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Phytopharmaceutical-Based Nanoformulations for the Prevention and Management of Peri-Implantitis: Current Advances and Future Perspectives

Anshkumar Bhuva*, Tazmeen Shafi[1], Shabia Showkat[2], Shah Samreen[3], Peer Samiq Masoodi[3]

*, [1],,[3,4],Adesh Institute of Pharmacy and Biomedical Sciences, Adesh University, Bathinda, Punjab, 151101 Email: anshpatel072@gmail.com

[2]Department of Allied and Healthcare, Guru Kashi University, Bathinda, Punjab, 151101 Email: bhattshabia@gmail.com

Abstract

Peri-implantitis is one of the most frequent and severe biological consequences of a dental implant and is characterized by the presence of microbial biofilms, persistent inflammation, and active progression of alveolar bone loss, which frequently results in implant failure. The problems with conventional treatment modalities include incomplete biofilm removal, antibiotic resistance, and unpredictable regenerative outcomes. Due to their antimicrobial, anti-inflammatory, antioxidant, and osteogenic activities, phytopharmaceuticals have been identified as promising therapeutic agents, but their clinical use is hampered by poor solubility, low bioavailability, and rapid degradation. Nanotechnology-based delivery systems have resolved these problems and enhanced drug stability, targeted drug delivery, sustained drug release, and penetration into peri-implant tissues and biofilms. This review aims to provide a summary of the pathophysiology of peri-implantitis, the recent developments of Phytopharmaceuticals-based nanoformulations, their molecular mechanisms of action and available pre-clinical and clinical evidence. This also includes a discussion of surface functionalization of implants, safety issues, regulatory issues, and prospects. In summary, nanoformulations prepared with phytopharmaceuticals could be a valuable tool in the management of peri-implant disease, and it would be beneficial for the longevity of implants.

Keywords: *Peri-implantitis; Phytopharmaceuticals; Nanotechnology; Nanoformulations; Dental Implants; Drug Delivery Systems; Oral Biofilms; Implant Surface Functionalization; Bone Regeneration; Precision Dentistry.*

1. Introduction

The high success rate, predictability of function and appearance, and the use of dental implants have made them the method of choice for replacing missing teeth. Despite these benefits, biological issues are important, and peri-implantitis is a major cause of implant failure. Chronic inflammatory disease of the soft and hard tissues surrounding Osseo integrated dental implants. It is defined as progressive loss of peri-implant bone, bleeding on probing, deepening of the probing depth and in severe cases, implant mobility and eventual implant loss. Despite differences in definitions and populations, the prevalence of peri-implantitis worldwide

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is variable, but systematic reviews suggest that approximately 20-25% of patients with dental implants will develop peri-implantitis during long-term follow-up (1). As a result, the prevention and treatment of peri-implant diseases is becoming a more and more prevalent clinical and economic challenge around the world. Peri-implantitis is thought to be multifactorial, resulting from a complex interplay among several factors, including microbial biofilm accumulation, host immune responses, genetic susceptibility, systemic conditions, and environmental risk factors. A dysbiotic biofilm forms on the surfaces of implants, which leads to the formation of an inflammatory cascade that includes the secretion of pro-inflammatory cytokines, reactive oxygen species (ROS), matrix metalloproteinases and osteoclast-activating mediators (2). These events lead to the destruction of the connective tissue and a gradual alveolar bone resorption around the implant. Poor oral hygiene, history of periodontitis, smoking, uncontrolled diabetes mellitus, inadequate maintenance therapy and prosthetic factors that promote plaque formation are among the common risk factors. Since several biological pathways can drive peri-implantitis, treatment frequently requires a comprehensive approach rather than a single intervention. The traditional methods of treatment include mechanical debridement, antiseptic irrigation, systemic or local antibiotic therapy, laser therapy, implant surface decontamination, regenerative procedures, and surgery (3). These modalities can be used to reduce microbial load and clinical parameters, but completely eradicating pathogenic biofilms is difficult due to the complex surface characteristics of dental implants and the emergence of antimicrobial resistance. Moreover, long-term antibiotic treatment can be linked with side effects, alteration of the oral microflora, and the development of resistant bacteria, which underscores the need for safe and effective alternatives to combat these pathogens (4). Phytopharmaceuticals have been the subject of extensive research, and there is significant interest in their use to treat peri-implant diseases as an adjunct or alternative. Medicinal plant-derived bioactive compounds such as polyphenols, flavonoids, terpenoids, alkaloids, and essential oils possess wide-ranging antimicrobial, anti-inflammatory, antioxidant, immunomodulatory, and osteogenic properties (5). Nevertheless, a lot of phytochemicals have restricted aqueous solubility and stability, fast metabolism and low bioavailability, which limit their clinical performance. New approaches to overcome these limitations involve innovative strategies that leverage recent advances in nanotechnology to improve drug solubility, protect bioactive molecules from degradation, enable controlled drug release, and increase drug penetration and retention in peri-implant tissues (6).

This review aims to summarize the current evidence on phytopharmaceutical-based nanoformulations for the prevention and management of peri-implantitis. Here, it covers the biological background of peri-implant disease, the therapeutic potential of bioactive compounds derived from plants, recent advances in nanotechnology-based delivery systems, available preclinical and clinical evidence, safety considerations, and future research directions. This review aims to shed light on novel approaches that could enhance the management of peri-implantitis, focusing on developments in phytopharmaceutical science and advanced nanomedicine, to achieve more effective, targeted, and sustainable outcomes.

