

Bioactive Biomaterials: Phenolic and Terpenic Compounds as Prospective Antibacterial and Antioxidant Additives for Electrospun Scaffolds

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Abstract: The application of electrospun scaffolds for musculoskeletal tissue repair, such as bone or tendon/ligament, is a growing field of research. They can mimic the fibrous architecture of native extracellular matrix, while simultaneously allowing to support cell attachment, proliferation, and ultimately tissue regeneration. However, implantation of electrospun scaffolds also faces the challenges of implant-associated infection or excessive oxidative stress. Both scenarios can result in serious inflammation, or fibrosis in the case of tendon injury repair, which might lead to failure of the implanted scaffold and strictly limited success of tissue healing. Modification of electrospun scaffolds via incorporation of compounds exerting antibacterial as well as antioxidant activity emerges as a promising approach to counteract these challenges. In this context, naturally derived compounds, such as those of phenolic or terpenic origin, are interesting candidates, because of their potential dual-action nature. In the first part of this review, the most promising candidate compounds to be incorporated into electrospun scaffolds for musculoskeletal tissue repair are examined. We discuss the mechanisms through which these compounds interact with Gram-positive and Gram-negative bacteria in regards to surface attachment, biofilm formation and virulence activity in general. We also highlight the most recent research on their antioxidant potential as well as their effect on cellular host inflammation pathways. In the second part of this review, particular emphasis is placed on strategies for incorporating these compounds into electrospun scaffolds. Finally, we propose future perspectives for research and development of functionalized electrospun scaffolds with bioactive character to advance translation into clinical application.

Keywords: electrospinning; antibacterial; oxidative stress; phytochemicals; musculoskeletal; tissue healing

1. Introduction

Over the last few decades, electrospinning has emerged as a versatile technique for producing nano- to microscale fibrous, biomimetic coatings, and scaffolds for implants, thereby significantly improving biocompatibility, bioactivity, tissue integration, and drug delivery [1,2]. Beyond standard methods, specialized approaches include dual electrospinning (two-nozzle systems) for multi-polymer fibers [3], co-axial electrospinning for core-shell architectures [4], or needle-less electrospinning [5]. Furthermore, mesh morphology



can be varied by the fabrication of random versus aligned fibers [6]. Material compositions are equally diverse, with polymer, oxide, carbon or composite bases (a polymer blend) [7]. Finally, recent advances have integrated bioactive components, such as nanosystems [8], proteins [9] metal oxides for catalysis [10], or agents for colorimetric or thermochromic sensors [11], into increasingly sophisticated designs. Consequently, electrospinning provides a powerful platform for the tailored delivery of bioactive compounds, particularly for the antibacterial antioxidants highlighted in this review.

Regarding bioactive electrospun implant materials used in musculoskeletal injuries, such as rotator cuff tear [12] or meniscus injury [13], the diverse options of integrating a bioactive moiety during electrospinning have been reported specifically for tissue engineering of tendons [14] or bone reconstruction in critical size bone defects [15]. Such bioactive materials are used as scaffolds that can also be combined with cells [16], with platelet rich plasma (PRP) to be sustainably released [17] with secretome of cells (conditioned medium) [18] or any compounds (natural [19,20] as well as synthetic [21]) to evoke a body response and accelerate tissue integration, revascularization and the healing process. Nevertheless, bioactive scaffolds may fail, caused by bio corrosion, low vascularization resulting in necrotic cores, or other mechanisms—particularly in non-biodegradable prosthetics that may in worst case result in fibrotic encapsulation surrounded by macrophages and foreign body giant cells [22].

Among two of the more prevalent causes of implant failure are poor tissue integration due to oxidative stress (OS) and bacterial infection [23–25].

1.1. Oxidative Stress Caused by Implants

Next to the release of radicals through the mitochondrial electron transfer chain, there are various other sources of reactive oxygen species (ROS) and reactive nitrogen species (RNS) such as NADPH oxidases [26]. Although these have their role in cell signaling and pathogen defense, if a spike of ROS/RNS tips the balance against antioxidants, it may result in OS. In a surgical setting, while anesthesia and surgical trauma are known to cause OS as part of the immune reaction and healing process, the foreign body response to the implant material [22] can further increase this problem not only acutely but also chronically through activated phagocytes among other cell types [27]. While an initial elevation of ROS levels during the first 48 h post-injury may help eliminate bacteria, and prevent infection [28], chronic OS is detrimental. Persistent ROS levels can impair ECM synthesis, and trigger an overexpression of components like fibronectin, laminin, and collagen—a hallmark of fibrotic “overshooting” [29]. Furthermore, ROS elevation lasting beyond one week may disrupt redox homeostasis, leading to prolonged M1 macrophage infiltration [30], and a deficiency in pro-resolving cytokines essential for regenerative healing [31]. Additionally, a link between OS and wear debris of implants and surrounding tissue has been suggested, implicating further complexity concerning implant performance and longevity [32]. Especially, when comorbidities and unhealthy lifestyle play a factor, this can lead to peri-implantitis, bone resorption and eventually implant failure [33]. To alleviate OS and thereby ameliorate wound healing as well as osseointegration, recent studies focusing on smart biomaterials have shown promising results by integrating either miRNA/siRNA to inhibit ROS pathways or antioxidants [34]. For example, implant surfaces coated with Titanium Oxide nanoparticles have been shown to reduce OS [35]. Combining the drug and shell material through electrospinning, in some cases ROS levels in the adjacent tissue directly facilitate a slow and sustained drug release by biomaterial that then blocks excessive ROS production over an extended time frame [36,37].

1.2. Implant-Associated Bacterial Infections

1.2.1. Fundamental Aspects of Implant-Associated Infections

A further substantial challenge is the development of implant-associated infection (IAI) [38–40]. Although IAIs occur relatively rarely, with 1–5%, depending on type of implant, body site, and whether it is a primary or revision surgery [41], they are linked to a detrimental outcome to the patient, and the health-care system [42]. IAI leads to prolonged antibiotic treatment, hospitalization, elevated morbidity, and mortality rates, and higher costs for the healthcare system [43]. In case of infection concerning implants for musculoskeletal tissue repair, such as bones, joints, and tendons, prolonged antibiotic treatment, and often surgical intervention, are required, aiming at resolving IAI [44,45]. While antibiotic resistance plays a part in this difficult-to-treat infection [46], a further major challenge is the presence of bacterial biofilms around the implant and implant-tissue intersection [47]. Bacterial biofilms are surrounded by a dense extracellular matrix containing extracellular polymeric substances (EPS), made up of various components such as polysaccharides, proteins, extracellular DNA (eDNA), and lipids, which confers protection against conventional antibiotics, and also the bactericidal activity of the host immune system [40]. The implant surface provides a unique substratum for bacterial attachment, because it leads to impairment of the antibacterial capacity of the host innate immune cells, such as neutrophils, as demonstrated in the landmark study

of Zimmerli et al. in 1984 [48]. Nowadays, it is assumed that the vast majority of IAs develops during the surgery itself due to unintentional inoculation of bacteria originating from the patient's own skin flora. The bacteria are believed to reside in the deeper dermal tissue layers [49], where the standard topical antiseptic procedure fails to eradicate them [50–52]. Infectious etiologies of IAs affecting musculoskeletal tissue are diverse, especially in the maxillo-facial and oral area, where various *Streptococcus* spp., *Porphyromonas* spp., *Prevotella* spp., and *Actinomyces* spp. as well as fungi, predominantly, *Candida albicans*, prevail [53,54]. However, when it comes to orthopedic bone, joint, and tendon infections, the main culprits are commonly of Gram-positive background and identified as *Staphylococcus* spp. (including *Staphylococcus aureus* and Coagulase-negative staphylococci, i.e., *Staphylococcus epidermidis*), *Streptococcus* spp., and *Enterococcus* spp., *Escherichia coli* as well as *Pseudomonas aeruginosa* as representatives for Gram-negative bacteria and strictly anaerobic *Cutibacterium* spp. [55–57].

1.2.2. Bacterial Adhesion and Biofilm Formation on Electrospun Scaffolds

The mechanisms of bacterial attachment to implants can vary greatly according to bacterial species and have been reviewed in great detail [40,58]. In general, bacterial adherence to implant material implies a three-step process. Firstly, physical forces direct bacteria towards the implant surface on a macroscale level. Secondly, once the bacteria are close enough to the implant surface, weak reversible intermolecular bonds, i.e., the van der Waals forces, govern initial contact with the implant surface [59]. Thirdly, stronger chemical bonds are being established between the bacterium and the implant surface, which is mediated by a conditioning film coating the implant surface [60]. The conditioning film occurs upon contact of the implant with bodily fluids, such as plasma, saliva or synovial components, resulting in protein absorption that alters the chemistry and roughness of the implant surface [61]. The interactions of bacteria with host matrix components deposited alongside the implant are mostly governed by adhesins, or in the case of Gram-positive coccoidal bacteria, the microbial surface components recognizing adhesive matrix molecules (MSCRAMMs) [62,63]. MSCRAMMs can recognize various different host proteins, among the most famous and most extensively studied ones are those of *S. aureus*. Among them are the fibronectin-binding proteins A or B, crucial for adhesion to fibrinogen and fibronectin, the clumping factor A or B, known for binding fibrinogen, enabling bacterial clumps aggregation and the collagen adhesin, considered a prototype MSCRAMM, mediating attachment to collagen [64]. While MSCRAMMs are predominantly described in the context of Gram-positive coccoidal bacteria, Gram-negative bacteria, such as *E. coli* or *Pseudomonas aeruginosa*, most often use either pili or fimbriae to mediate attachment to abiotic surfaces [65]. Following initial attachment and growth of bacteria, the quorum sensing (QS) system, a bacterial communication mechanism, sets in to fine tune biofilm and matrix formation. In brief, density-dependent signaling molecules (autoinducers) regulate gene expression, allowing synchronized group behaviors like biofilm formation and virulence. QS has been extensively studied and reviewed, and to date, many different QS systems across various bacteria are elucidated in great detail [66]. Across bacterial species, these QS systems are structured similarly. They generally involve the following four stages: production of autoinducers, accumulation, detection via receptors, and activation of target genes. QS systems are not only important for biofilm formation, but also for their dispersion, thereby regulating dissemination of bacteria to other sites, to start the process of biofilm formation anew. Although it has been documented that bacteria attach to, and form biofilms on various clinically utilized implant materials, such as titan, cobalt-chromium-molybdenum or polyethylene, similar reports for electrospun material intended for clinical application remains limited. Together with others, we have reported adhesion to, and biofilm formation on multiple electrospun materials *in vitro* [8,67,68], thereby highlighting the susceptibility of electrospun material to bacterial adhesion and biofilm formation, potentially also *in vivo*. Notably, several key aspects that modulate bacterial adhesion and biofilm formation on electrospun material have been reported, among them the material composition itself. The study by Clavijo-Grimaldo et al. reported that, when comparing polylactic-co-glycolic acid (PLGA), and polycaprolactone (PCL), PLGA was more susceptible to adhesion, and biofilm formation by *S. aureus*, *E. coli*, and *Enterococcus faecalis*, as compared to PCL or any mixture of PLGA and PCL [69]. Further, Sun et al. have shown that the incorporated concentration of hydrophilic polyvinyl alcohol (PVA) has a direct effect on bacterial adhesion [70]. With increasing concentrations of PVA, they observed a decrease in the adhesion of *S. aureus* and *E. coli*, which they attributed to the increased hydrophilicity of the material. Indeed, cell surface hydrophobicity (CSF) plays a crucial role for bacterial attachment [71]. A similar effect was observed in our previous study [67], where we noted a trend towards increased bacterial adherence correlating with an increase in CSF for DegraPol (DP) material. However, in the same study, we failed to observe such an effect-relationship to CSF for material fabricated from hyaluronic acid, and poly(ethylene oxide) (PEO) in different ratios. Beyond the material composition itself, it has been shown that fiber diameter directly affects the ability of bacteria to proliferate and therefore establish biofilm within the fibrous network. The highest proliferation rates were observed

when the fiber diameter was closest to the bacterial size itself [72]. When fibers were smaller, i.e., nanofibers, bacteria had to undergo conformational, and structural changes in order to colonize the material, with reduced proliferation rates and limited success. However, it needs to be noted that, (I) bacterial numbers required to cause, and maintain, infection in the presence of an implant can be as low as 100 colony forming units [48], and that, (II) bacteria undergoing structural changes can still cause infection, such as documented for the extreme case of *S. aureus* undergoing severe morphological deformation to fit the nanoscale sized osteocyte-canalliculi network in cortical bone during osteomyelitis [73,74].

