism (Prakasam et al., 2017). In humans, dental implants are the most common types of implants, which are widely utilized to replace damaged or malfunctioning dental parts throughout the world (Rupp et al., 2018). The dental implants are generally necessary for humans, when there is a dental damage due to accident, lifestyle changes including excessive smoking and alcohol consumption, and several

complications that lead to gum damage. Further, the usage of dental implants has been increased recently due to their safe clinical results and low cost (Sanguida et al., 2019). Conventionally, these dental implants are artificial materials, which are designed as teeth to replace the damaged or irregular teeth (Neldam and Pinholt, 2012). It can be noted that the history of dental implants to replace damaged dental parts in humans dated back to 600 AD, where the Mayan civilization has been found to utilize small sea shell parts resembling insertions with the purpose mandibular teeth substitution (Abraham, 2014). Due to the recent advantages in biomedical science and surgical techniques, dental implants are also defined as a surgical fixture of artificial implant material, which are placed into the jawbone and are allowed to be fused with the bone, similar to a natural teeth (Huang et al., 2017). Further, screws to fix the teeth and braces to align the teeth arrangement for facial symmetry were also considered as dental implants (Travess et al., 2004). Endosteal, subperiosteal and zygomatic are the classes of dental implants, which were classified based on the placement of implant “in the bone” or on top of the jawbone under the gum tissue. Zygomatic implants are distinct from conventional implants, where they are anchored in the zygomatic region of the bone rather than maxilla (Henri Diederich and Abou-Rabii, 2019). Generally, titanium and its alloys, such as nitinol were used as a common and successful materials for dental implant applications (Shah et al., 2019). However, these materials are identified to undergo corrosion and wear, which can lead to degradation into their ionic state, deposition in the surrounding tissues and inflammation (Park et al., 2020).

Nanomaterials are gaining essential significance due to their exclusive properties in various biomedical applications, ranging from drug delivery to biosensors (Jeevanandam et al., 2020a); Tan et al., 2019; Pan et al., 2021; Tan et al., 2020). Chemical and physical approaches are the commonly used synthesis methods to yield smaller sized novel nanomaterials (Jeevanandam et al., 2016). However, the toxicity toward bone cells (chemically synthesized nanomaterials are mostly toxic toward pre-osteoclast (RAW264.7) and pre-osteoblast (MC3T3-E1), depending on their dose and concentration), less biocompatibility depending on their size, surface, and composition, and high cost of these nanoparticles are the limitations of these nanomaterials, which has led to the introduction of biological approaches or biosynthesis, i.e., utilization of biomolecular extracts of microbes and plants (Ha et al., 2018; Rasouli et al., 2018). Among biosynthesis approaches, microbial-mediated synthesis of nanomaterial called nanobiomaterials has been identified to yield non-toxic nanomaterials, however, the process is tedious, requires high reaction time and difficult to fabricate nanomaterials with discrete architectures (Andra et al., 2019). Thus, currently, plant isolates are comprehensively employed to synthesize non-toxic nanomaterials with distinct morphologies and surface properties (Shanmuganathan et al., 2019). These plant-derived nanobiomaterials are recently under extensive research to be included as novel materials to manufacture the next generation dental implants as a potential alternative for conventional implant materials (Augustine and Hasan, 2020). This review is an overview of recent nanobiomaterials, which

are under extensive research for dental implant applications. Further, significance of these nanomaterials as dental implants, mechanism of action, drawbacks and future perspective will also be discussed.