2. Pathophysiology of Peri-Implantitis

Peri-implantitis is a complex inflammatory phenomenon characterised by the progressive loss of the soft tissues and alveolar bone around a successfully osseointegrated implant. Healthy peri-implant tissues are in a state of balance between the oral microbiota and the immune system, but peri-implantitis occurs when pathogenic biofilms attach to the implant surface and disrupt that balance. Many dental implants are rough, which facilitates osseointegration; however, the rough surface can also promote bacterial adhesion and biofilm formation, making it difficult to remove microbes completely (7). As biofilms get more complex, the microbial environment becomes dysbiotic, meaning that it is dominated by anaerobic Gram-negative bacteria such as Porphyromonas gingivalis, Tannerella forsythia, Treponema denticola, Fusobacterium nucleatum, and Prevotella intermedia. These microbes secrete virulence factors (lipopolysaccharides, proteases, toxins) which stimulate inflammatory responses in the host. Innate immune mechanisms are triggered in epithelial cells,

macrophages, dendritic cells and neutrophils following recognition of the microbial components by pattern recognition receptors such as Toll-like receptors (TLRs). This triggers signaling through the NF-κB and MAPK pathways, resulting in the secretion of pro-inflammatory cytokines, such as prostaglandin E_2, TNF-α, IL-1β, IL-6, and IL-8 (8). These mediators will recruit immune cells and promote chronic inflammation in peri-implant tissues. Continued inflammation also activates the NLRP3 inflammasome, leading to the maturation of IL-1β and IL-18, thereby amplifying tissue damage. Excessive production of reactive oxygen species (ROS) by neutrophils and macrophages is also a hallmark of oxidative stress and a mechanism of disease progression. While ROS have a beneficial role in killing microbes, excess ROS can damage lipids, proteins, mitochondria and DNA, which can hinder tissue repair (9). An increase in oxidative stress also activates the inflammatory cascade and induces apoptosis in fibroblasts and osteoblasts, leading to poor regeneration. Alveolar bone loss is primarily caused by an imbalance among RANK, RANKL, and OPG, with increased RANKL and decreased OPG levels favoring osteoclast formation, recruitment, and bone loss. Matrix metalloproteinases (MMPs), especially MMP-8 and MMP-9, break down the extracellular matrix and collagen, resulting in weaker peri-implant tissues (10). The degree of disease depends on such things as lack of plaque control, history of periodontal disease, smoking, diabetes, residual cement, mucosal inflammation, implant surface attributes and inadequate support therapy. These factors promote microbial colonization and can change immune responses, leading to ongoing inflammation and bone loss. Knowing the mechanisms is important for developing targeted treatments. Antimicrobial, antioxidant, anti-inflammatory, and osteoprotective phytopharmaceutical compounds, particularly those nanoformulated with advanced technologies, could act at several stages of the peri-implantitis process (11). Multimodal therapies could address the shortcomings of current treatments and improve implant outcomes and longevity.

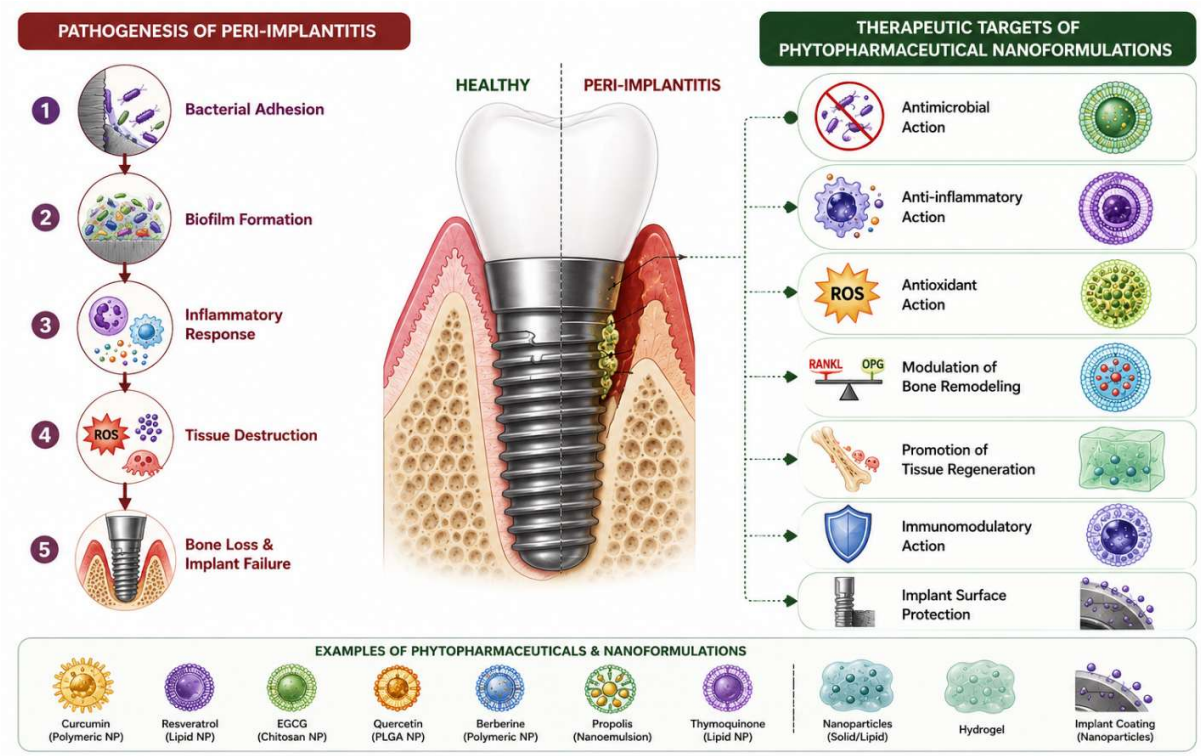

Figure 1: Pathogenesis of Peri-Implantitis and Therapeutic Targets of Phytopharmaceutical-Based Nanoformulations