1.2.3. Common Implant Modification Strategies to Prevent Bacterial Attachment

Due to the highly versatile nature of bacteria to survive, and cause infection even under challenging conditions, materials should be able to prevent bacteria from attaching and forming biofilms as effectively as possible. Therefore, various attempts have been made to render implant material, including electrospun scaffolds, more antibacterial. Classically, implants have been coated with either antibiotics or antibacterial metal nanoparticles, such as silver [75–77]. A recent report by Ielo et al. discusses the combination of silver nanoparticles with polyvinylpyrrolidone, showing beneficial antibacterial and anti-inflammatory properties [78]. There are various studies documenting good pre- and clinical efficacy for antibiotic coating or incorporation for IAI prevention in either dental or joint applications [79,80]. However, antibiotics are specific for target bacteria only and therefore could potentially fail to prevent infection by all causative agents. Furthermore, antibiotic resistance development raises concerns about efficacy of antibiotic coatings. Regarding metal nanoparticles, they show a broader range of target bacteria, and specificity can largely be neglected. Especially silver has been investigated and reviewed extensively for its antibacterial properties, and also its ease of application, such as the direct soaking of implants into a silver nanoparticle solution [81]. This approach has also been adopted for electrospun material in our recent study, where we observed a trend towards decreased biofilm formation on DP fibers soaked in silver nanoparticles [67]. Also, direct incorporation into the electrospinning process of silver nanoparticles can be employed, and has been reviewed recently [82]. This approach holds greater promises, as shown in the study by Ren et al. [83]. They incorporated colloiddally stable silver nanoparticles into PVA as well as into sodium alginate fibers, and demonstrated an inhibitory effect towards *S. aureus in vitro*, and improved infected wound healing *in vivo*. Although silver or other metal nanoparticles can have a strong antibacterial effect [84], its application raises frequent, and recurrent concerns, not only about its efficacy, which can vary drastically depending on application case, and study concept [85], but also, and most notably about its safety profile [86]. In addition, both, antibiotics and metal nanoparticles, although addressing the issue of bacterial infections, fail to address the highly relevant challenge of OS. Ideally, molecules to be incorporated into electrospun materials would show both these characteristics, namely an antioxidant, and a broad-spectrum antibacterial character. Of note, the desired molecules do not necessarily require a direct bacteriostatic or even -cidal effect. Modulation of the QS system, and its effect on adhesion, and biofilm formation, termed “quorum quenching”, represents a viable alternative, which has been reviewed recently in great detail [87–89]. A proposed advantage of quorum quenching is that the development of resistance may be minimal, as these molecules do not directly target essential bacterial processes but instead modulate virulence behavior.

1.2.4. Phenolic and Terpenic Compounds Exhibiting Dual Mechanisms of Action

While novel synthetic molecules that show a dual mechanism of action are being developed and investigated, plant-derived molecules, and such that derive from those, frequently possess exactly these two requirements [90]. Phenolic compounds are those that present with at least one phenol unit, their characteristic hydroxylated benzene ring. Among the many different classes of plant-derived phenolic molecules, extensive literature has been provided for the flavonoids, xanthones, coumarins, carotenoids, tannins, stilbenes, lignans, quinones, and phenolic acids in regard to their antibacterial [91,92] as well as antioxidant potential [93]. The most prominent ones to date with extensive literature coverage are those naturally occurring in *Origanum vulgare* or *Thymus vulgaris*, such as carvacrol [93], and its isomer thymol [94]. In addition, β -carotene, which can be found in various algae and plants, has also been frequently incorporated into electrospun material [95,96]. A further prominent molecule from the group of phenolic compounds represents curcumin from *Curcuma longa* [97]. However, curcumin for electrospinning application, and its antibacterial as well as antioxidant effects for medical applications have been reviewed recently [98,99], and will therefore not be discussed further in this review. Hence, for the following section of this review, a selection of well-known phenolic molecules with a dual character, which have also already been integrated into electrospinning processes, and fibrous material, will firstly be introduced more broadly. Then, compounds which have not yet been incorporated into electrospun material, but have been assessed for their

antioxidant and antibacterial potential, will be reviewed. There, to start, a group of compounds will be introduced which have proven antioxidant efficacy supported by a large body of evidence and reviewed literature, but which only more recently have gained attention in regards to their antibacterial potential. Concluding will be an overview of the available primary literature on promising phenolic and terpenic compounds which have only recently gained attention as subjects of interest for both their antioxidant and antibacterial potential.

2. Materials and Methods

A comprehensive literature search was conducted to identify publications for this narrative review. The defined search covered keywords including phenol, terpene, carotenoids, flavonoids, electrospinning, nanocarriers, tetrahedral framework nucleic acid (tFNA), metal and metal oxides, as well as antibacterial or antioxidant. For each of the phytochemicals discussed, the keyword combinations consisted of the compound name + “electrospinning”, as seen in Table 1. A PRISMA Flow Chart can be found in Supplementary Figure S1. Primary literature sources included PubMed, Web of Science, Google Scholar, Embase, and Scopus. To ensure the relevance of the selected studies, strict inclusion criteria were applied. Papers were required to directly address (i) phenols or terpenes functioning as antibacterial antioxidants and (ii) nanocarriers in the context of drug delivery, specifically demonstrating that a specific carrier can be successfully combined with electrospinning and that the nanocarrier can achieve sustainable release of an antibacterial antioxidant. Exclusion criteria implied (I) electrospinning of antibacterial material for the food sector, (II) manuscripts in different languages than English, (III) unavailability of the full version of the manuscript. In addition, the search was limited to papers published from 2000 to the present, to avoid presenting data which has already been summarized and discussed extensively. Based on the search terms, potential manuscripts were screened first based on the title followed by the abstract. Inclusion and exclusion criteria were applied to the abstract and also to the full-text manuscripts of papers passing the abstract screening. The literature research was carried out during January to April of 2026.

Table 1. Rationale for the selection of the nine target compounds—and not curcumin, thymol and carvacrol.

Phyto-Chemical	Total Citations (General)	Citations with <i>Electro-Spinning</i>	Citations with <i>Electro-Spinning</i> and <i>Musculo-Skeletal</i>	Decision	Bibliometric Rationale
Quercetin	35,099	80	1	included	High systemic relevance, but critical musculoskeletal deficit.
Rutin	11,712	21	0	included	Significant to literature volume, but no translational cross-over.
Ferulic acid	9067	30	0	included	Highly versatile polymer processing, but unexplored for muscle/bone/tendon repair.
Eugenol	8934	24	0	included	Broadly studied antimicrobial oil, but unmapped in structural frameworks.
Lutein	7937	1	0	included	Practically no electrospun lutein-containing biomaterials.
Lycopene	7689	7	0	included	Well-characterized carotenoid; restricted to few polymer screenings.
Emodin	3940	7	2	included	Emerging highly potential niche cluster targeting specific tissue repairs.
Fucoxanthin	1469	4	0	included	Underexplored marine asset with strong early <i>in vivo</i> efficacy data.
Bakuchiol	246	1	0	included	Severe global data gap; crucial introduction of a novel retinol alternative.
Curcumin	29,070	243	1	excluded	Saturated topic; covered by comprehensive electrospinning reviews [98,100–103]
Thymol	8247	54	0	excluded	Saturated field: electrospinning parameters fully established in food packaging context.
Carvacrol	3855	20	0	excluded	Saturated field: several electrospinning studies, particularly food packaging related.

The criteria to select 9 target compounds that exhibit antioxidant and antibacterial properties were based on a PubMed search where the *compound name* alone or with *electrospinning* and also *electrospinning AND musculoskeletal* were used as search terms (Figure 1 and Table 1). Our specific selection framework aimed to identify a distinct translational niche: compounds that possess strong individual therapeutic potential but remain significantly under-explored when combination options with delivery systems and electrospinning techniques are considered; these included Lycopene, Quercetin, Rutin, Ferulic acid, Emodin, Eugenol, Bakuchiol, Fucoxanthin and Lutein, respectively. Conversely, widely studied dual-bioactive phytochemicals such as Curcumin, Thymol, and Carvacrol were deliberately excluded from this review because the electrospinning area with such compounds incorporated into fibers has been explored quite extensively already.

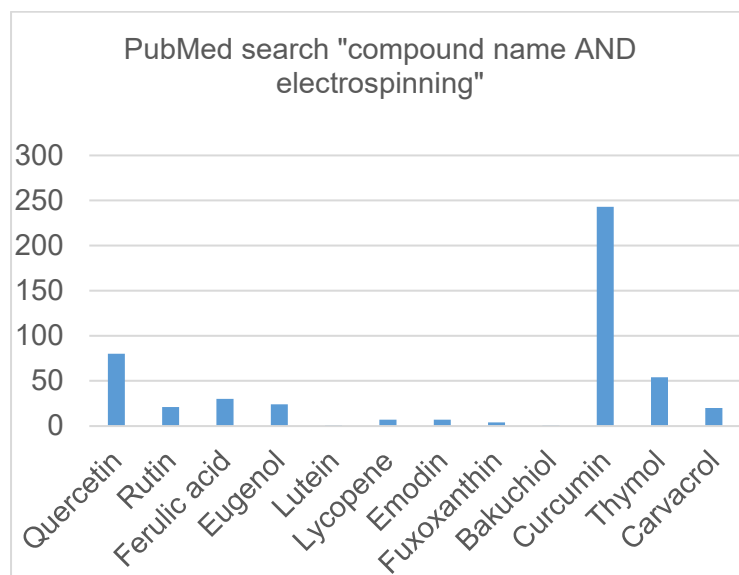


Figure 1. Number of publications found in PubMed for “*compound name AND electrospinning*” as a rationale for the selection of the nine target compounds.

2.1. Dual-Action Substances Incorporated into Electrospun Materials

β -carotene

β -carotene is an organic, strongly colored red to orange pigment abundant in fungi, plants, and fruits. It acts as precursors to vitamin A and has been extensively investigated for its application in the food industry [96]. However, studies have also shown its capacity to alleviate several chronic diseases including various types of cancer, cystic fibrosis, COVID-19, and more generally also its antimicrobial, antioxidant, and anti-inflammatory potential [95,104]. It has also been successfully integrated into electrospun material and assessed for both its antibacterial as well as antioxidant potential. Of note, β -carotene is highly sensitive to light and oxygen. The study by Fernandez et al. has been among the first to successfully integrate β -carotene into electrospun ultrathin fibers of zein prolamine [105]. They reported stable, and widely dispersed integration of the fluorescent antioxidant molecule in the zein fibers. The encapsulated compound showed a significant increase in light stability when exposed to UV-vis irradiation. In another study, a multilayer structure based on thermoplastic corn starch (TPCS) with an outer layer of PCL was developed via the electrohydrodynamic process of electrospinning [106]. β -carotene was directly incorporated into the PCL layer, which was then electrospun onto both sides of the TPCS film. The authors reported that addition of β -carotene did not improve barrier properties as compared to their counterparts, which were prepared without the active compound. Of note, both permeability values remained lower than those obtained for the pure TPCS. In addition, they noted that the stability of β -carotene was greatly affected by the annealing step even when it was encapsulated into the electrospun PCL layer. Furthermore, the antioxidant activity of the fibrous membrane containing β -carotene demonstrated 13.6% inhibition of free ABTS radicals, which was slightly lower as compared to β -carotene only, achieving 14.9% inhibition. Dabouian and colleagues also integrated β -carotene into PCL electrospun mats to develop scaffolds intended for bone tissue engineering [107]. The novel scaffolds supported the attachment, and proliferation of mesenchymal stem cells (MSCs). The presence of either 2% or 4% β -carotene induced MSCs to differentiate into osteoblasts during 21 days of culture, with concomitant expression of RUNX2, SOX9, and osteonectin. In addition, during the culture period, β -carotene loaded fiber mats induced the production of a calcified matrix. In another study, β -carotene was encapsulated into electrospun cyclodextrin (CD) nanofibers, with the aim of increasing its water-solubility and photostability for enhanced antioxidant bioactivity [108]. It was shown that β -carotene incorporated into both, β -CDs, and γ -CDs fibers, retained a vast amount of its antioxidant activity, achieving up to 70% of antioxidant activity as assessed by its capacity to scavenge free DPPH radicals. Furthermore, UV exposure of the fibers did not impair the antioxidant activity, thereby highlighting the stability of the otherwise light-sensitive β -carotene, when incorporated into electrospun fibers with CDs. Yoshikawa et al. loaded varying concentrations of β -carotene (1.2%, 2.4%, and 3.6%) into PCL fibers and assessed them for their potential as tissue engineering scaffolds as well as for their antibacterial properties [109]. Biological assessment using KUSA-A1 mesenchymal cells indicated enhanced cellular proliferation in response to the scaffolds, and increased osteocalcin production with β -carotene in a concentration dependent manner. In addition, the PCL fibers containing β -carotene showed a decrease in

growth of *E. coli* on the PCL fibers with increasing concentrations of β -carotene as assessed by optical density measurement of the bacterial culture. Finally, β -carotene has also been incorporated into PVA fibers and been assessed for its antioxidant as well as antibacterial potential [110]. At a concentration of 5% β -carotene, the PVA fibers demonstrated 62% scavenging activity of free DPPH radicals. Incorporated β -carotene (5%) also showed good activity against *S. aureus*, *Bacillus megaterium*, and *Serratia marcescens* as evaluated by the agar disc diffusion assay. Zone of inhibitions on agar plates showed 8 mm for both *S. aureus* and *S. marcescens*, and 15 mm for *B. megaterium*, for PVA fibers with β -carotene, resulting in a computed 63.25%, 66.25%, and 60.25% of growth reduction for *S. aureus*, *B. megaterium*, and *S. marcescens*, respectively.

2.2. Promising Antibacterial Substances with Demonstrated Antioxidant Activity

2.2.1. Lycopene

Antibacterial Properties

Lycopene is a naturally occurring carotenoid predominantly found in tomatoes and tomato-based products. It is well recognized for its antioxidant properties and its protective effects against oxidative stress-related disorders, including inflammation, obesity, and diabetes mellitus [111]. These antioxidant activities have been extensively reviewed [112–115]. More recently, lycopene has also gained attention for its antibacterial potential. Several *in vitro* studies demonstrated concentration-dependent antibacterial activity against a range of Gram-positive and Gram-negative bacteria, as well as fungi [116,117]. Although lycopene showed only limited direct growth inhibition of methicillin-resistant *S. aureus* (MRSA), it significantly attenuated bacterial virulence by suppressing α -hemolysin production and quorum sensing, thereby reducing host cell damage [118]. *In Vivo*, lycopene improved survival, reduced bacterial burden, and attenuated inflammatory responses in experimental *S. aureus* infection [118]. Furthermore, in a chronic *S. aureus* prostatitis model, lycopene enhanced the antibacterial efficacy of cephalexin while further reducing tissue inflammation, highlighting its potential as an adjunctive antimicrobial therapy [119].