CONVENTIONAL DENTAL IMPLANTS AND THEIR LIMITATIONS

Conventional dental implants are broadly made up of metals, ceramics, polymer or combination of all these materials as composites. In the category of metals, titanium, titanium alloys such as nitinol (nickel and titanium), stainless steel, gold alloys, tantalum, and cobalt chromium alloy are commonly used to fabricate dental implants. Further, alumina, beta-tricalcium phosphate, carbon materials, carbon-silicon, zirconia, bioglass, and zirconia-toughened alumina are the ceramics and polysulfone, polytetrafluoroethylene, polyurethane, polymethylmethacrylate, polyethylene, and polyether ether ketone are the polymers, which are used to fabricate conventional dental implants (Osman and Swain, 2015). These dental implants are usually beneficial for the replacement of single tooth without high costs, compared to the traditional fixation of dental prostheses (Vogel et al., 2013). Apart from cost-based advantages, conventional dental implants behave similar to natural teeth, last for a long time, prevent bone loss, provide stability to adjacent teeth, reduce gum disease complications and prevent facial sagging and premature aging-related issues (Li J. et al., 2020). Further, the mechanical strength of these materials, evaluated *via* both *in vitro* and *in vivo* studies, is on par with natural bone and dental tissues, which makes them the most common implant materials (Li J. et al., 2020). However, these materials undergo degradation during interaction with the biological fluids, leading to corrosion and wear, which can be deposited in the surrounding cells or tissues and cause inflammation (Apaza-Bedoya et al., 2017; Park et al., 2020). Furthermore, osteoporosis, immunocompromised patients of diabetes [3.89% of failure rate (Chrcanovic et al., 2014)], Acquired Immunodeficiency Syndrome (AIDS) condition [10% of failure rate (May et al., 2016)], smoking and radiotherapy in head and neck cancers are the factors that can lead to dental implant failures (Bazli et al., 2020). Additionally, conventional dental implants involve high initial costs for mandibular edentulous patients, compared to mucosa-borne dentures (Vogel et al., 2013). Thus, nanomaterials are currently under extensive research and are used in certain cases as a surface modifier of conventional dental implants or to fabricate novel nanomaterial-based implants for eliminating the limitations of conventional dental implants.

NANOMATERIALS IN DENTAL IMPLANT APPLICATIONS

Nanomaterials are recently incorporated in several aspects of dental applications, such as preventive dentistry, dental implants, restoration of implants, periodontics, endodontics, dental tissue engineering, and

scaffolds (Zafar et al., 2019). Among these applications, carbon, metal, polymer, and metal oxide nanoparticles and certain nanocomposites were used for dental implant applications.

Metal Nanomaterials

Metal nanomaterials, such as gold, silver, platinum, copper, and selenium possess enhanced antimicrobial properties. Hence, these nanomaterials find applications in the form of an antimicrobial, surface coating substance of the conventional dental implants, to prevent them from microbial attack-mediated degradation (Parnia et al., 2017). Likewise, these nanoparticles are incorporated with conventional dental implant materials, such as titanium and hydroxyapatite also possess osteointegration property for 12 weeks (Woźniak and Markuszewski, 2019). Recently, silver nanoparticles are deposited on the surface of commercially pure titanium *via* exposed air “laser ablation” to enhance the dental graft antibacterial property (Boutinguiza et al., 2018). Further, it has been identified that the chitosan-gold nanoparticles possess enhanced ability to deliver c-myc gene at the target site, which is a transcription factor belongs to myoblastosis family, that can control survival, differentiation, cell proliferation, and death. The c-myc delivery by the gold nanocomposite has facilitated dental implant osseointegration in ovariectomized rat model (Takanche et al., 2018). Furthermore, nanocrystalline titanium-copper alloy has demonstrated a strong biocompatibility, antibacterial, osseointegration, and mechanical properties to be a highly beneficial orthopedic material, especially for dental implant application (Moniri Javadhesari et al., 2020). Moreover, silver nanoparticle decorated graphene nanocomposites were identified to possess osteointegration property with enhanced antibacterial activity against an oral pathogen named *Aggregatibacter actinomycetemcomitans* along with *Streptococcus mutans*, *Candida albicans*, and *Lactobacillus acidophilus* (Peng et al., 2017).

Metal Oxide Nanomaterials

Nanosized metal oxides are highly stable, compared to metal nanoparticles, which brands them highly beneficial as antimicrobial agents with high osseointegration and mechanical property to be coated on the surface of the insert (Ghiciuc et al., 2017). Recently, silver and zinc nanoparticles embedded in the layers of titanium oxide nanotube has shown enhanced antimicrobial actions toward oral microbes, for instance *S. mutans*, *C. albicans*, and *Candida parapsilosis*, and are proposed to be beneficial toward the management of dental contagions (Roguska et al., 2018). Likewise, porous tantalum oxide nanoparticles along with calcium phosphate and osteoconductive elements were fabricated into a core-shell structure and are proposed as a next generation dental implant material (Fialho et al., 2021). Similarly, nanocomposites of titania-zinc oxide fabricated as thin films on the substrates of silicon exhibited enhanced biocompatibility and antibacterial activity, which can be a potential coating films for the dental implant applications (Goel et al., 2019).