3. Phytopharmaceuticals for Peri-Implantitis

Phytopharmaceuticals are medicinal products formulated from standardized plant extracts or purified phytochemicals with significant pharmacological activities suitable for disease prevention and treatment; in dentistry, there has been growing interest in phytochemicals found in plants, which have demonstrated broad-spectrum antimicrobial, anti-inflammatory, antioxidant, immunomodulatory and regenerative properties that collectively make them promising alternatives or adjuncts to traditional antibiotics, which primarily target the proliferation of microorganisms (12). One of the most extensively studied phytochemicals is curcumin, the main polyphenol from Curcuma longa (Turmeric), which shows remarkable antibacterial activity against important peri-implant pathogens like Porphyromonas gingivalis and Fusobacterium nucleatum, in addition to inhibiting the NF-κB signaling pathway and reducing the levels of pro-inflammatory mediators such as TNF-α, IL-1β, IL-6 and cyclooxygenase-2 and scavenging reactive oxygen species and promoting osteoblast differentiation and mineralization, thus supporting peri-implant bone regeneration (13). In the same way, resveratrol, a naturally occurring stilbene compound in grapes, berries and peanuts, has potent antioxidant and anti-inflammatory properties, being able to inhibit NF-κB and MAPK pathways and decrease the production of cytokines; resveratrol also reduces osteoclast differentiation by modulating the RANK/RANKL/OPG axis, and promotes osteogenesis and angiogenesis, both essential for peri-implant tissue integrity (14). Epigallocatechin-3-gallate (EGCG), the principal catechin of green tea, has been shown to have strong antimicrobial properties, disrupting the membrane of bacteria, inhibiting their biofilm formation, and reducing adhesion of bacteria to implant surfaces, in addition to its strong anti-inflammatory activity, reduction of inflammatory cytokines, decrease in oxidative stress, and stimulation of osteoblastic activity, which renders it as a valuable compound for localized delivery systems and coatings of implants (15). Another molecule found in fruits and vegetables and beneficial for peri-implant health is the flavonoid quercetin, which helps in bone preservation by inhibiting NF-κB activation, neutralizing free radicals, stimulating the body's own antioxidant defense mechanisms, promoting osteoblast proliferation, and inhibiting osteoclastogenesis. Berberine, an isoquinoline alkaloid extracted from Berberis species, is a broad-spectrum antibiotic, has anti-adhesion properties, promotes an anti-inflammatory macrophage phenotype and induces osteogenic differentiation through activation of the Wnt/beta-catenin pathway, which could make it useful in the treatment of bone regeneration and infection (16). Propolis, a resinous substance made by the honeybee, contains an array of flavonoids and phenolic compounds that deliver wound-healing properties such as increased collagen production and decreased microbial colonization, antibacterial and anti-inflammatory properties, which are useful for peri-implant soft tissue healing. The main component of clove oil, eugenol, has been used in dentistry for its antimicrobial, analgesic and anti-inflammatory effects for a long time, but must be used with dose control because of its possible cytotoxicity at higher concentrations (17). Aloe Vera (derived from Aloe barbadensis) contains active ingredients that promote fibroblast proliferation, collagen deposition, angiogenesis, and tissue regeneration, as well as antibacterial and anti-inflammatory activity, making it useful for improving peri-implant soft tissue healing. Another tree that has demonstrated potential for antimicrobial activity against oral pathogens is Azadirachta indica (Neem), which contains bioactive compounds such as azadirachtin and nimbidin that inhibit bacterial growth, reduce plaque accumulation, suppress inflammatory cytokines, and boost antioxidant levels, leading to improved peri-implant health (18). The active compound, thymoquinone, in Nigella sativa also exhibits strong antioxidant and anti-inflammatory properties, with the capability to inhibit the activation of NF-κB, alleviate oxidative stress, suppress the production of cytokines, and stimulate the differentiation of osteogenic cells. Despite these therapeutic properties, phytopharmaceuticals have not been widely used clinically, as they have low aqueous solubility, low bioavailability, short half-life, chemical instability, and poor retention at the target site, which reduce their therapeutic efficacy when administered using conventional formulations; to overcome these limitations, advanced nanotechnology-based drug delivery systems have been designed that can increase their stability,

bioavailability, controlled and targeted drug release, penetration into microbial biofilms, prolonged retention locally and decrease systemic exposure, thus maximizing their therapeutic potential in peri-implantitis prevention and management (19).

Table 1: Major Phytopharmaceuticals Investigated for Peri-Implantitis Management

Phytopharmaceutical	Plant Source	Major Bioactive Compound(s)	Primary Mechanism(s)	Potential Dental Application
Curcumin	Curcuma longa	Curcumin	Antimicrobial, anti-inflammatory, antioxidant, osteogenic	Peri-implantitis, bone regeneration
Resveratrol	Grapes (*Vitis vinifera*)	Resveratrol	Antioxidant, anti-inflammatory, anti-resorptive	Bone preservation around implants
EGCG	Camellia sinensis	Epigallocatechin-3-gallate	Anti-biofilm, antimicrobial, antioxidant	Implant coatings, plaque control
Quercetin	Fruits and vegetables	Quercetin	Antioxidant, anti-inflammatory, osteogenic	Prevention of peri-implant bone loss
Berberine	Berberis spp.	Berberine	Antibacterial, immunomodulatory, osteogenic	Local antimicrobial therapy
Propolis	Bee-derived plant resin	Flavonoids, phenolic acids	Antimicrobial, wound healing	Peri-implant soft tissue healing
Eugenol	Syzygium aromaticum	Eugenol	Antimicrobial, analgesic, anti-inflammatory	Local dental therapeutics
Aloe vera	Aloe barbadensis	Acemannan, anthraquinones	Wound healing, anti-inflammatory	Soft tissue regeneration
Neem	Azadirachta indica	Azadirachtin, nimbidin	Antimicrobial, antioxidant	Biofilm control
Thymoquinone	Nigella sativa	Thymoquinone	Antioxidant, anti-inflammatory, osteogenic	Bone preservation and inflammation control