Incorporation into Electrospun Meshes

Lycopene is globally well-studied, yet its delivery via electrospun systems remains an unexplored frontier in musculoskeletal regeneration. Optimized nanoformulations are required to address its low water solubility and high oxidation sensitivity. While recent evidence highlights its strong therapeutic promise, data is heavily restricted to preclinical stages. Standardized protocols, dosing regimes, and clinical validation are still needed to bridge the bench-to-bedside gap [120]. Reported electrospun matrices include whey protein isolate *Tricholoma lobayense* polysaccharide complex stabilized emulsions [121], PLA fibers reinforcing gluten films [122], lycopene microemulsions in zein [123], and tri-layer chitosan nanospheres within gelatin nanofibers [124].

2.2.2. Quercetin

Antibacterial Properties

Quercetin, a flavonoid widely distributed in fruits and vegetables, is particularly abundant in onions (*Allium cepa*) and is well known for its antioxidant, anti-inflammatory, antiviral, and anti-obesity properties [125]. In recent years, quercetin has also emerged as a promising antimicrobial compound with activity against a broad range of pathogens [126]. Several *in vitro* studies demonstrated antibacterial and antibiofilm activity against Gram-positive and Gram-negative bacteria, including *S. aureus*, MRSA, *P. aeruginosa*, *E. coli*, *Acinetobacter baumannii*, and *Streptococcus pneumoniae* [127–131]. Beyond direct growth inhibition, quercetin attenuated bacterial virulence by inhibiting α -hemolysin activity, disrupting membrane integrity, suppressing quorum sensing, reducing extracellular polymeric substance production, impairing biofilm formation and bacterial motility, and downregulating multiple virulence-associated genes [127–131]. Molecular docking studies further identified interactions with several proteins involved in quorum sensing, biofilm formation, toxin production, and multidrug resistance [128–132]. In addition, quercetin exhibited synergistic antibacterial effects when combined with several conventional antibiotics, including cefotaxime, piperacillin, and polymyxin E, enhancing bacterial killing and overcoming resistance mechanisms in multidrug-resistant bacteria [129,132].

Incorporation into Electrospun Meshes

Quercetin is a highly characterized flavonoid with proven osteogenic and immunomodulatory properties for bone reconstruction. However, only a singular paper directly evaluates it at the intersection of electrospinning and

musculoskeletal repair [133]. Non-electrospun applications in the area of bone healing rely primarily on isolated options like solid lipid nanoparticle-embedded hyaluronic acid hydrogels [134]. Although admittedly a lot of articles have been published regarding electrospun materials with quercetin. Existing electrospinning studies span general wound healing, anticancer, or acne applications utilizing carrier matrices such as cellulose acetate/PEG [135], bilayer PCL-PVP [136,137], PCL/poly(glycerol sebacate) small-diameter vascular prostheses [138], Glucantime/PCL membranes [139], colon-targeted shellac [140], PEO/curdlan films [141], cosmetic PVA setups [142], zein-ethyl cellulose coaxial configurations [143], oxygen-carrying silk fibroin hydrogel-fiber composites [144], and high-concentration PLA or PLA/PEO non-woven fabrics [145]. Reviewing these parameters is essential to establish optimal processing windows for musculoskeletal applications as so far only few papers have been published in this area.

2.2.3. Rutin

Antibacterial Properties

Rutin, a polyphenolic flavonoid widely distributed in fruits, vegetables, and beverages, exhibits diverse pharmacological properties, including antioxidant, anti-allergic, anticancer, and antidiabetic activities [146]. More recently, it has also attracted attention for its antimicrobial potential [147]. Several *in vitro* studies demonstrated antibacterial activity of rutin against a broad range of Gram-positive and Gram-negative bacteria, including *S. aureus*, *E. coli*, *Klebsiella pneumoniae*, *P. aeruginosa*, and *A. baumannii*, as well as antibiofilm activity, particularly against *K. pneumoniae* [148–151]. In addition to direct antibacterial effects, rutin exhibited synergistic or additive activity when combined with amikacin, especially against Gram-negative bacteria, enhancing bacterial killing through disruption of membrane integrity and increased cellular leakage [149,150]. Furthermore, rutin-loaded chitosan nanoparticles displayed substantially improved antibacterial and antibiofilm activity against multidrug-resistant *P. aeruginosa* compared with free rutin, accompanied by reduced expression of biofilm-associated genes, highlighting the potential of optimized delivery systems to enhance its antimicrobial efficacy [152].

Incorporation into Electrospun Meshes

Despite over 11,000 global results for rutin in a PubMed search, rutin has zero presence in musculoskeletal electrospinning literature. Encapsulation research is sparse and restricted to cellulose acetate/PEG [135], high-loading rutin/hydroxypropyl- β -cyclodextrin inclusion complexes in PVA [153], bioactive cellulose acetate/PEO fiber membranes [154], PVA/Eudragit L100 patches optimized via the Taguchi method [155], antibacterial chitosan oligosaccharide/PCL blends [156], neat PCL wound dressings [157], gelatin nanofibrous scaffolds hosting rutin nanoparticles to treat dental pulp stem cells [158], and PVA-chitosan composites [159]. Synthesizing these formulations helps determine how rutin can be structurally stabilized to exploit its anti-inflammatory and antibacterial capacity in load-bearing structures.

Comparison between Quercetin and Rutin

Quercetin and rutin are structurally related flavonoids, with rutin representing a glycosylated derivative of quercetin. Due to their close structural similarity, several studies have directly compared their antimicrobial properties. Both compounds demonstrated iron-chelating activity and inhibited the growth of various Gram-positive and Gram-negative bacteria, with quercetin generally exhibiting stronger antibacterial effects than rutin [160]. Similarly, both flavonoids showed antibiofilm activity against several bacterial species, including *S. aureus*, *E. coli*, and *Salmonella typhimurium*, while quercetin displayed stronger synergistic effects with antibiotics such as gentamicin and cefotaxime [160]. In models of multidrug-resistant *P. aeruginosa* wound infections, both quercetin and rutin reduced biofilm formation and improved wound healing, particularly when combined with gentamicin, although quercetin showed superior activity [161]. However, comparative studies also demonstrated species-dependent differences, with rutin exhibiting stronger antibacterial activity against *S. pneumoniae* and enhanced biofilm inhibition against *K. pneumoniae* compared with quercetin [148,162]. Overall, these findings highlight the complementary antimicrobial potential of both flavonoids, with quercetin often showing greater potency but rutin retaining activity against specific pathogens.

2.3. Substances with Promising Antibacterial and Antioxidant Properties

Based on our literature screening, we have selected nine promising compounds that exhibit antibacterial and antioxidant properties (Figure 2) and provide specific antibacterial evaluation outcomes in Table 2.

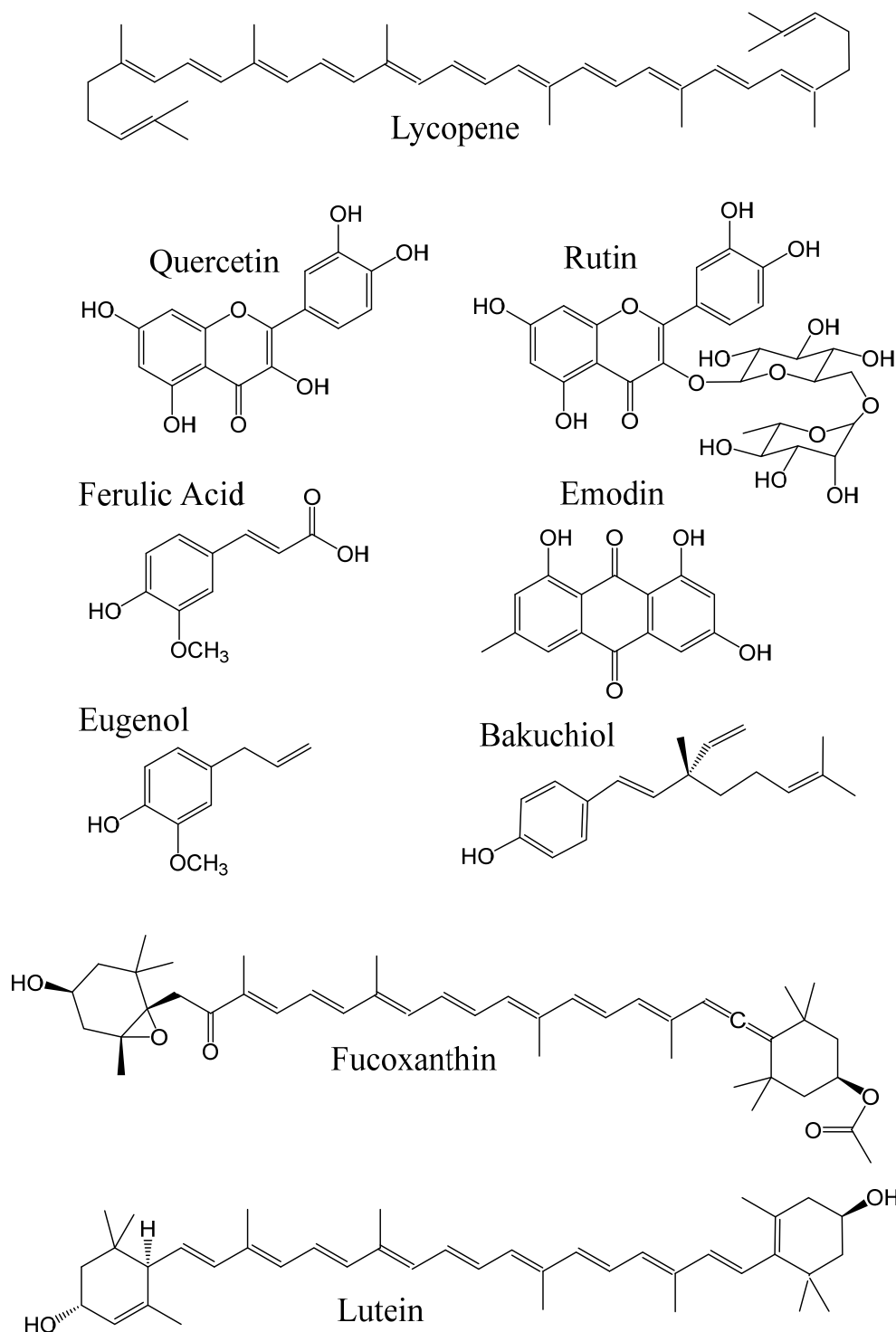


Figure 2. Overview of chemical structures. Antibacterial antioxidants selected for in-depth literature review—with phenolic compounds Quercetin, Rutin, Ferulic acid, Emodin, Eugenol and Bakuchiol; as well as terpenes Lycopene, Fucoxanthin and Lutein, respectively. Concentrations ranges studied in several reports are summarized in Table 2.

Table 2. Overview of the antimicrobial evaluation of selected phenolic and terpenic compounds according to Figure 2.