Carbon and Polymer Nanomaterials

Carbon-based nanoparticles, for instance carbon nanotubes, graphene, diamond nanoparticles, and quantum dots were also utilized as a coating or dental implant material. However, these carbon nanomaterials are incorporated with metallic or polymer nanomaterials as nanocomposites to retain their mechanical properties and enhance their biological properties. In a recent study, graphene incorporated with zinc oxide as nanocomposite film has been found possess ability to protect the surfaces of dental implants from cariogenic *S. mutans* bacteria (Kulshrestha et al., 2014). Likewise, carbon-based nanodots, nanotubes, nanofibers, fullerenes, graphene derivatives, and nanocrystalline diamonds were reported to be beneficial a surface functionalization material to improve the surface property of the dental implant (Kang et al., 2021). Besides, nanosized polymers or polymer matrix composites, such as natural or biopolymers namely poly (lactic acid) and chitosan, synthetic polymers including polyetheretherketone (PEEK) and glycidyl methacrylate/triethylene glycol dimethacrylate (BisGMA/TEGDMA) are widely fabricated as nanoparticles or incorporated with nanoparticles to exhibit enhanced efficiency in dental implant applications (Kadambi et al., 2021).

LIMITATIONS OF NANOMATERIALS AS DENTAL IMPLANTS

It may be noted that all the nanomaterials mentioned in the previous section are fabricated *via* either chemical or physical approaches. These nanomaterials possess significant properties, such as chemical compositions similar to teeth and its components, wettability, surface energy, and surface roughness, which makes them highly beneficial for the dental applications (Rasouli et al., 2018). However, the chemicals used for the fabrication of these nanomaterials are toxic toward human cells and high energies are involved in the nanomaterial formation, which has been identified as potential limitations to recommend them for large-scale commercial dental implant applications (Jeevanandam et al., 2020b). The toxicity of these chemical or physical synthesized nanomaterials depends on the type of reducing and stabilizing agent used for nanomaterial fabrication, size, morphology, and surface functional groups as well as their surface charge of nanomaterials (Ganguly et al., 2018; Qu et al., 2018). Further, it can be noted that the traces of reducing and stabilizing agents in the nanomaterials, will also affect their biocompatibility, bioavailability, bioreactivity, and eventually cause acute or chronic side effects (Zhang et al., 2017). Furthermore, the costs involved in the chemical and physical synthesis are higher to be recommended for large-scale commercial nanomaterial synthesis (Jamkhande et al., 2019). Thus, biosynthesis approaches *via* microbes and their extracts has been introduced as an effective green synthesis approach for the formation of nanomaterials with less toxicity and high biocompatibility, compared to conventional chemical and physical synthesis approaches (Khan and Lee, 2020). Fungi, bacteria and algae are the most common microbes, which find applications

toward the microbial production of nanomaterials (Yadav et al., 2020). Microbial nanomaterial fabrication outside the cellular space, especially using the biomolecules extracted from the microbes are extensively used to form nanoparticles, compared to the intracellular approach, where the extraction and purification of nanomaterials is tedious (Li et al., 2017). Even though, microbial synthesis is beneficial in yielding non-toxic, smaller sized nanobiomaterials, there are certain limitations that constrains their exploitation in large-scale biomedical applications (Kulkarni et al., 2021). Bacteria-mediated nanomaterial synthesis possess limitations, such as high time consumption and reduced control over the size, crystallinity, and morphology. Likewise, difficulties in down-streaming process and 24–120 h for nanomaterial formation are the limitations of fungal and algal-mediated nanobiomaterial synthesis (Jeevanandam et al., 2016). Hence, extracts of plants known as phytochemicals are introduced as an alternative and potential reducing and stabilizing agent for the formation of nanobiomaterials to be beneficial in biomedical applications, especially for dental implant applications as summarized in **Table 1**.