4. Nanotechnology-Based Drug Delivery Systems in Dentistry

The revolution in nanotechnology in modern dentistry has enabled the development of many novel drug delivery systems that can increase therapeutic efficacy, enable controlled drug release, and improve targeting of diseased tissues, especially in peri-implantitis. The nanocarriers, with a size range of 1–1000nm, are very promising for the delivery of phytopharmaceuticals due to their unique physicochemical characteristics,

including a high surface area to volume ratio, tunable surface chemistry and penetration of microbial biofilms (20). The main problem with phytopharmaceuticals is their poor aqueous solubility, low bioavailability, rapid metabolism and limited retention at the site of infection; however, these can be overcome with nanotechnology-based formulations that can be used to encapsulate bioactive compounds in biocompatible carriers that can protect them from degradation, increase their stability and allow for sustained or stimuli-controlled release of the drug with reduced systemic exposure and toxicity (21). Polymeric nanoparticles prepared from biodegradable polymers like PLGA, chitosan, alginate and gelatin are extensively studied as various nanocarriers because of their controlled release, good biocompatibility and strong mucoadhesive properties, with additional antimicrobial activity of chitosan and good tissue adhesion of alginate (22). Liposomes are lipid bilayer vesicles composed of phospholipids that can accommodate both hydrophilic and lipophilic compounds and can increase cellular uptake by resembling biological membranes. Curcumin and resveratrol have been encapsulated in liposomes, resulting in increased stability and greater therapeutic efficacy. Solid lipid nanoparticles and nanostructured lipid carriers also help improve drug loading, sustained release, and protection of sensitive phytochemicals; nanostructured lipid carriers have higher encapsulation efficiency and lower drug leakage. Another effective platform is the use of nano emulsions, which have small droplet sizes, thereby enhancing the antimicrobial activity of hydrophobic compounds by allowing them to penetrate more deeply into biofilms and inflamed tissues. The structural features of a hydrogel-based nanocomposite system, including high hydration, injection and the capacity to fill irregular peri-implant locations, with tissue repair and regeneration support, provide localized delivery advantages (23). Electro spun nanofibers are similar to the extracellular matrix, encourage cell adhesion and proliferation, and act as a reservoir for controlled drug release, which helps with tissue regeneration and infection control. Mesoporous silica nanoparticles also offer other advantages because of their high surface area, ordered pore structure and the ability to achieve controlled and stimuli-responsive drug release, such as when the pH drops and during oxidative stress that occurs during inflammation. Recent developments have led to multifunctional nano formulations that combine antimicrobial, anti-inflammatory, antioxidant, and regenerative activities, which can be further strengthened by surface functionalization with targeting ligands or bioactive molecules (24). Moreover, nanoengineered coatings for implants that provide sustained release of phytopharmaceuticals are also effective at inhibiting bacterial colonization and promoting osseointegration. In summary, nanotechnology plays a significant role in augmenting the therapeutic potential of phytopharmaceuticals by overcoming their pharmacokinetic limitations and enabling targeted, localized therapy, thus providing an attractive approach to enhance the management of peri-implant diseases with reduced dependence on conventional antibiotics (25).

5. Phytopharmaceutical-Based Nano formulations for the Prevention and Management of Peri-Implantitis

The combination of phytopharmaceuticals and nanotechnology has been proposed as a therapeutic approach for the prevention and control of peri-implantitis, highlighting the great potential of bioactive natural compounds and their capacity to serve as efficient drug transporters via nanomaterials. Nano formulations can not only enhance stability, solubility, and bioavailability of phytochemicals but also enable targeted delivery, sustained drug release, improved penetration across microbial biofilms, and longer drug retention times at peri-implant sites, while minimizing systemic toxicity, to maximize therapeutic efficacy (26). Among the different phytopharmaceutical nano formulations studied, curcumin-containing nanoparticles are the most studied, since curcumin is a molecule with strong antimicrobial, anti-inflammatory, antioxidant, and osteogenic activities, but with poor aqueous solubility and rapid metabolic degradation in its free form. The entrapment of curcumin in polymeric nanoparticles, liposomes, solid lipid nanoparticles and nanostructured lipid carriers has greatly facilitated its sustained release, cellular uptake and physicochemical stability, which

has led to improved inhibition of periodontal pathogens, suppression of the production of pro-inflammatory cytokines like TNF-α, IL-1β and IL-6, reduction in oxidative stress, and promotion of osteoblast proliferation and mineralization. Similarly, resveratrol-loaded nanoparticles have been shown to have improved bioavailability and therapeutic effects by inhibiting osteoclast differentiation, decreasing the production of inflammatory mediators, and modulating the RANK/RANKL/OPG, SIRT1, and NF-κB signaling pathways, thereby improving angiogenesis and bone regeneration (27). However, nanoencapsulation of epigallocatechin-3-gallate (EGCG) has also shown great promise, as nanoparticles can enhance the chemical stability of EGCG, as well as enhance its antibacterial activity against peri-implant pathogens, Porphyromonas gingivalis, Fusobacterium nucleatum, and others; inhibit the formation of biofilm; limit adhesion of bacteria to implant surfaces; and stimulate osteogenic differentiation. The nanoparticles have been shown to exhibit increased antioxidant activity, more effective inhibition of inflammatory signaling pathways, suppression of osteoclast genesis, and protection against inflammatory bone loss in the case of quercetin-loaded nanoparticles, and superior antimicrobial potency, better macrophage modulation, and faster osteogenic differentiation for berberine nano formulations (28). Propolis-loaded nanoparticles and nanoemulsions have been shown to promote wound healing, collagen production, neo angiogenesis, and antibacterial activity, and to maintain therapeutic levels within peri-implant tissues. Similarly, nano formulations of thymoquinone, eugenol, aloe vera, and neem extracts have been shown to exhibit better drug stability, prolonged drug release, and enhanced antimicrobial and anti-inflammatory activities in experimental studies. Besides traditional nanoparticles, hydrogel-based nanoformulations have also been widely studied, as they offer a highly biocompatible system for local drug delivery that continuously releases phytochemicals, favors tissue regrowth in peri-implant defects, is biodegradable, and can be injected (29). Electrospun nanofibers containing phytopharmaceuticals are also similar to the native extracellular matrix, with the capacity to attract fibroblasts, induce osteoblast proliferation, stimulate the generation of new blood vessels, and release drugs in a controlled manner while preventing bacterial colonization. An innovative approach is to apply nanomaterials containing phytopharmaceuticals to the surface of titanium implants, thus providing bioactive antimicrobial coatings that prevent early bacterial adhesion, suppress inflammatory reactions, and promote osseointegration right after the implant procedure (30). In response to peri-implantitis' multifaceted pathophysiology, multifunctional nanoformulations that can achieve antimicrobial, antioxidant, anti-inflammatory, immunomodulatory, and osteogenic effects have been increasingly developed to overcome its multifaceted nature by delivering these activities via a single carrier. While the majority of the available evidence comes from in vitro experiments and animal studies, the results, as a whole, clearly show that nano formulations based on phytopharmaceuticals are significantly superior to conventional formulations of phytochemicals for improving therapeutic efficacy and promoting peri-implant tissue regeneration. However, additional well-designed clinical trials, uniform manufacturing processes, long-term safety studies, and regulatory approval are needed before these advanced nanoformulations are regularly used in clinical implant dentistry (31).

