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Evaluation of Natural Extracts as Promising Components of Bioactive Coatings for Orthopedic Implants

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The development of drug-eluting bioactive coatings for orthopedic implants has gained increased interest in recent years with an intent to reduce postoperative complications and improve tissue regeneration at the implant interface. Due to the remarkable benefits of natural polyphenolic components, such as antioxidant, antimicrobial, anti-inflammatory, anti-cancer and bioactive activity, and their ubiquitous availability in nature, they are promising candidates for incorporation into bioactive coatings of advanced medical devices in future clinical applications. However, further research is needed to address all challenges. This review aims to highlight the prosperity of natural compounds widely available in nature loaded in implantable devices, summarize the "state of the art" in this field, identify the challenges, and accordingly suggest the optimal preparation methods and characterization.

Keywords: polyphenols, bioactive coatings, orthopedic implants, deposition techniques, encapsulation, characterization

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INTRODUCTION

Despite evident advances in the development of implantable orthopaedic devices and usually favourable surgical outcomes, revision surgeries are still occasionally required due to infection, inadequate stability, and aseptic loosening (Levent et al., 2021). Current implants are generally made of biocompatible metallic materials (medical grade stainless steel, titanium, titanium alloys, etc.), which have adequate mechanical stability and corrosion resistance but insufficient biological response necessary for tissue growth around the implant (Hench and Jones, 2005). A viable approach to improve osteointegration of implants is by preparation of drug-eluting bioactive coatings for implants with osteoinductive, osteoconductive (Song et al., 2021a), biocompatible, antimicrobial, and anti-inflammatory effects (Bagherifard, 2017). Thus far, mostly synthetic bioactive substances such as growth factors (Yu et al., 2022), osteoclast inhibitors (Bjelić and Finšgar, 2022), antibiotics (Li et al., 2022), and anti-inflammatory drugs (Gherasim et al., 2021) have been at the forefront for this purpose. However, their main disadvantages are associated with their possible incompatibility and high cost. For example, commercially available growth factors are fairly unstable and are produced using recombinant technology, making them extremely expensive. Therefore, the focus has been on preparing simple, inexpensive, and, most importantly, effective bioactive coatings (Córdoba et al., 2015).

Natural compounds such as polyphenols (anthocyanidins, catechins, flavanones, flavones, flavonols, isoflavones, hydroxybenzoic acids, hydroxycinnamic acids, lignans, and tannins) are of great interest in pharmaceutical, nutraceutical, and medical fields due to their antioxidant,

TABLE 1 | Summary of natural compounds included in bioactive coatings for implants, matrix/substrate used, and benefits reported in the literature.