PLANT-DERIVED NANOBIMATERIALS AS DENTAL IMPLANTS

In recent times, several nanobiomaterials have been fabricated using plant extracts to be employed in the dental implant applications, as an alternative to conventional dental implants as shown in **Figure 1**. Recently, it has been reported that the 71.5 nm sized spherical gold nanobiomaterial, that are synthesized *via* the aqueous bark extract of *Salacia chinensis*, can be utilized for dental implant application. The *in vitro* studies revealed that the synthesized nanobiomaterial possess superior stability in blood components, such as 2% of human serum albumin 0.2 M of histidine and 0.2 M cysteine of 2% bovine serum albumin. Further, the study showed that the phytosynthesized nanomaterial are cyto-compatible and compatible toward blood, such as periodontal fibroblasts and erythrocytes. Besides, the gold nanobiomaterial increased the cell viability of human MG-63 bone osteosarcoma cell lines, which indicates that the nanomaterial possess enhanced osteoinductive potential, which can be useful for dental graft treatment as a “bone inductive agent” (Jadhav et al., 2018). Similarly, another study showed

TABLE 1 | Advantages and limitations of conventional and nanomaterial-based dental implants.

Dental implant materials	Advantages	Limitations	References
Metals, ceramics, polymers, alloys, and composites	Low cost, compared to prostheses and behave similar to natural tooth	Degradation in biological fluids, corrosion and wear, and leading to inflammation	Vogel et al., 2013; Apaza-Bedoya et al., 2017; Li J. et al., 2020; Park et al., 2020
Physical and chemical synthesized nanomaterials	Chemical compositions similar to teeth and its components, wettability, surface energy, and surface roughness	Toxicity toward human cells, low biocompatibility, bioavailability, and high cost for synthesis	Zhang et al., 2017; Rasouli et al., 2018; Jeevanandam et al., 2020b
Microbial synthesized nanobiomaterials	Less toxicity, high biocompatibility, and biological property	Longer synthesis time, reduced control in stability, and tedious down-streaming process	Jeevanandam et al., 2016; Khan and Lee, 2020
Plant-derived nanobiomaterials	Less toxicity, control in stability, ease in down streaming process, biocompatibility, and bone induction ability	Difficult to modify shape, lack of in-depth dental studies	Sundeep et al., 2017; Jadhav et al., 2018

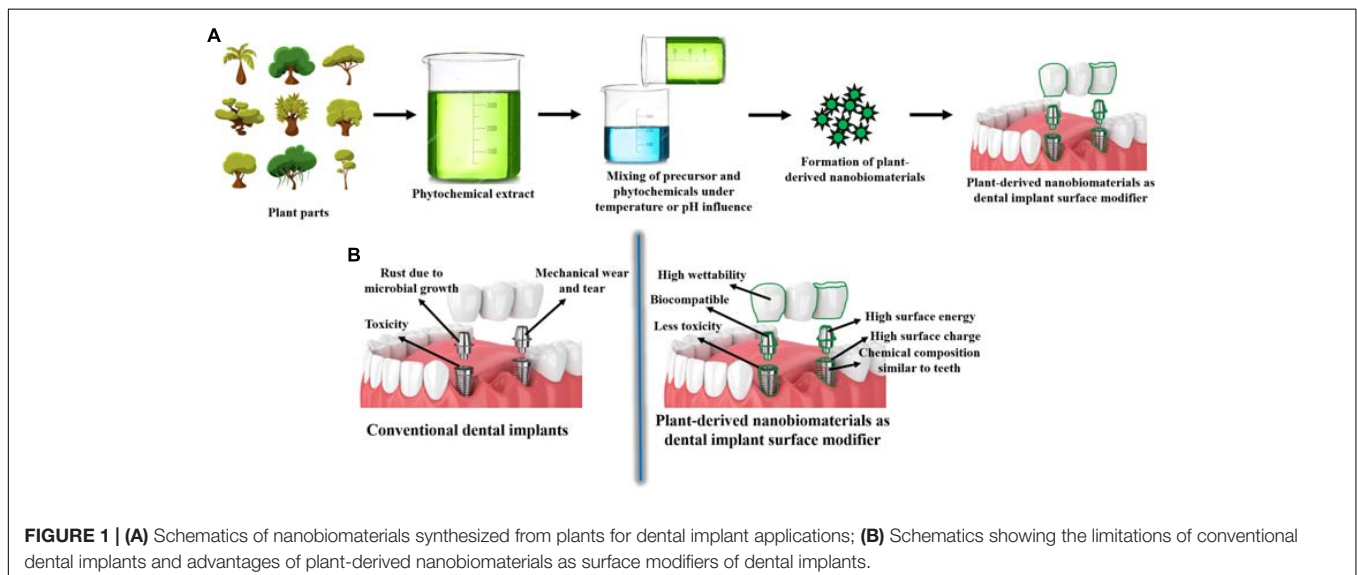


FIGURE 1 | (A) Schematics of nanobiomaterials synthesized from plants for dental implant applications; (B) Schematics showing the limitations of conventional dental implants and advantages of plant-derived nanobiomaterials as surface modifiers of dental implants.