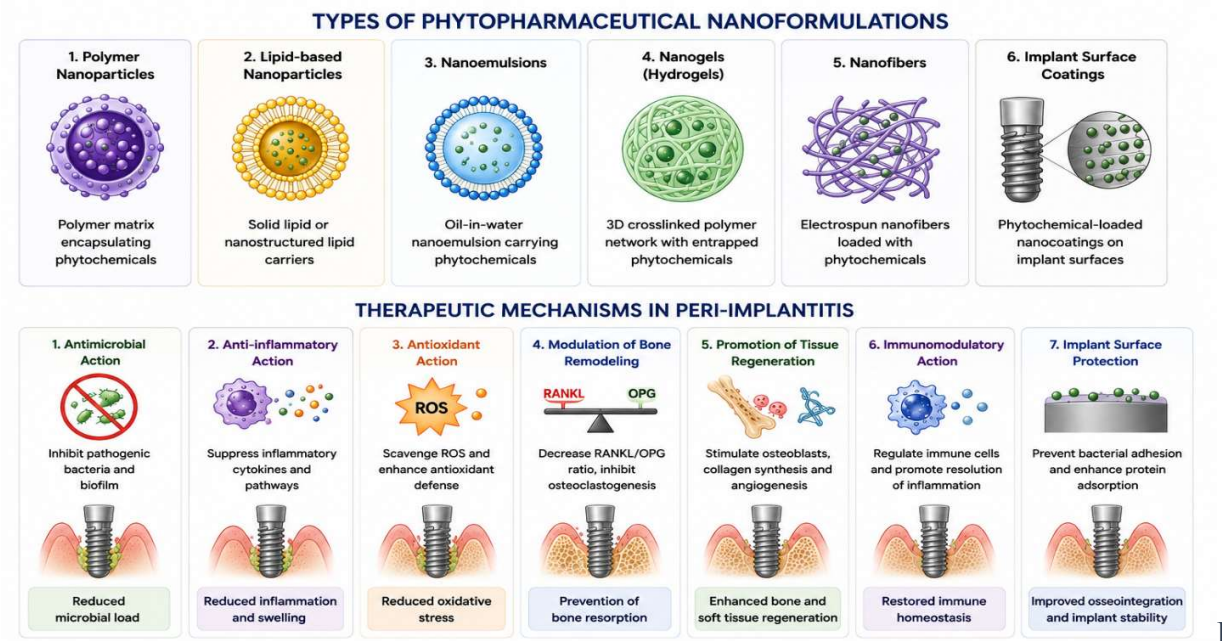

Figure 2: Types of Phytopharmaceutical Nanoformulations and Their Therapeutic Mechanisms in Peri-Implantitis

6. Molecular Mechanisms of Action

The therapeutic efficacy of phytopharmaceutical-based nanoformulations in the prevention and management of peri-implantitis is attributable to their ability to simultaneously modulate multiple molecular pathways involved in microbial infection, inflammation, oxidative stress, immune regulation, and bone remodeling. One of the main mechanisms is the inhibition of pathogenic oral microorganisms and the disruption of mature biofilms colonizing implant surfaces (32). Nanoformulations enable more efficient penetration of phytochemicals through the extracellular polymeric matrix of bacterial biofilms, resulting in higher intracellular accumulation and antimicrobial activity against important peri-implant pathogens such as Porphyromonas gingivalis, Tannerella forsythia, Treponema denticola, Fusobacterium nucleatum, and Aggregatibacter actinomycetemcomitans. The plant-derived compounds curcumin, epigallocatechin-3-gallate (EGCG), berberine, quercetin, and eugenol affect the integrity of bacterial cell membranes, quorum sensing, biofilm maturation, and bacterial adhesion to titanium implant surfaces, thereby reducing microbial colonization and disease progression (33). Apart from their antimicrobial properties, phytopharmaceutical nanoformulations also exhibit strong anti-inflammatory activity by modulating multiple intracellular signaling pathways. The Toll-like receptors (TLRs) activated by bacterial lipopolysaccharide (LPS) normally trigger the nuclear factor-kappa B (NF-κB), mitogen-activated protein kinase (MAPK), and nucleotide-binding oligomerization domain-like receptor protein 3 (NLRP3) inflammasome pathways, resulting in increased production of pro-inflammatory mediators such as tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1β, IL-6, IL-8, cyclooxygenase-2 (COX-2), and prostaglandin E_2. These signaling cascades can be effectively suppressed by phytochemicals in nanocarriers, thereby reducing inflammatory cytokines, limiting leukocyte infiltration, and preserving peri-implant soft tissues (34). An additional essential therapeutic mechanism is its reduction of oxidative stress, a key factor in peri-implant tissue loss. Activated neutrophils and macrophages produce excessive amounts of ROS, resulting in lipid peroxidation, mitochondrial dysfunction, DNA damage, induction of apoptosis in osteoblasts and fibroblasts, and activation of osteoclasts. Polyphenolic compounds like curcumin, resveratrol, quercetin and thymoquinone (TQ) have potent antioxidant properties that directly scavenge reactive oxygen species (ROS) and indirectly stimulate the expression and activity of superoxide

dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx) and heme oxygenase-1 (HO-1) by activating the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway (35). By preserving redox homeostasis, oxidative tissue injury is reduced, and peri-implant tissues heal. In addition, phytopharmaceutical nanoformulations regulate the receptor activator of nuclear factor-kappa B (RANK), receptor activator of nuclear factor-kappa B ligand (RANKL), and osteoprotegerin (OPG) signaling axis, which governs bone remodeling. In peri-implantitis, RANKL is overexpressed, and OPG is down-regulated, promoting osteoclast differentiation and rapid resorption of the alveolar bone. Nano delivered phytochemicals are found to block the expression of RANKL, stimulate OPG generation, prevent the maturation of osteoclasts, and prevent the proliferation and differentiation of osteoblasts by suppressing the activation of the osteogenic pathways such as bone morphogenetic protein (BMP), Wnt/β-catenin, phosphoinositide 3-kinase/protein kinase B (PI3K/Akt), extracellular signal-regulated kinase (ERK), and runt-related transcription factor 2 (RUNX2) (36). These molecular events contribute to higher collagen production, alkaline phosphatase activity, extracellular matrix mineralization, increased angiogenesis, and new bone formation in the vicinity of dental implants. In addition, some phytopharmaceuticals act on macrophages, inducing a switch between the pro-inflammatory M1 and anti-inflammatory M2 phenotypes, thereby promoting the resolution of inflammation and tissue repair. These biological effects are further enhanced by recent advances in nanotechnology that enable the controlled release of drugs, enhanced cellular uptake, prolonged retention at peri-implant sites, and stimulus-responsive delivery in response to the acidic microenvironment or oxidative stress of inflamed tissues. These multitarget molecular mechanisms collectively set phytopharmaceutical-based nanoformulations apart from more traditional monotherapeutic strategies and lend them promise as effective therapeutic platforms capable of treating infection, inhibiting inflammation, preventing oxidative damage, maintaining alveolar bone integrity, and regenerating peri-implant tissues (19).

7. Preclinical and Clinical Evidence

Although most of the data currently come from in vitro and animal studies, the growing body of preclinical and clinical evidence has demonstrated the therapeutic potential of phytopharmaceutical nanoformulations for peri-implantitis prevention and management. Consistent in vitro studies have shown that nanoencapsulation improves the antimicrobial activity of phytochemicals against peri-implant pathogens compared with their conventional formulations. Polymeric nanoparticles, liposomes, and nanostructured lipid carriers loaded with curcumin have demonstrated better inhibition of the growth of Porphyromonas gingivalis, Fusobacterium nucleatum, Tannerella forsythia and Aggregatibacter actinomycetemcomitans, along with the disruption of mature biofilms and the decrease of bacterial adhesion to the surfaces of titanium implants (37). Epigallocatechin-3-gallate (EGCG), quercetin, berberine, propolis, and thymoquinone nanoformulations have also shown similar improvements, as they exhibit extended antimicrobial effects, increased cellular uptake, and deeper penetration into the biofilm than their free forms. Human gingival fibroblasts, periodontal ligament cells, osteoblasts and mesenchymal stem cells have also demonstrated excellent biocompatibility of phytopharmaceutical-loaded nanoparticles and stimulated cell proliferation, migration, collagen synthesis, alkaline phosphatase activity, extracellular matrix mineralization and expression of osteogenic markers, such as runt-related transcription factor 2 (RUNX2), osteocalcin, osteopontin and bone morphogenetic protein-2 (38). These nanoformulations also suppress NF-κB and MAPK signaling pathways, leading to a significant reduction in the production of inflammatory mediators such as tumor necrosis factor-α, interleukin-1β, interleukin-6, cyclooxygenase-2, prostaglandin E_2, and reactive oxygen species, and promoting tissue regeneration. These findings have been confirmed in animal studies with experimental peri-implantitis and periodontitis models in rats, rabbits and dogs. Administration of phytopharmaceutical-loaded nanoparticles has shown important effects in reducing inflammatory cell infiltration, periodontal pocket depth, bacterial load and alveolar bone loss and in promoting new bone formation, collagen deposition, angiogenesis and implant

osseointegration at the local level. Curcumin-loaded hydrogels and chitosan nanoparticles, resveratrol-loaded lipid nanoparticles, and EGCG-coated titanium implants have resulted in better peri-implant bone preservation and faster tissue healing than conventional treatments (26). Nanoengineered implant coatings containing antimicrobial phytochemicals have also been shown to provide sustained drug release, decreased early bacterial colonization and improved implant stability during healing. Although these are promising preclinical studies, clinical data are relatively sparse. A few RCTs and pilot clinical trials have shown improvements in clinical parameters, including plaque index, bleeding on probing, probing pocket depth, clinical attachment level, and peri-implant mucosal inflammation, as well as reductions in microbial load, with the use of phytopharmaceuticals in local delivery systems, herbal gels, mouth rinses, and implant coatings (39). These outcomes suggest the promise of clinical benefits from therapies based on phytopharmaceuticals, but few studies have specifically evaluated the use of more advanced nanoformulations in peri-implantitis patients. The number of patients in most clinical trials is limited, follow-up is short, and treatment is heterogeneous. In addition, little comparative data exists between different nanocarriers, phytochemicals combinations, doses and methods of administration, which makes it difficult to set up standardized clinical indications. Also, differences in nanoparticle composition, encapsulation efficiency, nanoparticle release, and production methods lead to inconsistencies in reported outcomes (40). Thus, long-term multicenter clinical trials with standardized nanoformulations using a larger number of patients, long-term follow-up, and thorough safety evaluation are needed to validate the efficacy of the nanoformulations, optimize the treatment protocol, and introduce the nanoformulations into routine clinical practice for peri-implant disease management based on a strong biological rationale and therapeutic promise.