(Natural) Bioactive Compound	Matrix/Substrate	Benefit	References
Polyphenolic extract from green tea (Camellia Sinensis)	Chemically pretreated Ti6Al4V allowing the functionalization *via* -OH groups	Promoting osteoblast differentiation and mineralization	Cazzola et al. (2018)
Organosolv Alcell lignin extracted from North American hardwoods (maple, birch, poplar)	Electrophoretic deposition of hydroxyapatite (HA) and lignin or HA, lignin, and Ag on Ti substrate	Protection of HA lattice and prevention of HA decomposition during sintering	Erakovic et al. (2014)
Unmodified and modified pectin Rhamnogalacturonan-I isolated from potato and apple	Nanocoating on Ti substrate	Improving hydrophilicity and increasing mineralized matrix formation of osteoblastic cells *in vitro*	Gurzawska et al. (2014)
Taxifolin and quercitrin	Covalent immobilization with APTES as a coupling agent on Ti substrate	Anti-inflammatory and anti-fibrotic potential on human gingival fibroblasts, osteoinductivity	Córdoba et al. (2015)
Aloe vera gel extract acemannan	Silver oxide and silica-doped HA coatings on Ti alloy, dip coated with acemannan and chitosan	Controlled release of acemannan, improved osteointegration with new bone formation *in vivo*	Banerjee and Bose, (2019)
Polycaffeic acid	The coating produced by combined oxidative and UV light-assisted polymerization on 316L stainless steel substrate	Enhanced wettability, bioactivity	Aguilar et al. (2019)
Tannins from Terminalia chebula extract	poly (D,L-lactide) carrier drop casted on Ti6Al4V	Antibacterial effect, controlled release	Shukla and Bhathena, (2015)
Naringin	Loaded electrospun nanoscaffold made of poly (ε-caprolactone) and poly (ethylene glycol)-block-poly (ε-caprolactone)	Controlled release, enhanced functions of osteoblasts, and suppress the formation of osteoclasts	Ji et al. (2014)
Gallic acid	Film of crosslinked gallic acid and hexamethylenediamine on magnesium alloy	Corrosion mitigation	Chen et al. (2019)
Tannic acid	Tannic acid and gelatin layer-by-layer coatings on various substrates (Ti, glass, silicon, sensors)	Enhanced osteogenesis *in vitro* and bone formation *in vivo*	Yang et al. (2019)
Quercitrin	Covalently coated on Ti surface	Decreased osteoclastogenesis *in vitro* and *in vivo*	Córdoba et al. (2018)
	Covalent immobilization on Ti surface with APTES	Decreased bacterial adhesion, increased human gingival fibroblasts attachment, enhanced soft tissue integration	Gomez-Florit et al. (2016)
Quercetin	Loading the titania nanotubes formed by anodic oxidation of Ti-6Al-7Nb and coating them with chitosan	Achieving controlled release of quercetin with the future potential of treating postoperative infections and inflammation and improving osteointegration	Mohan et al. (2016)
Caffeic acid	Composite dextran-caffeic acid/tetraaniline coating on Mg alloy prepared *via* electrophoretic deposition of self-assembled colloidal particles and photo-crosslinking	Corrosion mitigation, improved cytocompatibility	Li et al. (2020)
Curcumin, vitamin K2	Dual drug solution added on top of plasma-sprayed HA coatings on Ti substrate	Enhanced osteoblast cell adhesion and proliferation, lower *in vitro* osteosarcoma cell proliferation, improved tissue-implant contact *in vivo*	Sarkar and Bose, (2020)

antimicrobial, anti-inflammatory, bioactive, and anti-cancer effects (Fang and Bhandari, 2010). With their diverse benefits, abundance, and resulting affordability, they can be employed in a wide range of pharmaceutical and biomedical applications by incorporating them into suitable formulations that promote controlled release (Lewandowska et al., 2013; Agrawal, 2015; de Araújo et al., 2021). Thus far, numerous attempts have been made to use polyphenols for oral drug delivery, successfully improving the oxidative stability, light insensitivity, and bioavailability of poorly water-soluble bioactive compounds (Wang et al., 2018; Ahmadi et al., 2019). In combination with biocompatible, porous, and biodegradable polymers, they show promise for wound dressing due to the breathability, ability to absorb excess exudate, and antibacterial activity of the biofilms obtained (Fras Zemljič et al., 2020; Maver et al., 2020). In addition, polyphenols have been shown to have selective toxicity toward cancer cells and a protective role on healthy cells. Therefore, they are great candidates for grafting onto ferrimagnetic materials to stimulate anti-cancer activity and hyperthermia simultaneously (Córdoba et al., 2015). It was previously suggested that polyphenols grafted onto bioactive glasses are effective as bone substitutes in cancer treatment (Cazzola et al., 2017). While many studies (Fraga et al., 2010; Gorzynik-Debicka et al., 2018; Enaru et al., 2021) have confirmed the benefits of bioactive substances from natural sources, references regarding their incorporation into bioactive coatings