Compound	Evaluated Bacteria	Evaluated Concentrations	Effect with Antibiotics	References
Lycopene	<i>S. aureus</i> , <i>E. coli</i> , <i>S. pyogenes</i> , <i>P. aeruginosa</i>	2–32 µg/mL ¹ 25–250 mg/mL ²	• Cephalixin: <i>S. aureus</i>—enhanced³ • Piperacillin: <i>P. aeruginosa</i>, <i>S. pneumoniae</i>, <i>A. baumannii</i>, <i>E. coli</i>—enhanced³ • Piperacillin: <i>S. aureus</i>—reduced • Cefotaxime: <i>P. aeruginosa</i>, <i>S. pneumoniae</i>, <i>E. coli</i>—enhanced³ • Cefotaxime: <i>S. aureus</i>, <i>E. coli</i>—reduced	[116–119]
Quercetin	<i>S. aureus</i> , <i>E. coli</i> , <i>P. aeruginosa</i> , <i>S. pneumoniae</i> , <i>A. baumannii</i> , <i>S. marcescens</i> , <i>C. violaceum</i>	20–500 µg/mL ¹ 1812 µg/mL ²	• Polymyxin E: <i>E. coli</i>—enhanced³ • Gentamicin: <i>P. aeruginosa</i>, <i>E. coli</i>, <i>S. typhimurium</i>—enhanced³ • Cefotaxime: <i>S. aureus</i>, <i>S. typhimurium</i>—enhanced³	[125–132, 160–162]
Rutin	<i>S. aureus</i> , <i>S. epidermidis</i> , <i>E. coli</i> , <i>K. pneumoniae</i> , <i>E. faecalis</i> , <i>B. subtilis</i> , <i>P. mirabilis</i> , <i>E. cloacae</i> , <i>P. aeruginosa</i> , <i>A. baumannii</i>	128 µg/mL– 50 mg/mL ^{1,2}	• Amikacin: <i>S. aureus</i>, <i>S. epidermidis</i>, <i>E. faecalis</i>, <i>B. subtilis</i>, <i>E. coli</i>, <i>K. pneumoniae</i>, <i>P. mirabilis</i>, <i>E. cloacae</i>, <i>P. aeruginosa</i>, <i>A. baumannii</i>—enhanced³ • Amikacin: <i>S. epidermidis</i>—indifferent • Cefotaxime: <i>S. aureus</i>, <i>S. typhimurium</i>—enhanced³	[146–152, 160–162]
Ferulic acid and derivatives	<i>S. aureus</i> , <i>E. coli</i> , <i>P. aeruginosa</i> , <i>L. monocytogenes</i> , <i>P. gingivalis</i> , <i>A. actinomycetemcomitans</i> , <i>E. hormaechei</i> , <i>K. pneumoniae</i> , <i>E. faecalis</i> , <i>A. baumannii</i> No effect: <i>F. nucleatum</i> , <i>P. intermedia</i> , <i>S. mitis</i>	1–5300 µg/mL ¹	• Sodium fosfomycin: <i>E. coli</i>—enhanced³ • Ceftriaxone: <i>E. coli</i>—enhanced³ • Gentamicin: <i>E. coli</i>—enhanced³ • Tetracycline: <i>E. coli</i>—enhanced³ • Ciprofloxacin: <i>A. baumannii</i>—enhanced³ • Gemifloxacin: <i>A. baumannii</i>—enhanced³ • Norfloxacin: <i>S. aureus</i>—enhanced³ • Erythromycin: <i>S. aureus</i>—enhanced³ • Tetracycline: <i>S. aureus</i>—enhanced³	[163–172]
Emodin	<i>S. aureus</i> , <i>S. suis</i> , <i>H. parasuis</i>	1.5–1000 µg/mL ¹	• Ampicillin: <i>S. aureus</i>—enhanced³ • Gentamicin: <i>S. aureus</i>—enhanced³	[173–183]
Eugenol	<i>S. aureus</i> , <i>K. pneumoniae</i> , <i>E. faecalis</i>	100–8330 µg/mL ¹	• Tetracycline: <i>S. aureus</i>—enhanced³ • Cefotaxime: <i>S. aureus</i>—enhanced³	[169, 184–190]
Bakuchiol	<i>S. aureus</i> , <i>P. aeruginosa</i> , <i>E. coli</i> , <i>E. faecalis</i> , <i>E. faecium</i> , <i>S. mutans</i> , <i>S. sanguinis</i> , <i>S. salivarius</i> , <i>S. sobrinus</i> , <i>L. acidophilus</i> , <i>L. casei</i> , <i>L. plantarum</i> , <i>A. viscosus</i> , <i>P. gingivalis</i>	1–1280 µg/mL ¹	• Colistin: <i>A. baumannii</i>—enhanced³	[191–198]
Fucoxanthin	<i>S. aureus</i> , <i>S. epidermidis</i> , <i>S. agalactiae</i> , <i>S. pneumoniae</i> , <i>S. pyogenes</i> , <i>E. faecalis</i> , <i>Enterococcus</i> spp., <i>B. subtilis</i> , <i>E. coli</i> , <i>K. oxytoca</i> , <i>K. pneumoniae</i> , <i>A. iwoffii</i> , <i>P. aeruginosa</i> , <i>P. mirabilis</i> , <i>S. marcescens</i> No effect: <i>A. israelii</i> , <i>A. parvulum</i> , <i>M. multacida</i> , <i>P. niger</i> , <i>P. gingivalis</i> , <i>C. acnes</i> , and <i>V. parvula</i>	62.5–1000 µg/mL ¹ 4.25 mg/mL ²	• Cefotaxime: <i>S. aureus</i>—enhanced³ • Cefotaxime: <i>S. aureus</i>—indifferent	[199–202]
Lutein	<i>L. monocytogenes</i> , <i>P. aeruginosa</i>	0.25–1019.5 µg/mL ¹	• Tobramycin: <i>P. aeruginosa</i>—indifferent	[203–205]

¹ Concentrations from various broth microdilution assay types (MIC, MBC, biofilm inhibition, gene expression, virulence factor activity etc.), ² Concentrations from agar disc diffusion assay, ³ Enhanced can either mean a synergistic or an additive effect.

2.3.1. Ferulic Acid and Derivatives

Ferulic acid (FER) is a phenolic compound commonly present in the cell walls of seeds, leaves, and roots of many fruits, vegetables, cereals, and grains. It is well known for its diverse biological activities, including antioxidant, anti-inflammatory, antibacterial, and anticancer [206].

2.3.2. Antibacterial Properties

FER, a naturally occurring phenolic compound, has demonstrated broad antimicrobial and antibiofilm properties against various bacterial pathogens. *In Vitro* studies reported antibacterial activity against both Gram-positive and Gram-negative bacteria, including *E. coli*, *P. aeruginosa*, *S. aureus*, *Listeria monocytogenes*, and *A. baumannii*, with activity mediated in part by disruption of bacterial membrane integrity, leakage of intracellular components, and induction of oxidative stress [163,165,166]. Beyond direct antibacterial effects, FER strongly inhibited biofilm formation, extracellular polymeric substance production, and bacterial motility, accompanied by modulation of genes involved in biofilm regulation, QS, and cyclic-di-GMP signaling [164,165,167]. FER also demonstrated synergistic effects with multiple antibiotics, including fosfomycin, ceftriaxone, gentamicin, tetracycline, ciprofloxacin, and gemifloxacin, enhancing bacterial killing through mechanisms such as membrane destabilization and increased ROS production [165,166]. *In Vivo*, FER improved survival and reduced bacterial burden in a murine sepsis model when combined with quinolone antibiotics [166]. Studies against oral pathogens and MRSA further highlighted its antibiofilm and QS-modulating potential, including inhibition of AI-2 signaling and reduction of mature biofilms [167,168]. Computational analyses suggested interactions of FER with biofilm-associated and virulence-related proteins, including MrkB, MrkH, and Sortase A [164,169]. Furthermore, esterified FER derivatives enhanced antibiotic synergy by potentially modulating efflux pump activity, particularly NorA-mediated resistance in *S. aureus* [170,171]. Finally, incorporation of FER into electrospun polymeric scaffolds improved antibacterial and anti-adhesive properties against *S. aureus*, highlighting its potential for biomaterial-based antimicrobial applications [172].

2.3.3. Antioxidant Properties

FER has recently been reviewed extensively for its pharmacological properties, including its antioxidant and anti-inflammatory activities [207,208]. Beyond its direct free radical scavenging capacity, emerging evidence suggests that FER and its derivatives can modulate OS originating from different cellular sources. Nazaré et al. demonstrated that although ethyl ferulate exhibited lower cell-free radical scavenging activity compared with FER, it showed stronger inhibition of ROS and superoxide production in activated neutrophils, highlighting its potential to regulate inflammation-associated oxidative stress [209]. In cellular models of β -amyloid-induced toxicity, FER reduced ROS generation, preserved mitochondrial function, inhibited cytochrome c release and apoptosis, and modulated antioxidant pathways [210]. Furthermore, FER demonstrated concentration-dependent antioxidant activity and reduced nitric oxide and ROS production in LPS-stimulated macrophages, supporting its anti-inflammatory potential [211]. Importantly, FER retained its antioxidant properties when incorporated into electrospun polymeric scaffolds, suggesting potential applications in bioactive biomaterials [172].

2.3.4. Incorporation into Electrospun Meshes

Although there was no hit in our PubMed search for the terms *ferulic acid*, *electrospinning* and *musculoskeletal*, in Google scholar, there was one reference where FER has shown potential for bone regeneration via biomimetic, dually cross-linked injectable poly(L-glutamic acid)-based nanofiber composite hydrogels with self-healing, osteogenic, and angiogenic properties [212]. For other applications, it has been loaded into conductive, aligned PCL/gelatin/polypyrrole/graphene scaffolds for nerve repair [213], and pure poly(ferulic acid)-hybrid nanofibers to minimize vascular thrombosis and intimal hyperplasia [214]. Additional delivery matrices include Maillard-crosslinked PVA/wheat gluten/glucose films [215], PCL/collagen hydrolysate nanofibres [216], chitosan-coated PCL, silk sericin/PCL/cellulose acetate mats [217], extended-release core-shell ethylcellulose/PVP structures [218], and clog-free coaxial configurations with a zein/FER core and acetic acid sheath [219]. Consolidating these processing techniques provides a necessary blueprint for translating FER into musculoskeletal repair electrospun designs.

2.3.5. Emodin

Emodin is a naturally occurring anthraquinone compound found in several commonly used Chinese medicinal herbs, including *Rheum palmatum*, *Polygonum cuspidatum*, and *Polygonum multiflorum*. It has been used in traditional Chinese medicine for more than 2000 years, and increasing scientific evidence recently reviewed suggests that emodin exhibits a broad range of pharmacological effects, such as antibacterial, antioxidant, anticancer, and hepatoprotective [220].

2.3.6. Antibacterial Properties

The antibacterial and antibiofilm properties of emodin have recently been reviewed [173]. Several studies demonstrated potent antimicrobial activity of emodin, particularly against *S. aureus* and MRSA, with low MIC values and synergistic effects when combined with β -lactam antibiotics such as ampicillin and oxacillin [174,175]. *In Vivo*, emodin improved survival and reduced bacterial burden in MRSA infection models, while mechanistic studies indicated that its antibacterial activity is primarily mediated through disruption of bacterial membrane integrity and altered membrane properties rather than interference with cell wall synthesis or resistance mechanisms [175]. Emodin also exhibited broad antibiofilm activity by inhibiting biofilm formation, reducing extracellular polymeric substance production, and modulating the expression of quorum sensing-, adhesion-, and virulence-associated genes in pathogens including *Streptococcus suis* and *S. aureus* [176,179,180]. Further studies revealed that emodin can impair bacterial metabolism and membrane function by interfering with fatty acid and phospholipid synthesis, disrupting proton motive force, and increasing membrane permeability [177,178]. Against MRSA biofilms, emodin enhanced the efficacy of ampicillin, reduced extracellular DNA and protein components of the biofilm matrix, and downregulated key biofilm-associated genes [181]. Additionally, incorporation of aloe-emodin into gentamicin-loaded bone cement improved antibacterial activity against *S. aureus*, highlighting its potential in antimicrobial biomaterial applications [182]. Finally, particle size optimization was shown to influence emodin efficacy, with smaller particles exhibiting enhanced antibacterial activity due to improved dissolution properties [183].

2.3.7. Antioxidant Properties

Emodin's antioxidant properties have been extensively investigated, particularly in the context of cardiovascular and inflammatory diseases [221,222]. Recent studies suggest that emodin can mitigate OS across various disease models by reducing ROS production, enhancing antioxidant defenses, and modulating inflammatory pathways. In a murine model of LPS-induced sepsis, aloe-emodin reduced inflammatory responses, enhanced antioxidant enzyme activity, and modulated the PI3K/Akt/mTOR signaling pathway [223]. In cellular models of intervertebral disc degeneration, emodin protected cells from IL-1 β -induced OS, apoptosis, and inflammatory mediator production, while suppressing NF- κ B-related signaling [224]. Similarly, emodin alleviated intestinal ischemia–reperfusion injury by reducing OS, inflammation, and apoptosis through mechanisms involving Akt and heme oxygenase-1 signaling [225]. Furthermore, emodin improved age-related redox imbalance by decreasing oxidative damage and strengthening antioxidant capacity, particularly in aged animals [226]. Together, these findings highlight emodin as a potential antioxidant and anti-inflammatory compound with activity across diverse pathological conditions.

2.3.8. Incorporation into Electrospun Meshes

Emodin represents an ideal niche compound with only two musculoskeletal electrospinning applications so far. These early developments demonstrate outstanding potential: preventing peritendinous adhesions via a novel polylactic acid–Aloe emodin conjugate nanofiber membrane [227], and driving bone injury repair via osteogenic emodin-loaded hydroxyapatite/PCL fibers [228]. Other general delivery studies with electrospinning utilize filament-forming PVP K90 [229], core-shell architectures featuring a PVP core and a chitosan-PCL shell [230], or coaxial PVP cores wrapped in a hygroscopic cellulose acetate sheath for biphasic release [231]. The presented review targets this emerging cluster to accelerate emodin releasing scaffold optimization.

2.3.9. Eugenol

Eugenol is a naturally occurring volatile phenolic aromatic compound mainly obtained from clove oil. This small molecule is widely known for its local anesthetic, anti-inflammatory, and preservative properties. Both clinical and experimental studies have demonstrated that eugenol possesses strong inhibitory activity against a broad range of pathogenic microorganisms, including bacteria, fungi, and viruses [232].

2.3.10. Antibacterial Properties

The antimicrobial, antibiofilm, and quorum-quenching properties of eugenol have recently been reviewed [184]. Additional studies have further demonstrated its antibacterial potential against a broad range of pathogens. Eugenol and its derivatives exhibited antibacterial activity against *S. aureus*, including MRSA, with synergistic effects observed in combination with antibiotics such as tetracycline and cefotaxime [185,186]. In MRSA and methicillin-susceptible *S. aureus*, eugenol inhibited biofilm formation, eradicated established biofilms, reduced expression of

biofilm- and virulence-associated genes, and disrupted bacterial membrane integrity, resulting in reduced colonization *in vivo* [187]. Furthermore, eugenol impaired staphyloxanthin biosynthesis by inhibiting crtM expression and CrtM enzyme activity without affecting bacterial growth, suggesting additional anti-virulence properties [188]. Combination approaches with other phenolic compounds further enhanced its antibacterial activity against MRSA [190]. Eugenol also inhibited growth and biofilm formation of colistin-resistant *K. pneumoniae*, accompanied by membrane disruption and reduced expression of biofilm-associated genes [189]. In addition, molecular studies indicated potential interactions of eugenol with Sortase A of *E. faecalis*, supporting its antibiofilm activity against multidrug-resistant strains [169]. Together, these findings highlight eugenol as a multifunctional antimicrobial compound with direct antibacterial, antibiofilm, and anti-virulence activities, although optimization of efficacy and safety remains necessary.