Table 2: Representative preclinical and clinical studies on phytopharmaceutical-based nanoformulations for peri-implantitis management.

Author (Year)	Phytopharmaceutical	Nanoformulation	Study Model	Key Findings
Moballegh Nasery et al. (2020)	Curcumin	Polymeric nanoparticles	In vitro	Enhanced antimicrobial and anti-inflammatory activity
Shahbazi et al. (2021)	EGCG	Chitosan nanoparticles	In vitro	Inhibited biofilm formation and bacterial adhesion
Yang et al. (2022)	Resveratrol	Solid lipid nanoparticles	Rat model	Reduced bone loss and promoted osteogenesis
Zhang et al. (2022)	Quercetin	PLGA nanoparticles	Cell culture	Improved osteoblast proliferation and antioxidant activity
Li et al. (2023)	Berberine	Polymeric nanoparticles	Animal model	Enhanced bone regeneration and reduced inflammation
Silva et al. (2023)	Propolis	Nanoemulsion	In vitro	Strong antibacterial and wound-healing effects
Chen et al. (2024)	Curcumin	Injectable hydrogel	Rat peri-implantitis model	Sustained drug release and enhanced bone regeneration
Recent Clinical Studies (2023–2025)	Herbal nanoformulations	Local delivery systems	Human studies	Improved probing depth, plaque control, and peri-implant health

8. Advanced Strategies and ImpPlant Surface Functionalization

Recent developments in the fields of nanotechnology and biomaterials have gone beyond the traditional use of phytopharmaceuticals in drug delivery to multifunctional implant surface modifications and smart therapeutic platforms for peri-implantitis prevention. Much research has been done to develop implant surfaces that are both biologically and mechanically compatible and to minimize bacterial adhesion to the implant surface, as the first step in peri-implant disease is bacterial adhesion to the surface of the implant (41). Nanoengineered implants, such as titanium implants, have shown great promise in achieving these goals by coating them with nanomaterials containing phytopharmaceuticals that release them locally and over time at the implant–tissue interface. Curcumin, epigallocatechin-3-gallate, quercetin, berberine, and other plant-based compounds have been found to inhibit bacterial adhesion, decrease the formation of biofilms, suppress the production of inflammatory cytokines, and increase the proliferation of osteoblasts, all of which improve the stability and long-term clinical performance of implants when applied as surface coatings (33). Chitosan, poly(lactic-co-glycolic acid), alginate, gelatin, and hyaluronic acid have been used as bases for developing biodegradable polymer coatings that can serve as carrier matrices due to their very good biocompatibility, controlled degradation behaviour, and capacity to provide sustained drug release. Besides the conventional coatings, electrospun nanofibrous membranes filled with phytopharmaceuticals have proven to be promising scaffolds for guided bone regeneration and for peri-implant tissue repair (42). They have an extracellular matrix-like structure that promotes cell adhesion, proliferation, angiogenesis, and extracellular matrix deposition, and acts as a source of a constant release of antimicrobial and anti-inflammatory phytochemicals. Another novel approach is injectable nanocomposite hydrogels, which can be used to fill irregular bone lesions, remain closely associated with the surrounding tissues and ensure the controlled release of phytochemicals, while favoring tissue regeneration, especially for localized treatment of peri-implant defects. A more recent study examined stimuli-responsive, or "smart," nanocarriers that could release therapeutic agents in response to changes in pH, ROS, enzyme activity, or inflammatory mediators in diseased peri-implant tissues, thereby increasing site-specific drug delivery and reducing undesirable drug exposure (43). Furthermore, hybrid nanoplatforms containing phytopharmaceuticals, metallic nanoparticles, bioactive ceramics, mesoporous silica nanoparticles, and biodegradable polymers have shown synergistic antimicrobial and osteogenic effects and are promising candidates for next-generation implant coatings. Surface nanotopography is also of key importance in the response of cells, and surfaces of implants that have been nano-patterned are reported to improve protein adsorption, fibroblast attachment, osteoblast differentiation and bone-to-implant contact, in addition to decreasing bacterial adhesion. The multifunctional implants that incorporate phytopharmaceuticals into these nanostructured surfaces offer an additional biological benefit by fighting infection and aiding tissue repair. The advent of new technologies such as three-dimensional (3D) printing, additive manufacturing, and biofabrication has paved the way for the fabrication of personalized drug-eluting implants that meet patients' anatomical and clinical needs (44). In addition, AI and computational modelling are increasingly being used to optimize the selection of phytochemicals, the design of nanoparticles, the release kinetics of drugs and the surface properties of implants, thus speeding up the development of precision nanomedicine for implant dentistry. While these cutting-edge approaches are still in their nascent, experimental and preclinical stages, these advances hold great promise for the future of implant systems that can prevent peri-implantitis and improve long-term implant success through intelligent design. Future translational studies should be directed towards scalable manufacturing, long-term biocompatibility, regulatory approval, and well-designed clinical studies to assess the safety and clinical efficacy of these novel multifunctional implant technologies (45).