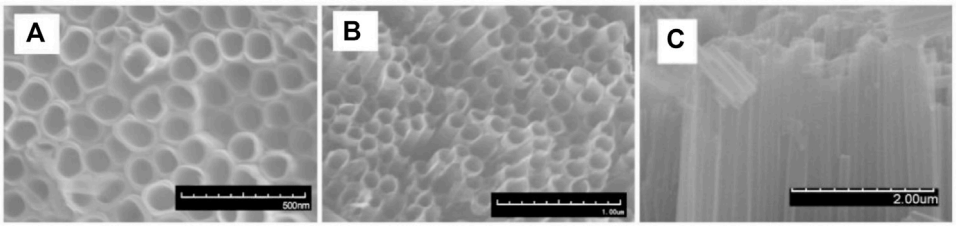

FIGURE 1 | SEM images of titania nanotubes prepared by anodization of Ti substrate: **(A,B)**, top view **(C)** cross-sectional view. Reprinted with permission from (Tong et al., 2021).

for orthopedic implants are limited. The objective of this review is to highlight the advantages and challenges of bioactive substances isolated from plants or microorganisms in implantable devices and to summarize the current research data in this field. The masucript will also focus on the preparation of such coatings by suggesting deposition techniques, encapsulation methods to maintain the efficacy of the otherwise unstable bioactive substances, and characterization required to evaluate the properties of the coatings obtained, allowing their improvements to achieve optimal bioactive coatings in the future.

THE DEVELOPMENT OF BIOACTIVE COATINGS LOADED WITH NATURAL COMPOUNDS FOR ORTHOPEDIC IMPLANTS

In the development of coating for the implant, synthetic drugs, polyphenols alone, or polyphenol-rich extracts from natural sources are either immobilized on the substrate (implant) or deposited in combination with other materials on the substrate using well establised deposition techniques. Several studies confirm that incorporating polyphenols meets the requirements for use in bioactive implant coatings, such as osteoinductivity, osteoconductivity, biocompatibility, corrosion inhibition, and antibacterial and anti-inflammatory activity, and, more importantly, contributes to their improvement. The bioactive coatings for implants containing natural compounds developed to date, the benefits obtained, and related references are listed in **Table 1**.

COATING DEPOSITION TECHNIQUES

Various coating deposition techniques have been developed to ensure uniformity, desired thickness, sufficient load-bearing mechanical properties, controlled release, and high adhesion to the implant (Asri et al., 2016; Ehlert et al., 2011). The simplest yet very effective are dip coating (Babu et al., 2004; Banerjee and Bose, 2019), drop casting (Shukla and Bhathena, 2015), and layer-by-layer deposition techniques (Yang et al., 2019). However, over the years, immense progress has been made by implementing electrophoretic deposition (Erakovic et al., 2014), electrospinning (Ji et al., 2014), plasma spraying (Sarkar and Bose, 2020), physical vapor deposition (Aktug et al., 2019), chemical vapor deposition (Youn et al., 2019), sol-gel (Omar et al., 2020), and biomimetic deposition, the latter being especially prosperous by encountering heterogeneous nucleation and crystal growth of the coating with bone-like properties (Koju et al., 2017). Nevertheless, not all are suitable for the deposition of fairly sensitive natural bioactive compounds, as they would not withstand the working conditions (e.g., high processing temperatures). It was shown previously that titania nanotubes (**Figure 1**)prepared by anodization of pure Ti or its alloys are very promising. They combine the ability to integrate bioactive compounds in their hollow structure and allow bioactivity enhancement by cell attachment to nanotopographic surface properties (Mohan et al., 2016).

The importance of 3D printing should also be emphasized because it can be used for the production of tailorable bioactive coatings and can in the future easily enable the fabrication of personalized implant coatings by varying the coating material as well as the type and dosage of bioactive compounds to be released from the matrix (Li et al., 2019; Maver et al., 2021).