that the 32.4 nm sized flake-like shaped silver nanoparticles synthesized *via* aqueous leaf extract of *Mangifera indica*, which can be beneficial for the dental restoration applications. “Glass ionomer cement” (GIC) was employed to strengthen the synthesized silver nanobiomaterials, which improved the low wear of conventional GIC, enhanced their mechanical strength with exclusive protective features against *Staphylococcus aureus* and *Escherichia coli*. Therefore, these nanobiomaterial reinforced GIC can be useful to improve the mechanical strength of the conventional dental implant materials by blending with them as a composite or as a surface coating to improve their antibacterial activities (Sundeep et al., 2017).

Likewise, the polyphenols extracted from the *Anogeissus latifolia* plant leaves has been utilized for the fabrication of gold nanobiomaterials for the management of pain in dental tissue implantation applications. The nanobiomaterial exhibited enhanced stability in human serum albumin, cysteine, histidine, and bovine serum albumin, and improved biocompatibility as well as cytocompatibility toward periodontal fibroblasts and erythrocytes *in vitro*. Further, the study revealed that the gold nanobiomaterial improved the cell viability of MG-63 cell lines with strong antinociceptive activity, which is beneficial for dental pain management applications during tissue implantation (Wang and Wang, 2020). Moreover, plant synthesized zinc oxide nanoparticles has also been proposed to be a potential nanobiomaterial with *in vitro* osteogenic activity and antibacterial property for dental implant applications (Li Y. et al., 2020). Moreover, silver nanoparticles synthesized *via* white pepper oleoresin (Paul et al., 2020), *Oleo europaea* extract (Umaï et al., 2020), clove and cinnamon extracts synthesized with zinc oxide nanoparticles (Mohapatra et al., 2020), exhibited enhanced antimicrobial activities against oral pathogens. These can be beneficial as a surface modifier of conventional dental implants, to prevent microbial attacks or infections. All these studies demonstrated that the plant-mediated synthesis of nanobiomaterials are highly significant for dental implant applications. It is conceivable that advancements in modern synthesis techniques, will lead to greater success in producing novel phytonanobiomaterials as dental implants.

FUTURE PERSPECTIVES AND CONCLUSION

It is noteworthy that noteworthy *in vitro* research findings and breakthroughs are increasingly being reported in the context of plant-synthesized nanobiomaterials for dental implant applications, especially as a surface modifier of

implants. Nevertheless, numerous challenges and critical shortcomings could also be noticed with regards to plant-mediated nanobiomaterial fabrication. Even though, plant-mediated synthesis can yield smaller sized bionanomaterials in short time, their stability is not comparable with conventional approaches. Also, the shape of the resultant nanobiomaterials are spherical and polydispersed in most cases and pH variations are required to transform their morphologies and dispersity. However, addition of chemicals to alter pH may also lead to increase in toxicity of these phytosynthesized nanobiomaterials. Thus, it is necessary to incorporate novel techniques in plant-mediated nanomaterial to eliminate limitations and improve their efficiency. Moreover, there are no reports, which shows that the plant-mediated nanomaterials are toxic or less efficient in dental implant applications. Also, it can be noted that the nanobiomaterials that are synthesized *via* plant extracts for dental applications in recent times are standalone nanobiomaterials. Hence, nanobiocomposites can be synthesized *via* plant extracts in the future, to render them beneficial toward large-scale commercial surface-modified dental implant applications with exclusive biomedical properties.

AUTHOR CONTRIBUTIONS

JJ and SP conceived and designed the structure of the minireview. JJ contributed to literature exploration and analysis, illustration, and writing the manuscript, which was reviewed, amended, and finalized by SP and MD. All authors ratified the submitted and revised versions.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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