2.3.11. Antioxidant Properties

The antioxidant properties of eugenol and its derivatives, including bis-eugenol, have been extensively investigated and summarized in previous reviews [233–236]. Recent studies further support its broad antioxidant and anti-inflammatory potential. In a model of hydrogen peroxide-induced OS in pancreatic islet cells, eugenol reduced oxidative damage markers, enhanced total antioxidant capacity, and modulated antioxidant enzyme activity, including catalase and superoxide dismutase [237]. Comparative analyses of eugenol, bis-eugenol, and clove essential oil demonstrated effective free radical scavenging and ferric ion reduction, while also protecting macrophages against OS [236]. These compounds additionally influenced inflammatory responses by modulating nitric oxide production, TLR4 expression, and cytokine secretion, with bis-eugenol and clove essential oil showing particularly pronounced anti-inflammatory effects [238]. Furthermore, eugenol supplementation during porcine *in vitro* embryo production reduced ROS levels and improved developmental outcomes, supporting its potential to mitigate OS in diverse biological systems [239].

2.3.12. Incorporation into Electrospun Meshes

Eugenol is a major antibacterial agent with so far zero musculoskeletal/electrospinning literature tracking. It has been embedded into annealed ultrathin PHBV fibers [240] and PLA/chitosan oligosaccharide films via metal-organic framework inclusion complexes [241]. It has also been evaluated alongside curcumin, piperine, and rutin in PCL wound dressings [157], nozzle-less electrospun gelatin nanofibers [242], antifungal acacia gum/PVA/ β -cyclodextrin setups [243,244], and superhydrophobic PVA/ethyl cellulose bilayer membranes for air purification [245]. Additional scaffolds include antibacterial nano-Halimolobos Concha/PCL/PEG membranes [246], glutaraldehyde-crosslinked zein packaging [247], core-shell cellulose acetate/gelatin films [248], and biodegradable zein/PEG nanofibrous webs [249]. Strikingly, self-standing functional webs can be electrospun without any polymer matrix using concentrated aqueous cyclodextrin derivative inclusion complexes (HP- β -CD, HP- γ -CD, M- β -CD) [244]. Compiling these strategies clarifies how highly volatile components, such as eugenol, can be successfully trapped within structural electrospun matrices and be controlled released from them.

2.3.13. Bakuchiol

Bakuchiol is a meroterpenoid phenol that was first isolated from the seeds of *Psoralea corylifolia* in 1966 [250]. It has already been applied as a therapeutic agent in many indigenous medicine systems, most notably in Ayurveda and traditional Chinese medicine. More recently, also the western hemisphere has started to value its promising therapeutic effects, most notably for dermal applications, such as photoaging [251]. Bakuchiol shares similar effects to the more commonly known group of retinol compounds. However, documentation of its antibacterial as well as antioxidant potential remains limited.

2.3.14. Antibacterial Properties

Bakuchiol, a meroterpenoid phenolic compound isolated from *Psoralea corylifolia*, has demonstrated broad antimicrobial and antibiofilm activity against clinically relevant pathogens. Early studies showed potent antibacterial effects against a range of oral bacteria, including *Streptococcus* spp., *Enterococcus* spp., *Lactobacillus* spp., *Actinomyces viscosus*, and *Porphyromonas gingivalis*, with low MIC values and rapid bactericidal activity [191]. Beyond direct antibacterial effects, bakuchiol exhibits strong anti-virulence properties by targeting QS systems in *P. aeruginosa*. It inhibits both the PQS and las QS pathways, reducing production of virulence factors, impairing bacterial motility, and strongly suppressing biofilm formation without affecting bacterial growth [192,193]. Bakuchiol also shows potent activity against *S. aureus*, including ciprofloxacin-resistant strains and MRSA, by

inhibiting biofilm formation, disrupting DNA gyrase activity, and eliminating bacterial persisters [194–196]. Mechanistically, its antibacterial activity is primarily linked to membrane disruption through phospholipid interactions, altered bacterial metabolism, OS modulation, and impaired iron homeostasis [195,197]. Importantly, bakuchiol displayed synergistic effects with antibiotics, including colistin, restoring activity against multidrug-resistant Gram-negative pathogens and improving outcomes in infection models [196,197]. Finally, structural modification of bakuchiol through ester and ether derivatives did not improve antibacterial potency compared with the parent compound, highlighting bakuchiol itself as a promising antimicrobial scaffold [198].

2.3.15. Antioxidant Properties

Bakuchiol has been extensively investigated for its antioxidant properties, particularly in the context of skin aging, but recent studies have highlighted broader protective effects against OS and inflammation [252]. In a murine model of early brain injury, bakuchiol reduced oxidative damage by lowering ROS-related markers, lipid and DNA oxidation products, and NADPH oxidase activity, while enhancing antioxidant defenses and preserving mitochondrial integrity. Additionally, bakuchiol reduced apoptosis through modulation of key apoptotic regulators [253]. Beyond direct antioxidant activity, bakuchiol was shown to scavenge free radicals, inhibit tyrosinase activity, and suppress inflammatory responses by reducing nitric oxide production, iNOS and COX-2 expression, and pro-inflammatory cytokine release in activated macrophages [254,255]. In models of inflammatory arthritis, bakuchiol decreased disease severity, inflammatory markers, and tissue alterations while improving systemic parameters [256]. Furthermore, bakuchiol protected against LPS-induced oxidative and inflammatory damage in zebrafish embryos by restoring mitochondrial function, enhancing antioxidant enzyme activity, and reducing inflammatory mediator expression [257]. Finally, in *Caenorhabditis elegans*, bakuchiol promoted stress resistance and extended lifespan through activation of the DAF-16 pathway and increased antioxidant capacity [258]. Together, these findings demonstrate the broad antioxidant and anti-inflammatory potential of bakuchiol across diverse biological systems.

2.3.16. Incorporation into Electrospun Meshes

Bakuchiol represents an extreme literature deficit with respect to electrospinning and musculoskeletal applications, heavily justifying a closer review. It is occasionally mentioned in broad nerve regeneration overviews. Non-electrospinning bone setups rely on intricate π - π conjugations and catechol-group mussel-stimulated polydopamine to couple oxidation-sensitive bakuchiol-loaded hybrid liposomes with short fibers [259]. Globally, only our work on electrospun DegraPol®/Bakuchiol meshes evaluated *in ovo* [19], along with a singular exploration of a gelatin-PVA-EDTA blend carrying a bakuchiol nanoemulsion for burn wounds [260], constitute the entire electrospinning footprint of this natural retinol alternative.

2.3.17. Fucoxanthin

Fucoxanthin is a xanthophyll compound belonging to the group of carotenoids, and can naturally be found in marine algae, including brown macroalgae, and diatoms. It is a natural antioxidant and since 2017 onwards, has gained popularity in the research community. It is linked to assumed benefits for various disease types, thanks to its antibacterial, antioxidant, anti-inflammatory, skin-protective, anti-obesity, and anti-diabetic characteristics [261,262].

2.3.18. Antibacterial Properties

The antibacterial potential of fucoxanthin, a marine-derived carotenoid, has recently been reviewed and compared with other carotenoids such as astaxanthin [200]. Based on available evidence, fucoxanthin appears to have greater translational potential due to its antibacterial activity at lower concentrations compared with astaxanthin. Reported antibacterial effects of fucoxanthin range from 62.5–1000 $\mu\text{g/mL}$, with stronger activity generally observed against Gram-positive bacteria, including *S. aureus*, *S. epidermidis*, *E. faecalis*, and various *Streptococcus* species, compared with Gram-negative pathogens [199,200]. In contrast, limited activity was observed against obligate anaerobic oral bacteria, suggesting a selective antimicrobial spectrum [199]. Further studies confirmed antibacterial activity against both Gram-positive and Gram-negative bacteria, including *S. aureus*, *E. faecalis*, *Bacillus subtilis*, and *P. aeruginosa* [201]. Additionally, fucoxanthin demonstrated additive and synergistic effects when combined with cefotaxime against *S. aureus*, including clinical isolates, resulting in enhanced bactericidal activity [202]. These findings suggest that fucoxanthin may represent a promising adjunctive antimicrobial compound, particularly against Gram-positive pathogens.

2.3.19. Antioxidant Properties

Fucoxanthin has recently gained attention for its diverse pharmacological activities, including its antioxidant potential and ability to modulate OS-related pathways [263]. In cellular models of oxidative injury, fucoxanthin protected cells against H₂O₂-induced damage by reducing ROS accumulation, limiting cellular injury, increasing glutathione levels, and activating the Nrf2/HO-1/NQO1 antioxidant pathway [264]. However, its effects appear to be concentration-dependent, as higher concentrations may induce OS in certain cell types [265]. Studies in immune cells further demonstrated antioxidant activity through enhanced glutathione balance and reduced ROS production, although anti-inflammatory effects were limited in some models [266]. Fucoxanthin and its metabolites, fucoxanthinol and amarouciaxanthin A, also reduced OS in hepatic stellate cells by modulating NADPH oxidase activity and antioxidant gene expression [267,268]. In animal models, fucoxanthin alleviated oxidative and inflammatory damage associated with drug-induced liver injury by reducing inflammatory mediators, OS markers, and tissue damage while enhancing antioxidant responses [269]. Furthermore, fucoxanthin protected neuronal cells against β -amyloid-induced oxidative damage through activation of the Nrf2 pathway and downstream antioxidant enzymes [270]. Comparative studies suggest that fucoxanthin and fucoxanthinol exert neuroprotective effects by activating Nrf2/Keap1/ARE signaling and scavenging radicals within cellular membranes and cytoplasm [271]. Together, these findings highlight fucoxanthin as a promising antioxidant compound with broad protective effects across different pathological models.

2.3.20. Incorporation into Electrospun Meshes

Fucoxanthin is an under-explored marine carotenoid with three total electrospinning papers and zero electrospinning/musculoskeletal links (Table 1). These sparse studies investigate fish gelatin nanofibers [272], ROS-responsive PLA/PEGDA-EDT@rGO-fucoxanthin membranes designed to attenuate osteoarthritis [273], and polymer-free, electrospun hydroxypropyl- β -cyclodextrin encapsulation systems [274]. The latter demonstrated strong systemic bioactivity *in vivo*, reducing mouse serum cholesterol and attenuating testicular histopathology. Hence, reviewing fucoxanthin introduces a critical perspective on reducing OS during structural tissue healings.

2.3.21. Lutein

Lutein is a natural dihydroxy carotenoid and belongs to the family of non-vitamin A carotenoids. It can be found in yellow-colored fruits and green leafy vegetables such as spinach and lettuce, where it is highly abundant. It has gained interest in the scientific and medical community, owing to its reported anti-cancer, anti-inflammatory, antioxidant and antimicrobial properties [275].

2.3.22. Antibacterial Properties

Lutein, a carotenoid compound, has demonstrated promising anti-virulence and antibiofilm properties despite limited direct antibacterial activity. Liu et al. showed that lutein targets the pore-forming toxin listeriolysin O from *L. monocytogenes*, inhibiting toxin oligomerization, reducing host cell damage, and limiting intracellular bacterial replication. In a murine infection model, lutein improved survival and reduced bacterial burden in infected tissues [203]. In *P. aeruginosa*, lutein strongly inhibited biofilm formation and disrupted established biofilms in a concentration-dependent manner without significantly affecting planktonic growth [204,205]. These effects were associated with reduced extracellular polymeric substance production, impaired bacterial motility, decreased production of virulence factors such as pyocyanin, rhamnolipids, and elastase, and downregulation of QS-related genes, including las and rhl systems [204,205]. Molecular docking studies further supported interactions of lutein with key QS proteins, including LasI, LasR, RhII, and RhIR [204]. Importantly, lutein enhanced the antibiofilm activity of tobramycin, resulting in improved eradication of biofilm-associated bacteria compared with antibiotic treatment alone [205]. Similar QS-modulating effects have also been reported for the structurally related carotenoid zeaxanthin, suggesting a broader anti-virulence potential among carotenoid compounds [276].

2.3.23. Antioxidant Properties

Lutein has been extensively investigated for its antioxidant and anti-inflammatory properties across various disease models [277]. Recent studies further support its ability to modulate OS and inflammatory responses. In cell-free assays, lutein demonstrated radical-scavenging activity, while cellular models showed protection against oxidative damage through reduction of ROS production and modulation of antioxidant defenses [278,279]. In microglial and neuronal cell models, lutein reduced OS-induced inflammation by enhancing antioxidant responses, regulating iron metabolism, increasing anti-inflammatory IL-10 production, and decreasing pro-inflammatory

cytokines such as TNF- α , IL-6, and IL-8 [279,280]. Comparative analysis of lutein stereoisomers demonstrated that both all-E and Z-forms reduced oxidative stress and inflammatory signaling by enhancing antioxidant enzyme activity, increasing glutathione levels, and suppressing cytokine secretion, with some Z-isomers showing enhanced protective effects at lower concentrations [281]. Furthermore, in a rat model of cadmium-induced oxidative injury, lutein supplementation restored antioxidant capacity, reduced oxidative damage markers, and improved biochemical indicators of tissue injury, highlighting its systemic protective potential [282].