ENCAPSULATION METHODS FOR EXTRACT PRESERVATION AND IMPROVED SOLUBILITY IN BODY FLUIDS

Despite the many advantageous properties of bioactive compounds of natural origin, they often lack stability and solubility in body fluids (Parisi et al., 2014; Wildman et al., 2016; Lu et al., 2016). To ensure their maximum efficacy, various encapsulation methods have been established over the years to 1) protect the active compounds from undesirable environmental factors such as light, temperature, moisture, oxygen, etc., thereby reducing their reactivity and spoilage, 2) to allow controlled release of the compounds, 3) to mask the taste and odor (e. g. in food industry), and 4) to achieve the desired dosage and dispersion of the compounds in the matrix (Sonawane et al., 2020). The recently developed encapsulation methods are already explained in detail by several references (Fang and Bhandari, 2010; Munin and Edwards-Lévy, 2011; Castro-Rosas et al., 2017) and are generally divided into physical, physiochemical, or chemical methods as shown in **Table 2**, with the main principle of incorporating the core material (bioactive compound) into the wall material in reservoir or

TABLE 2 | Classification and a short description of encapsulation methods used for active compounds (Munin and Edwards-Lévy, 2011).

Physical Methods	Physiochemical Methods	Chemical Methods	Other Methods
Spray drying	Encapsulation by cooling of emulsions	*In situ* polymerization	Encapsulation in yeasts
Encapsulation using supercritical fluids	Emulsification-solvent removal methods	Interfacial polycondensation and interfacial crosslinking	Co-crystallization
—	Methods based on ionic interactions (ionic gelation, acidic precipitation, complex coacervation, layer-by-layer process)	—	Molecular inclusion
—	Methods based on hydrophobic interactions (micelles, liposomes)	—	Freeze-drying

matrix manner to preserve its biological, chemical, and physical properties (Munin and Edwards-Lévy, 2011; Sonawane et al., 2020).

To the best of the authors' knowledge, very few, if any, studies have been found on the encapsulation of natural compounds by the methods mentioned above for use in coatings for orthopedic implants (Cazzola et al., 2018; Gamna and Spriano, 2021; Riccucci et al., 2021; Riccucci et al., 2022). Nevertheless, they are promising for future research as they have been extensively studied for use in the food industry. Therefore, a more in-depth evaluation of some of the methods is presented below. Spray drying is one of the most frequently used encapsulation techniques due to its simplicity, low operating cost, adequate yield, uniform, spherical particle size, and high stability of the obtained capsules (Mahdavi et al., 2014). Its disadvantage lies mainly in the application of high processing temperatures, which can lead to the degradation of thermally sensitive compounds (Belščak-Cvitanović et al., 2011; Sun-Waterhouse et al., 2013; González et al., 2019; Chaumun et al., 2020; Goëlo et al., 2020). However, an example of the aromatic evergreen tree *Laurus nobilis L.*, rich in phenols, which has been alongside gallic acid (GA) encapsulated by the spray drying method in different polymer matrices, allowed yields ranging from 73 to 99%, while *in vitro* drug release testing simulated body fluids (SBF) allowed controlled release (Chaumun et al., 2020).

Furthermore, encapsulation methods using supercritical fluids (SCFs) have been established as green technologies. They are a promising alternative to conventional methods because they do not require the use of harmful organic solvents and have suitable operating parameters, especially when using supercritical CO_2 (SC-CO_2) with the critical point of 31°C and 73.8 bar, offer the possibility of dissolving both polar and nonpolar bioactive compounds, produce practically no waste, and have high encapsulation efficiency. Depending on the role of SC-CO_2, which can act as a solvent, solute, or anti-solvent, three encapsulation methods were developed, namely Rapid Expansion of Supercritical Solutions (RESS), Particles from Gas Saturated Solutions (PGSS™), and Supercritical Anti Solvent (SAS), respectively (Weidner et al., 2004; Munin and Edwards-Lévy, 2011; Kravanja et al., 2018; Klettenhammer et al., 2020). In a study by Gonçalves et al. (Gonçalves et al., 2016), PGSS™ was used to encapsulate epigallocatechin gallate (EGCG) to preserve its chemical stability using modified n-octenyl succinate anhydride starch, soybean lecithin, and barley-β-glucan as polymer carriers. The obtained products showed no cytotoxicity, improved storage stability, and maintenance of antioxidant activity with all polymer carriers at an encapsulation efficiency of about 80%. Furthermore, β-glucan and lecithin facilitated the intracellular activity of EGCG, and lecithin as a carrier promoted a more sustained EGCG release in SBF (Gonçalves et al., 2016).