9. Safety, Toxicity, and Regulatory Considerations

While the use of phytopharmaceutical-based nanoformulations is highly promising in peri-implantitis management, several safety, toxicity and regulatory issues need to be resolved before clinical translation. Phytopharmaceuticals, however, given their natural origin and wide therapeutic window, are generally safer than synthetic drugs, but their biological activity depends on the plant species, growing conditions, extraction methods, and phytochemical composition. This is because such variability can affect efficacy, reproducibility, and safety, underscoring the need for standardized production processes and quality control. When using phytochemicals as nanocarriers, there are also safety issues regarding nanoparticle size, charge, composition, and biodegradability (46). Although nanoparticles can facilitate drug delivery, they can cause oxidative stress, inflammation, or cytotoxic effects due to their prolonged presence. So, careful investigation of the biocompatibility of nanoparticles becomes of utmost importance. Biodegradable polymers like alginate, chitosan, gelatin and poly(lactic-co-glycolic acid) are generally regarded as safe because they are metabolized into non-toxic metabolites. Likewise, lipid-based systems such as liposomes and solid lipid nanoparticles are known to possess good biocompatibility and low immunogenicity (47). By contrast, some inorganic nanoparticles, especially those of metals, may be dose-dependent toxins unless they are carefully designed. The full toxicological characterization is essential and should include in vitro tests for cytotoxicity, genotoxicity, immunotoxicity, hemocompatibility, and pharmacokinetics, as well as long-term in vivo studies. Furthermore, certain plant-derived ingredients, including propolis and essential oils, can cause allergic reactions or mucosal irritation in some people, so it is important to optimize their dosage and carefully select the right patients. Regulatory-wise, nanoformulations for phytopharmaceuticals are complex and must be evaluated in accordance with pharmaceutical and nanotechnology standards. The regulatory authorities like FDA and EMA demand information about product quality, stability, safety and effectiveness. But until there are harmonised guidelines for nanophytopharmaceuticals worldwide, approval procedures remain complicated. Commercialization is also affected by manufacturing problems, such as reproducibility, scalability, and storage stability (48). Although the preclinical results are promising, well-designed clinical trials are needed to validate long-term safety and efficacy. The successful translation of these novel therapies into standard clinical practice will depend on the collaborative efforts of researchers, clinicians, and regulatory bodies.

10. Current Challenges and Future Perspectives

Although significant advances have been made in the formulation of phytopharmaceuticals for the treatment of peri-implantitis at the nanoscale, several obstacles still hinder their successful translation into clinical practice. A key constraint is the lack of standardized phytopharmaceutical preparations since the type of plant, the extraction techniques, the conditions for cultivation and the phytochemical composition of the plant can result in variable therapeutic effects. Likewise, the use of various synthesis methods, the efficiency of drug loading, the size distribution, and the release rate make it challenging to compare results across studies or define a standard treatment. The bulk of the published evidence comes from in vitro studies and small animal models; well-designed, multicenter randomized clinical trials with long follow-up periods are rare. Also, the safety, pharmacokinetics, biodegradation, and possible cumulative effects of repeated oral exposure to nanoparticles have not yet been studied. Significant barriers to commercialisation include manufacturing scalability, cost-effectiveness, quality control and regulatory approval. Future studies are needed to synthesize nanoformulations with multiple therapeutic functions that could exert antimicrobial, anti-inflammatory, antioxidant, immunomodulatory, and osteogenic properties through controlled drug release. Site-specific drug delivery may be further enhanced by smart nanocarriers sensitive to pH, reactive oxygen species, enzymes and/or inflammatory biomarkers, which can further reduce the systemic exposure. A combination of phytopharmaceuticals and advanced technologies such as 3D bioprinting, bioactive implant coatings, tissue-engineered scaffolds, and regenerative biomaterials offers an opportunity to improve implant longevity and

peri-implant tissue regeneration. Furthermore, the use of Artificial Intelligence, Machine Learning, and Computational Modeling is anticipated to speed up the screening of phytochemicals, optimization of nanoparticles, and personalized treatment designs, which will contribute to the advancement of precision implant dentistry (49). Future investigations should also focus on sustainable, green nanotechnology strategies for synthesizing nanoparticles to enhance environmental and safety outcomes in manufacturing. In conclusion, interdisciplinary cooperation will help overcome current scientific, technological, and regulatory limitations and, ultimately, enable the development of safe, efficient, and personalized therapeutic approaches using phytopharmaceutical-based nanoformulations for peri-implantitis prevention and management in the clinic.

11. Conclusion

Peri-implantitis is one of the most complex and difficult to treat biological complications of dental implants, which is a multifactorial process including microbial biofilms, chronic inflammation, oxidative stress and continuous alveolar bone loss. Whilst traditional therapeutic methods can provide some control of the disease, they have drawbacks, including incomplete biofilm removal, antibiotic resistance, and unpredictable regeneration success, which have led to the investigation of alternative treatment options. Due to their broad-spectrum antimicrobial, anti-inflammatory, antioxidant, immunomodulatory, and osteogenic activities, phytopharmaceuticals are now emerging as promising therapeutic agents. Nevertheless, they have limited clinical use due to their low solubility and bioavailability, high degradation rate and short half-life at the target site. Nanotechnology has been able to solve many of these challenges by improving drug stability, enabling targeted and sustained delivery, enhancing their bioavailability to penetrate the biofilm, and exerting localized therapeutic action. The nanophytopharmaceuticals, which are advanced nanocarriers including polymeric nanoparticles, lipid-based systems, hydrogels, nanofibers, and implant surface coatings, have shown promising results in inhibiting microbial colonization, dampening inflammatory pathways, maintaining peri-implant bone, and improving tissue regeneration. Additionally, the development of novel technologies such as smart nanocarriers that respond to specific stimuli, bioactive coatings for implants, 3D printing, and artificial intelligence-guided formulation design has broadened the scope of precision implant dentistry. While these encouraging developments have been made, much of the current evidence is preclinical, and high-quality clinical trials are needed to confirm long-term efficacy, safety, optimal doses, and cost-effectiveness. Future studies should focus on standardisation of phytopharmaceutical formulations, feasibility of large-scale production, regulatory harmonisation, and multidisciplinary collaboration for successful clinical translation. In conclusion, phytopharmaceutical-based nanoformulations hold potential as a novel therapeutic strategy that could revolutionize the prevention and treatment of peri-implantitis by offering safer, more targeted, and regenerative options to enhance implant longevity and patient outcomes.

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