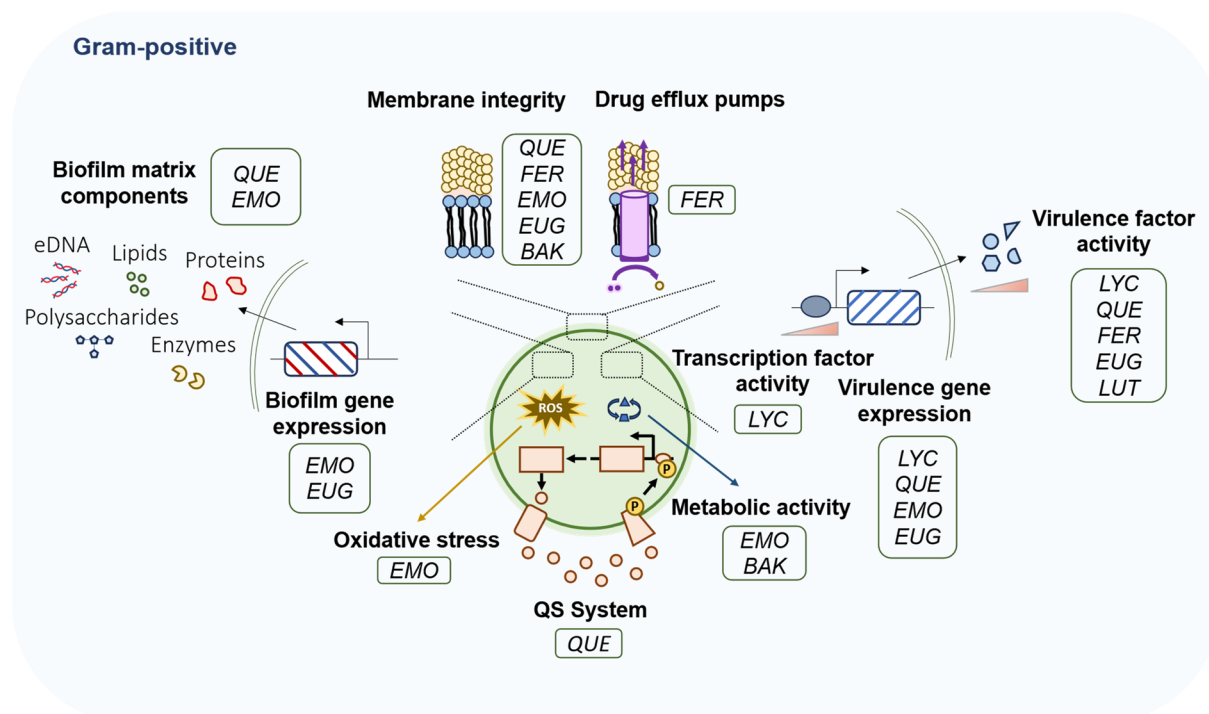
2.3.24. Incorporation into Electrospun Meshes

Despite high total publication tracking for the compound itself, lutein's integration into electrospun biomaterials is limited to one study, documenting lutein-loaded PVA/sodium alginate nanofibers and their resulting release dynamics [283]. Compiling its baseline parameters is crucial to opening new paths for this compound within musculoskeletal scaffolding.

2.4. Comparative Antibacterial, Antibiofilm, and Antioxidant Properties

Across the reviewed compounds, a common pattern emerges in which natural products do not act as uniformly potent bactericidal agents but rather display a spectrum of antibacterial, antivirulence, antibiofilm, and host-protective antioxidant activities. Their therapeutic relevance may therefore depend less on direct pathogen killing alone than on their ability to simultaneously modulate microbial behavior, biofilm persistence, and host–pathogen interactions.

Nevertheless, substantial differences in intrinsic antibacterial potency are apparent (Table 2). Emodin and bakuchiol show the strongest direct antibacterial activity, particularly against Gram-positive organisms, including MRSA and other clinically relevant pathogens. Bakuchiol additionally exhibits rapid bactericidal activity and activity against persister cells, whereas emodin combines comparatively low inhibitory concentrations with limited resistance development and reported *in vivo* efficacy. Eugenol occupies an intermediate position, while ferulic acid, fucoxanthin, and lutein generally require substantially higher concentrations for direct growth inhibition. Across the compounds, Gram-positive bacteria tend to be more susceptible than Gram-negative species, consistent with differences in membrane architecture and permeability (Figure 3).



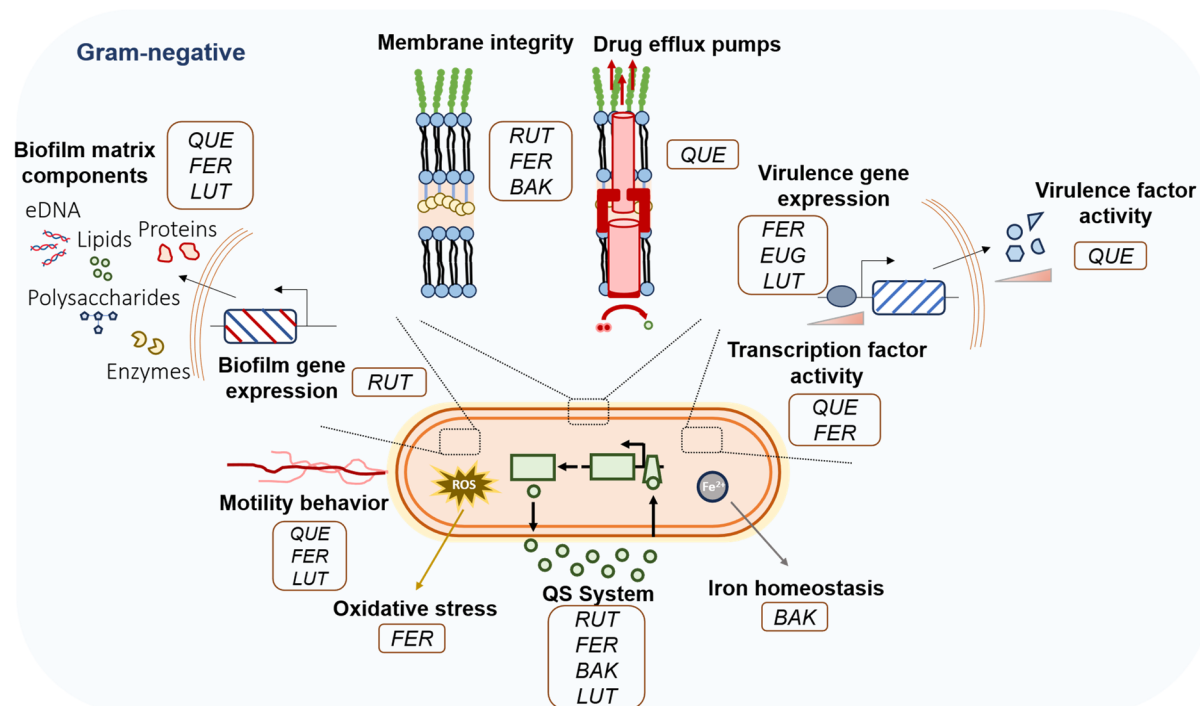


Figure 3. Graphical Illustration of reported targets for the antibacterial antioxidants in Gram-positive (above) and Gram-negative bacteria (below). Summarized are major target groups. For more details on the respective targets of action, consider the text section of the compound of interest. LYC, lycopene; QUE, quercetin; RUT, rutin; FER, ferulic acid and derivatives; EMO, emodin; EUG, eugenol; BAK, bakuchiol; LUT, lutein. Fucoxanthin is absent because no targets have been reported to date.

Importantly, the apparent hierarchy of antibacterial potency must be interpreted in the context of considerable methodological heterogeneity. Reported MICs vary between studies and assay formats, particularly for poorly water-soluble phenolic and terpenic compounds. Although broth microdilution (BMD) is most commonly used, agar diffusion can substantially underestimate the activity of lipophilic compounds because their diffusion through the water-rich agar matrix is limited, an effect particularly relevant for compounds such as lycopene [199]. Etest-based approaches may provide more continuous concentration-dependent MIC estimates than the geometric two-fold dilution steps used in BMD, but their application to natural compounds remains limited because standardized commercial strips are generally unavailable. Consequently, antibacterial concentrations obtained with different assay formats should not be interpreted as directly interchangeable. This methodological dependency is illustrated in Figure 4, which integrates experimentally reported antibacterial and antioxidant concentration ranges.

Despite differences in direct antibacterial potency, a particularly consistent feature is the reported antivirulence and antibiofilm activity, frequently observed at subinhibitory concentrations. Ferulic acid, eugenol, emodin, bakuchiol, and lutein inhibit biofilm formation and, in several studies, affect established biofilms through mechanisms including reduced adhesion and motility, suppression of extracellular polymeric substance production, and interference with quorum-sensing (QS) pathways. QS modulation is particularly notable because it occurs across structurally diverse compounds: emodin and bakuchiol interfere with major bacterial signaling systems, eugenol and lutein reduce QS-regulated gene expression and virulence-factor production, and ferulic acid and fucoxanthin modulate pathways associated with bacterial communication and biofilm persistence. Thus, antivirulence activity may represent a more broadly conserved antimicrobial property of these compounds than direct bactericidal activity.

Additional mechanisms further distinguish the compounds. Membrane perturbation has been reported for emodin, bakuchiol, and eugenol, resulting in increased permeability and loss of membrane integrity, while emodin and bakuchiol additionally interfere with bacterial respiration, ATP balance, iron utilization, and redox homeostasis. These effects may also explain the frequently reported potentiation of conventional antibiotics by ferulic acid, emodin, eugenol, and bakuchiol. Increased membrane permeability, inhibition of efflux mechanisms, metabolic or oxidative disruption, and attenuation of biofilm-associated tolerance can collectively enhance antibiotic susceptibility. Bakuchiol-mediated disruption of iron homeostasis represents an additional mechanism reported to potentiate colistin activity.

In contrast to the variability in antibacterial potency, antioxidant activity is a highly conserved property across the compounds (Table 3), although its apparent magnitude is likewise strongly assay-dependent. DPPH, ABTS, ORAC, and TEAC assays measure different aspects of antioxidant capacity and differ in radical accessibility, solvent compatibility, reaction kinetics, and endpoint determination. For example, the smaller ABTS radical cation is accessible to larger compounds such as rutin more readily than the sterically hindered DPPH radical, whereas ORAC captures kinetic protection against physiologically relevant peroxy radicals that endpoint-based DPPH measurements may miss. Accordingly, quercetin shows particularly strong kinetic antioxidant behavior in ORAC assays [284], while comparisons of quercetin across TEAC, DPPH, and other assays demonstrate marked method-dependent variation [285]. More broadly, the correlation between TEAC and DPPH measurements across 37 phenolic compounds was only 0.4314 [286], with similar discrepancies reported for phytochemicals extracted from cherry leaves [287]. Figure 4 therefore presents experimentally assessed concentration ranges rather than assuming direct equivalence between assay systems, incorporating data for lycopene [288–290], quercetin [291,292], rutin [292,293], and the concentration ranges summarized in Tables 2 and 3. Where antibacterial and DPPH-based antioxidant ranges overlap without reported cytotoxicity, these regions indicate experimentally supported windows of potential dual activity.

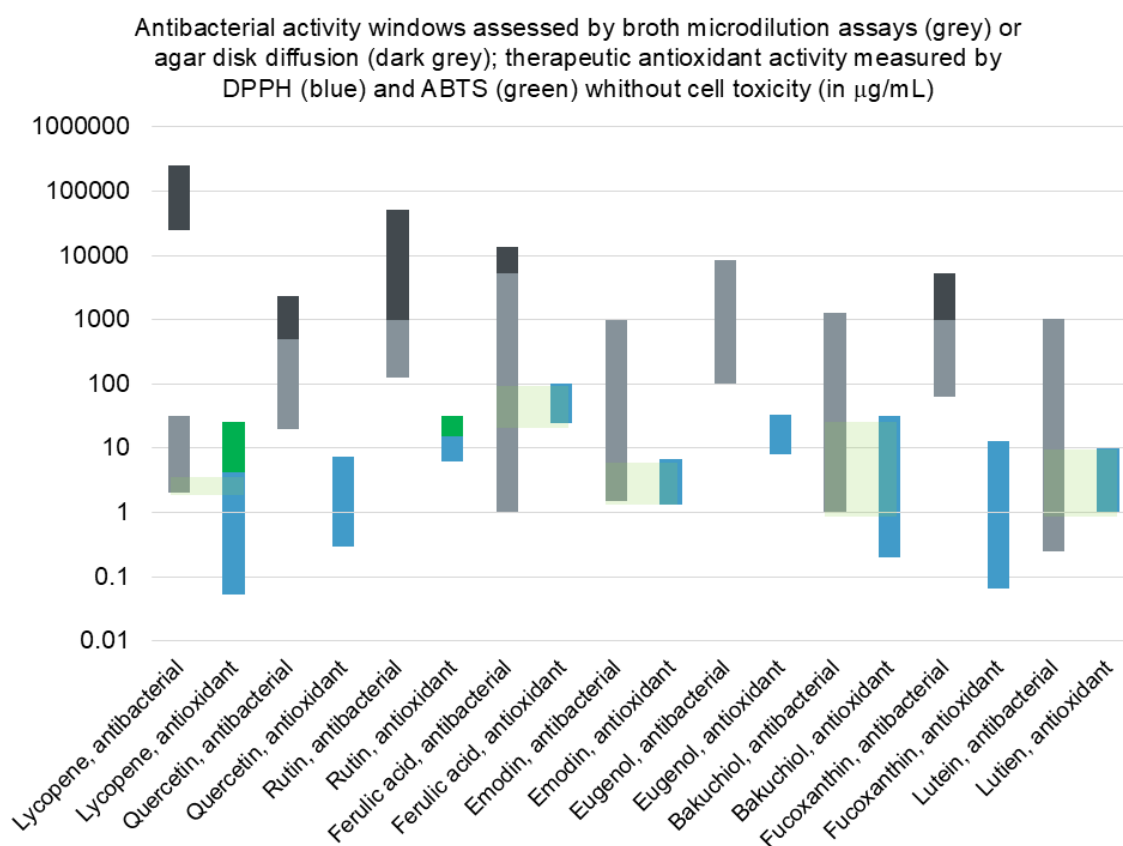


Figure 4. Balanced experimentally assessed therapeutic windows for antibacterial (grey: broth microdilution assays; dark grey: agar disk diffusion assays) and antioxidant (blue: DPPH assay; dark green: ABTS assay) activity based on literature taken from Tables 2 and 3 with additional references specifically for Lycopene, antioxidant, DPPH [288,290]; Lycopene, antioxidant, ABTS [289]; Quercetin, antioxidant, DPPH [291]; Quercetin, antioxidant, ABTS [292]; Rutin, antioxidant, DPPH [293], Rutin, antioxidant, ABTS [292]. Where concentration windows of antibacterial and antioxidant activity (based on DPPH) overlapped, ranges were marked in light green, indicating the compounds' therapeutic windows of experimentally assessed dual activity without cytotoxicity.