Among physiochemical methods, there are several emulsion-based encapsulation variants (Munin and Edwards-Lévy, 2011; Markočič et al., 2012; Lu et al., 2016). Poly (lactic acid) (PLA) nanoparticles containing a polyphenol aureusidin with high antioxidant activity were prepared by an emulsification-solvent evaporation technique in which PLA and aureusidin were dissolved in acetone and injected into an aqueous solution of polyvinyl alcohol (PVA). The encapsulation efficiency of the final product ranged from 68 to 98% at a drug loading of 60% (Roussaki et al., 2014). In addition, methods based on ionic interactions have gained increasing interest over the years due to their simplicity. Ionotropic gelation is typically used to prepare sodium alginate beads by mixing the bioactive compound/drug solution and sodium alginate, which is then dripped into a solution of divalent ions (e.g., Ca^{2+}) using a syringe. Upon the contact, ionic crosslinking occurs between the carboxylate groups of the guluronate groups (G-blocks) of the alginate backbone and the divalent ions, creating a hydrogel network (Burdick et al., 2005; Giri et al., 2016). A study was conducted for the preparation of alginate microspheres for the encapsulation of blueberry residues. After dissolving sodium alginate and blueberry residues in ultrapure water, they were dripped into a $ZnCl_2$ solution, which aided in microencapsulation with a resulting encapsulation efficiency of up to 100%. However, phenolic dissolution measurements showed an almost immediate burst release that reached a plateau within the first 10 min (Bittencourt et al., 2018). Such high-diffusion rates through the porous alginate structure indicate certain limitations in its use for drug delivery, hence various fillers were added to improve the structure. In a study by Bušić et al., natural fillers such as whey proteins, cocoa powder, and carob powder were added to the alginate for encapsulation of polyphenols from dandelion (*Taraxacum officinale L.*). The fillers enabled higher retention of antioxidant capacity, high encapsulation yield, and prolonged release of polyphenols in simulated gastric fluids (SGF) and simulated intestinal fluids (SIF) (Bušić et al., 2018).

Another commonly used method of microencapsulation is molecular inclusion, which generally refers to cyclodextrins formed by enzymatic modification of starch. β-cyclodextrin and its derivatives are most commonly used as they are inexpensive, are not inclined to cause irritation, and are easy to prepare (Singh et al., 2019). Polyphenols from pomegranate fruit (Diamanti et al., 2017), tea (Song et al., 2021b), cornelian cherry (*Cornus mas L.*) (Popović et al., 2021), St. John's wort (*Hypericum perforatum*) (Kalogeropoulos et al., 2010), olive leaf (Mourtzinos et al., 2007), etc. have been successfully encapsulated in β-cyclodextrins. Moreover, a study of olive leaf encapsulation, it was demonstrated that the aqueous solubility of polyphenolic content increased by more than 150% (Mourtzinos et al., 2007).

As mentioned above, many encapsulation methods have successfully preserved the stability of natural bioactive compounds while allowing their controlled release and ensuring high encapsulation yields. The choice of method depends on the active compound and encapsulation material, their properties, application, and cost. A detailed analysis of the obtained capsules is essential to determine their usefulness for the application or necessary improvements in the future.