Table 3. Overview of the antioxidant evaluation of selected phenolic and terpenic compounds.

Compound	Model System/Assay	Evaluated Concentrations	Key Findings	Main Mechanisms	References
Ferulic acid and derivatives	Cell culture: RAW 264.7 macrophages, neutrophils, β -amyloid-treated neuronal cells	Cell culture: 25–100 $\mu\text{g/mL}$	- Decrease of ROS, NO, cytokine-linked oxidative stress - Strong radical scavenging - Preserved activity in biomaterials	- Direct radical scavenging - Modulation of leukocyte ROS - Mitochondrial protection - Antioxidant enzyme regulation (peroxiredoxin) - Anti-inflammatory signaling (ERK1/2)	[172,209–211]
	Assays: DPPH scavenging, ROS/OS reduction, NO reduction, superoxide suppression, mitochondrial protection, apoptosis modulation, antioxidant signaling				
Emodin	Cell culture: IL-1 β -stimulated nucleus pulposus cells, OGD/R injury model	Cell culture: 1.35–6.756 $\mu\text{g/mL}$ <i>In Vivo</i> : 20–150 mg/kg	- Decrease of ROS, oxidative damage marker - Increase of SOD, GSH-Px - Improved tissue protection - Reduced apoptosis	- PI3K/Akt/mTOR modulation - NF-κB suppression - HO-1-dependent protection - Enhancement of endogenous antioxidant defenses	[223–226]
	<i>In Vivo</i> : LPS-induced sepsis (mouse), intestinal ischemia–reperfusion injury (mouse), age-related brain oxidative stress (rat)				
Eugenol	Assays: ROS reduction, antioxidant enzymes, apoptosis modulation, inflammatory redox markers (cytokines), PI3K/Akt/HO-1/NF- κ B pathway modulation	Cell culture: 8–33 $\mu\text{g/mL}$ <i>In Vivo</i> : 10–100 mg/kg	- Decrease of MDA, ROS, NOX-like stress - Increase of TAC, SOD, CAT - Improved embryonal development	- Direct radical scavenging - Enhancement of antioxidant enzymes - Anti-inflammatory signaling (TLR4 downregulation) - Modulation of glutathione balance	[237–239]
	Cell culture: RAW 264.7 macrophages, H ₂ O ₂ -stressed pancreatic islets, embryo culture systems <i>In Vivo</i> : Porcine embryo development model				
Bakuchiol	Assays: DPPH scavenging, ROS/OS reduction, lipid peroxidation, total antioxidant capacity, antioxidant enzymes, NO reduction	Cell culture: 0.2–32 $\mu\text{g/mL}$ <i>In Vivo</i> : 10–50 mg/kg	- Decrease of ROS, MDA; oxidative DNA damage - Increase of SOD, GSH-Px - Mitochondrial protection - Lifespan extension (<i>C. elegans</i>)	- ROS suppression - Mitochondrial stabilization - Inhibition of inflammatory ROS (NOX2) - Nrf2-linked protection (indirect evidence)	[253–258]
	Cell culture: RAW 264.7 macrophages, zebrafish embryo oxidative stress model <i>In Vivo</i> : Mouse early brain injury, rat arthritis, <i>C. elegans</i> aging model				
Fucoxanthin	Cell culture: Hepatic L02 cells (H ₂ O ₂), hepatic stellate cells (TGF β 1-induced ROS), neutrophils/mononuclear cells, PC12 neurons	Cell culture: 0.065–13 $\mu\text{g/mL}$ <i>In Vivo</i> : 100–500 mg/kg	- Decrease of ROS, LDH release - Increase of GSH, Nrf2, HO-1, NQO1 - Protection against hepatotoxicity and neurotoxicity	- Strong Nrf2/Keap1 pathway activation - HO-1 induction - NOX inhibition - Mitochondrial protection	[264–271]
	<i>In Vivo</i> : Rat paracetamol-induced liver injury, rodent oxidative stress models Assays: DPPH scavenging, ROS/OS reduction, antioxidant enzymes, lipid peroxidation, membrane permeability				
Lutein	Cell culture: BV-2 microglia (H ₂ O ₂), SH-SY5Y neurons (glutamate), Caco-2 cells, RBC hemolysis assay	Cell culture: 1–10 $\mu\text{g/mL}$ <i>In Vivo</i> : 200 mg/kg	- Decrease of ROS, MDA, pro-inflammatory cytokines - Increase of SOD, CAT, GSH-Px, TAC - Neuroprotection	- Radical scavenging - Enzymatic antioxidant upregulation - Anti-inflammatory cytokine modulation - Membrane/cytoplasmic accumulation effects	[278–282]
	<i>In Vivo</i> : Rat cadmium-induced oxidative stress model Assays: ABTS scavenging, ROS/OS reduction, lipid peroxidation, antioxidant enzymes, inflammatory redox markers (cytokines), total antioxidant capacity				

Table 3. Cont.

Lycopene	Cell culture: Porcine IVF embryos, H ₂ O ₂ -stressed SH-SY5Y neuroblastoma cells	• Decrease of ROS and OS • Preservation of SOD and CAT activity • Mitochondrial protection • Reduced apoptosis • Strong DPPH and ABTS radical scavenging	• Direct radical scavenging • ROS suppression • Preservation/modulation of endogenous antioxidant defenses • Mitochondrial stabilization • Suppression of mitochondria-dependent apoptosis	[288–290]
	Assays: DPPH, ABTS and hydroxyl radical scavenging, ROS/OS reduction, antioxidant enzymes (SOD, CAT), mitochondrial membrane potential/permeability, apoptosis modulation			
Quercetin	Cell culture: Cytotoxicity assessment of quercetin and glycosylated derivatives in two cell types	• Strong DPPH and ABTS radical scavenging	• Direct radical scavenging • Electron-donating/reducing antioxidant capacity • Antioxidant activity dependent on molecular structure/glycosylation	[291,292]
	Assays: DPPH, ABTS, FRAP, total phenolic content.			
Rutin	Cell culture: UVA/UVB-exposed human keratinocytes and fibroblasts (rutin + ascorbic acid).	• Rutin + ascorbic acid reduced UV-induced ROS and enhanced antioxidant activity • Increased CAT, SOD, and thioredoxin reductase activity • Reduced inflammatory and apoptotic signaling	• Direct radical scavenging • Modulation of Nrf2 signaling • Enhancement of endogenous antioxidant defenses • NF-κB suppression • Inhibition of caspase-associated apoptosis	[292,293]
	Assays: DPPH, ABTS, FRAP, ROS/OS reduction, antioxidant enzymes, lipid/protein oxidation, inflammatory and apoptotic signaling			

Mechanistically, carotenoids such as fucoxanthin and lutein appear to act predominantly through host-protective antioxidant and anti-inflammatory pathways, including Nrf2 activation, induction of HO-1, SOD, CAT, and GPx, and stabilization of mitochondrial function. Phenolic compounds show a broader combination of direct antimicrobial and host-directed effects, including modulation of NF- κ B, PI3K/Akt, and MAPK signaling. This distinction broadly reflects chemical class: phenolic compounds tend to exhibit stronger direct antibacterial, membrane-active, antibiofilm, and antibiotic-potentiating effects, whereas carotenoids display comparatively weak direct antibacterial activity but pronounced antioxidant and cellular protective effects. Importantly, however, these activities remain concentration- and exposure-dependent, and several compounds can also exert detrimental effects on host cells at higher concentrations or prolonged exposure.

A further limitation is the comparatively sparse evidence for activity against obligate anaerobes, which is particularly relevant for applications involving oral biofilms. Ferulic acid showed no antibacterial activity against *Fusobacterium nucleatum* and *Prevotella intermedia*, or against the facultative anaerobe *S. mitis* [167]. Similarly, fucoxanthin showed activity against several Gram-positive and, to a lesser extent, Gram-negative bacteria, but no detectable activity against the anaerobic species *Actinomyces israelii*, *Atopobium parvulum*, *Peptostreptococcus niger*, *P. gingivalis*, *C. acnes*, and *Veillonella parvula* [199]. For lycopene, quercetin, rutin, emodin, and eugenol, antibacterial activity has primarily been investigated using aerobic or facultatively anaerobic model organisms [294], leaving their efficacy against obligate anaerobes insufficiently characterized. Lutein has been reported primarily as an antivirulence rather than bactericidal agent against *L. monocytogenes* [203]. Bakuchiol represents a notable exception, having demonstrated antibacterial activity against the obligate anaerobe *P. gingivalis* [295].

Taken together, these findings indicate that the therapeutic potential of the reviewed natural compounds cannot be adequately characterized by MIC values alone. Their value instead appears to arise from compound-specific combinations of direct antibacterial activity, biofilm and virulence interference, antibiotic potentiation, and host-protective antioxidant effects. At the same time, comparisons across compounds require careful consideration of assay methodology, physicochemical properties, cytotoxicity, and the limited evidence available for obligate anaerobic microorganisms.

2.5. Dual Active Compound Delivery Strategies for Electrospun Scaffolds

While many reviews on agents to reduce OS, and simultaneously fight against bacterial contamination focus primarily on the antibacterial antioxidants themselves [90], the second part of this review article prioritizes a set of corresponding (nano) delivery systems that could potentially be combined with electrospinning to fabricate bioactive fibers. Researchers frequently focus on selecting a specific antibacterial antioxidant to address a clinical problem, while the one crucial question remains how to deliver it effectively to the target tissue and to also increase its efficacy. Generally, nanosystems—such as nanoparticles, nanocapsules, or nanosheets—act as vehicles to deliver various antibacterial antioxidant moieties to locally confined target tissues or cells. Such nanosystems can be easily integrated into electrospun fiber meshes [8]. Another class of vehicles includes biological macromolecules, and assemblies, including extracellular vesicles (EVs) [296], nucleic acids [297], or liposomes, with recent designs to overcome liposome instability during electrospinning [298]. Finally, metals, and metal oxides (both easily incorporated in an electrospun mesh [10]) can also deliver antibacterial antioxidants, as demonstrated for various gases, including hydrogen (H₂(g)), a gas that is known for its antioxidant properties, but also for damaging bacterial cell membranes, and paradoxically induce ROS within bacteria to kill them [299]).

The following subchapters focus on delivery systems that can simply be combined with electrospinning via blending, emulsion or other techniques—to fabricate efficient antibacterial meshes that simultaneously exhibit antioxidative properties, envisioned to be applied in regenerative medicine, particularly for musculoskeletal applications. Beyond the phenolic and terpene derivatives discussed previously, these systems can be applied to a wider range of antibacterial antioxidants, exemplified for different other compound classes.

2.6. Nanosystems

2.6.1. Nanoparticles

Nanoparticles can be easily integrated into electrospun fibers. In blend electrospinning, nanoparticles are directly dispersed into the polymer solution before electrospinning. As the fibers form, the nanoparticles become entrapped throughout the inner matrix and the surface of individual fibers [8,300]. Also coaxial electrospinning can be used, where the nanoparticles are incorporated in the cores of the core-shell fibers. Furthermore, post modification techniques are applied, such as spray deposition, dip coating, physical vapor depositions or ultrasonic coating [301]. Creating hybrid systems, the bioactive nanoparticles incorporated within electrospun fibers allow a controlled and sustained release to the target tissue [302]. Important to note, there are different types of

nanoparticles used for this kind of drug delivery, among them metals or metal oxides, like silver [67] or titanium dioxide [303]; bioceramics like copper-doped amorphous calcium phosphate [8] or bioglass nanoparticles [304]; or polymeric nanoparticles, exemplified by chitosan-based nanoparticles that release ciprofloxacin [305].

Curcumin (CUR), a phenolic antibacterial antioxidant has gained increasing attention in the medical field [306] (Figure 5). It is a natural dimerization product of ferulic acid (Figure 5). Hence, CUR-based nanotherapeutic strategies have been recently reviewed [307]. For instance, Hu et al. developed a targeted delivery system for CUR, and dihydromyricetin (DHM) (Figure 5) to treat liver fibrosis. These agents exhibit potent anti-inflammatory, anti-fibrotic, and antioxidant properties [308]. The researchers utilized a PLA-PEG-cycloRGD framework, co-assembling CUR, and DHM to form bioactive nanoparticles that serve as efficient drug delivery vehicles. Similarly, CUR was combined with oleanolic acid to fabricate oleanolic acid-coated CUR nanoparticles, significantly enhancing CUR's efficacy in preventing gastrointestinal disorders, particularly gastric ulcers [309].