THE TECHNIQUES FOR THE BIOACTIVE COATING CHARACTERIZATION

Further characterization of the obtained implant coatings containing natural bioactive compounds can be divided into three important segments: 1) characterization for qualitative and/or quantitative analysis of the chemical composition, interactions, and morphology data, 2) *in vitro* release testing required for the optimization of controlled release formulations to achieve desired release kinetics of bioactive compounds, and 3) cell culture characterization. As mentioned above, the first segment includes chemical composition determination techniques such as secondary ion mass spectrometry (SIMS), X-ray photoelectron spectroscopy (XPS), or Fourier transform infrared spectroscopy (FTIR). Combining these with techniques for determining morphology, topography, and other surface-specific features, such as scanning electron microscopy (SEM), transmission electron microscopy (TEM), atomic force microscopy (AFM), 3D tomography, quartz crystal microbalance (QCM), adhesion and contact angles (CA) measurements, enables a comprehensive analysis of bioactive coatings and a better understanding of the correlation between the physiochemical properties of the coatings and the results of bioactive compound release and bioactivity. Considering the known antioxidant activity of natural extracts or isolated bioactive compounds, several conventional spectrophotometric methods can be employed to test antioxidativity, namely the 1,1′-diphenyl-2-picrylhydrazyl (DPPH) free radical scavenging assay, determination of total phenolic content using the Folin-Ciocalteu reagent, total flavonoid content, proanthocyanidins, etc. (Sultana et al., 2009). However, chemiluminescent probes, electrochemical sensors, spectroscopic, fluorescent-dependent, spectrophotometric, and chromatographic methods have been applied to detect reactive oxygen species (ROS) associated with oxidative stress generated at the cellular level *in vivo* and *in vitro* systems (Prasad et al., 2019). *In vitro* release testings of bioactive compounds are typically performed using one of the seven types of USP dissolution apparatuses or their variations (e.g., Franz diffusion cells) and provide as a result a cumulative percentage of released active compound in SBF detected by UV-Vis, high performance liquid chromatography (HPLC) or enzyme-linked immunosorbent assay (ELISA) over a selected period of time, which can be evaluated using known kinetic models (Kravanja and Finšgar, 2021). Depending on the type of bioactive compound and the prepared coating system, studies have reported successful controlled release of natural bioactive compounds has been reported in studies, lasting between 6 and 100 days (Ji et al., 2014; Shukla and Bhathena, 2015; Mohan et al., 2016; Banerjee and Bose, 2019; Sarkar and Bose, 2020). Lastly, cell culture characterization is useful for evaluating antimicrobial activity against selected microorganisms causing postoperative infections (Shukla and Bhathena, 2015), bioactivity (e.g., fluorescent microscopy to determine osteogenic differentiation of mesenchymal stem cells or osteoblast adhesion to the coatings) (Rožanc et al., 2021), and biocompatibility of the prepared coatings by testing cytotoxicity on healthy cells (e.g., WST-1 assay, MTT assay, etc.) (Felice et al., 2013; Sarkar and Bose, 2020).

SUMMARY AND OUTLOOKS

Polyphenols are a promising alternative to synthetic drugs for reducing postoperative complications by incorporating them into bioactive coatings for orthopedic device implantation. This is due to their remarkable biological activity and abundant occurrence in natural sources from which they can be easily isolated using various extraction methods. However, before they can be used in clinical practice, several challenges must be addressed.

For example, polyphenols are inherently subjected to light and heat sensitivity, oxidation reactions, and poor solubility in body fluids. Therefore, the selected application requires careful consideration of the coating deposition technique, which should not operate under processing conditions that are hazardous to the bioactive compounds. To preserve their efficacy, encapsulation of bioactive compounds is a particularly convenient solution that simultaneously contributes to their localized controlled release from the prepared formulations by modifying their pharmacokinetics. While cellular viability data are already available for singular bioactive compounds, further studies surrounding the cytotoxicity of complex systems of multiple bioactive compounds in polyphenol-rich extracts are needed before they can be implemented in coatings. On this basis,

appropriate characterization of the developed coatings is crucial as it can evaluate the relationship between interaction, morphology, release kinetics, and bioactivity.

Ongoing research has shown that applying natural bioactive compounds in coatings that stimulate osteogenesis *in vitro* and bone formation *in vivo* has been an initial success. Profound studies are still required to consider current limitations and to fabricate optimized medical implants that exhibit long-term osteointegration and prevent postoperative infection and inflammation.

AUTHOR CONTRIBUTIONS

MK, MF, and KK conceived and designed the review. KK has written and edited most of the manuscript. MM, ŽK and MF reviewed the manuscript. ŽK and MF are responsible for the financial part of the projects listed in fundings. All authors accepted the final version of the manuscript.

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