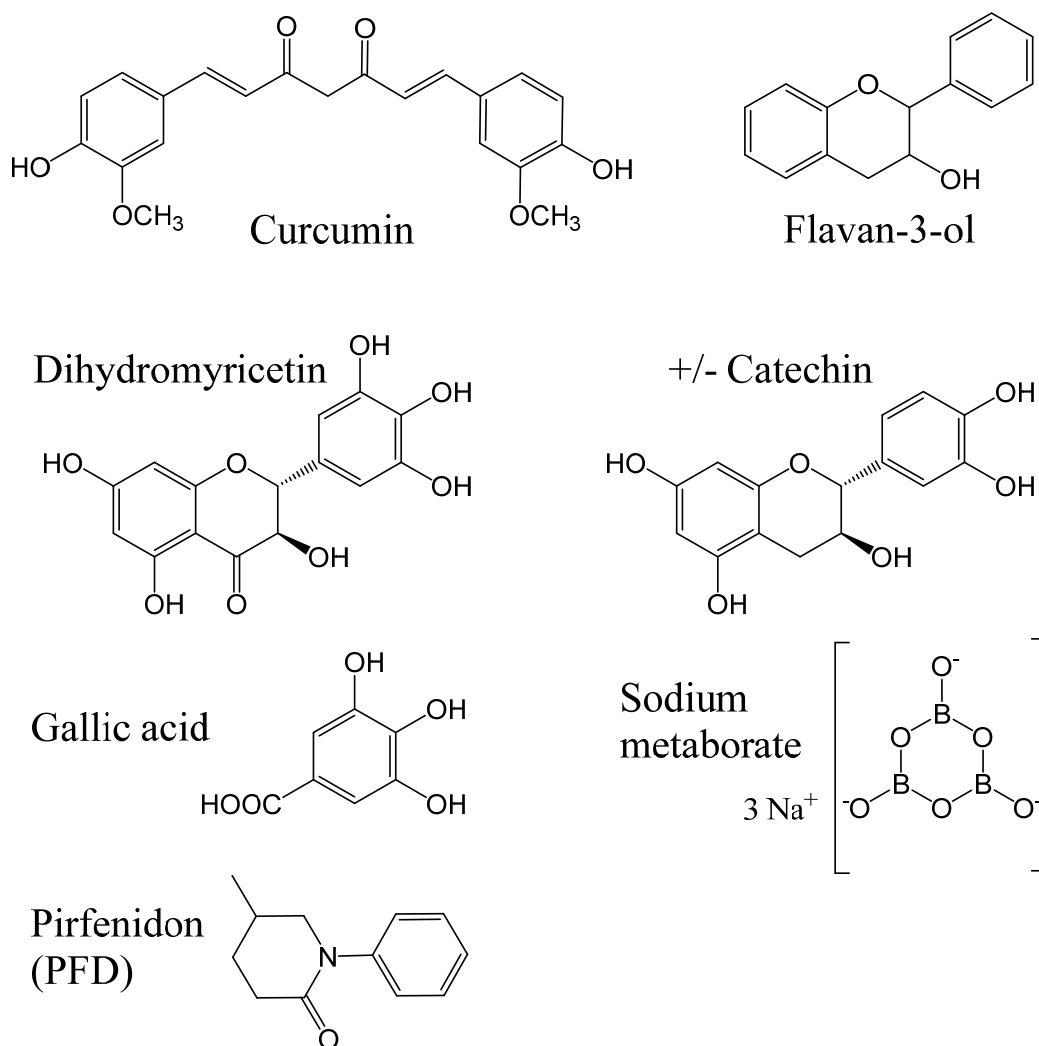


Figure 5. Further chemical structures of compounds with antibacterial and antioxidant properties.

In a separate study, pulmonary fibrosis was addressed using rapamycin-loaded mixed micelle nanoparticles, which were coated with macrophage membranes via a co-incubation method [310] to improve the system's biomimetic properties.

Given the role of the gaso-transmitter hydrogen sulfide (H₂S) in blood pressure regulation, and its antibacterial characteristics via interaction with disulfide bonds of proteins [311], Tain developed a nanoparticle carrier for the delivery of sodium thiosulfate, a H₂S precursor. In a rat model of chronic kidney disease (CKD), these nanoparticles successfully reduced hypertension in juvenile subjects. The therapeutic effect was attributed to the restoration of nitric oxide (NO) signaling, and an increase in L-arginine levels, both of which are typically impaired in CKD [312]. H₂S delivery has further shown promise in treating osteoporosis, periodontitis, muscle atrophy, arthritis, and disc herniation [313]. Various H₂S-releasing devices have been reviewed, including platforms such as silk fibroin, hyaluronic acid, chitosan, iron oxide nanoparticles, and zwitterionic nanoparticles [313].

Furthermore, Mn_3O_4 nanoparticles have demonstrated significant SOD-, and CAT-mimetic activities, as well as hydroxyl radical scavenging capabilities [314]. These nanozymes—nanomaterials that emulate the catalytic functions of natural enzymes like MnSOD—were reported to outperform CeO_2 nanoparticles that are efficient in ROS scavenging, and cytoprotection [315,316] as well as when used as antibacterial moieties [317]. As for the CeO_2 nanoparticles (nanoceria), their efficacy is highly dependent on their size, and synthesis method, with the underlying mechanism involving the reversible $\text{Ce}^{3+}/\text{Ce}^{4+}$ redox couple [316] (Figure 6). Specifically, Ce^{3+} facilitates the reduction of superoxide ($\text{O}_2^{\cdot-}$) to hydrogen peroxide (H_2O_2), while Ce^{4+} reacts with H_2O_2 to regenerate Ce^{3+} , and produce oxygen as well as water [316]. Based on this catalytic cycle, CeO_2 nanoparticles effectively mimic SOD, and CAT functions, classifying them as intrinsic nanozymes.

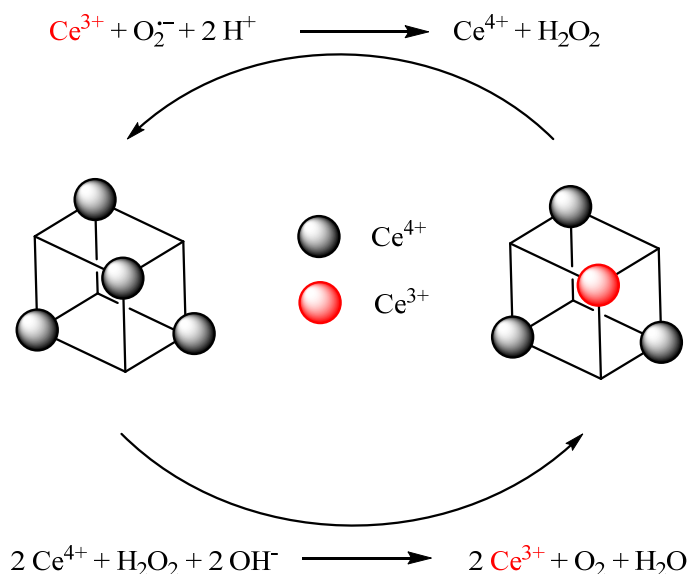


Figure 6. While Ce(III) reduces superoxide anion radical to hydrogen peroxide, the resulting Ce(IV) undergoes a disproportionation reaction with hydrogen peroxide, and hydroxide anion to yield oxygen, and water. Thus, the Ce(III)/Ce(IV) ions are catalyzing the ROS reduction to final harmless products.

Coming back to phenolic compounds and terpenes, several studies using nanoparticles for their sustained delivery have been reported. For example, quercetin has been reviewed with respect to different nanoformulations—where solid-lipid nanoparticles have been attributed beneficial effects and sustained release kinetics [318]. Also, metallic nanoparticles have been used to deliver polyphenols and flavonoids whose basic structural entity is the Flavan-3-ol moiety (Figure 5) [319]. Also ferulic acid loaded nanoparticles have been applied in skin with positive outcomes, substantiating that the nanoparticle system as delivery vehicle combined with electrospinning to form hybrid nanocomposites is a valuable option also for this kind of compound [320]. For eugenol, zein-caseinate-pectin colloidal complex nanoparticles have been designed, uniformly sized 140 nm and with a spherical shape [321]. Reports on nanoparticle vehicles to deliver lycopene [322], lutein [323] or thymol in silica sphere nanoparticles furthermore emphasize the practicability of nanoparticles for drug delivery [324].

2.6.2. Nanocapsules

A further powerful hybrid delivery system can be created by the combination of nanocapsules and electrospun meshes. Compared to liposomes, nanocapsules possess a solid outer shell, which renders them mechanically tougher and in turn more resistant against the harsh organic solvents that may be utilized during the electrospinning process. Examples for nanocapsule/electrospun mesh nanocomposites cover topical drug delivery systems like chemotherapeutic Paclitaxel that was enclosed in oil-core polymeric nanocapsules and suspended in a polymer solution containing a hydrophilic drug Doxorubicin for electrospinning [325]. For controlled Quercetin delivery, biodegradable poly lactic acid nanocapsules were developed [326]. Also Ferulic acid delivery via nanocapsules was reported to be a beneficial option [327]. Finally, also eugenol nano-encapsulation has been reported and shows that phenolic antibacterial antioxidants can be delivered via hybrid nanocapsule/electrospun fiber systems [328].

Excessive fluoride is known to inhibit proteins, disrupt organelles, alter pH levels, and cause electrolyte imbalances [329]. To mitigate fluoride-induced OS, PLGA-based nanocapsules were developed to encapsulate a synergistic mixture of the antioxidant ($\pm$)-catechin hydrate, and the chelator sodium metaborate [330] (Figure 5).

Compared to the free formulation, the nanocapsule system significantly reduced ROS levels in the liver, brain, and kidney of fluoride-treated rats. The most pronounced effects were observed when both agents were co-incorporated, highlighting their synergistic potential [330]. Antibacterial catechin has furthermore been reported in a combination with the antibacterial enzyme lysozyme, classified as glycosidase that splits polysaccharide chains, such as the β -1,4 links between N-acetylmuramic acid, and N-acetylglucosamine in the peptidoglycan of the microbial cell wall of Gram-positive bacteria [331].

2.6.3. Nanocrystals

Nanocrystals in combination with electrospun meshes is highly efficient, because the bioactive ingredients can be combined with the fibers as a pure solid drug; as has been shown for Quercetin [332]. Furthermore, gallic acid (Figure 5) renowned for its antioxidant, anti-inflammatory, and antibacterial properties [333,334], was processed into nanocrystals (GC-NCs) and integrated into a polyacrylic acid matrix via co-gelation to form a hydrogel (GC-NCs-Gel). When applied to a rat full-thickness skin defect model, this hydrogel was found to promote neovascularization, epidermal regeneration, and collagen deposition [335].

2.6.4. Nanosheets

The combination of nanosheets with electrospun fibers is a further option of sustained drug delivery. For example, nanosheet incorporation into electrospun polyacrylonitrile membranes has been reported to yield a flexible triboelectric nanogenerator [336]. With regards to antibacterial antioxidants, antibacterial silicon-hydrogen (Si-H) nanosheets have been developed for the treatment of osteoarthritis. These nanosheets are particularly effective as they continuously generate hydrogen in situ to scavenge ROS. Additionally, their injectable nature facilitates minimally invasive application [337].

Taken together, nanosystems—including nanoparticles, nanocapsules or nanosheets—provide design option for various kinds of antibacterial antioxidants, among them phenols and terpenes that were specifically addressed in the first part of this review. Relative abundance of literature declines in the order of nanoparticles where a huge of reports exist, followed by less publications dealing with nanocapsules and even less with nanosheets. This may be due to practical reasons. The generation of bioactive nanoparticles can basically be realized by top down approaches like milling, laser ablation or nanolithography [338] and etching; or via bottom up approaches, such as flame spray pyrolysis [339], sol gel processing, hydrothermal or solvothermal synthesis [340]. These approaches are well established and some of them low-cost methods (for example milling). As nanocapsule delivery systems feature a core-shell structure, the generation of bioactive nanocapsules may be more challenging. Because these systems handle sensitive, biologically active compounds, the synthesis methods must use mild temperatures and minimize toxic solvents to prevent denaturation. Advanced fabrication methods are therefore needed, such as interfacial polymerization [341], nano precipitation [342], solvent evaporation or layer-by-layer techniques [343]. For nanosheet generation, even more sophisticated (and expensive) methods may be used, such as top down exfoliation methods [344] that break the weak Van der Waals forces holding layered bulk materials together to isolate individual, highly stable 2D sheets; or the bottom up approach like the self-assembly of bioactive templates.

2.7. Natural Biomacromolecules

2.7.1. Nucleic Acids

In contrast to the traditionally linear nucleic acids, tetrahedral framework nucleic acids (tFNA) have different advantages as they profit particularly from a combination with electrospun fibers. The tFNA represent 3D rigid DNA nanostructures resembling Origami nanodevices, that are more resistant facing enzymatic degradation than classic nucleic acids do [345]. The sharp-edged tetrahedral geometry of the tFNA facilitates passing through cell membranes, promoting the transfer into the cell. Furthermore, the tFNA allow an easy incorporation of drugs. While the combination of electrospinning and tFNA lead to a permanent fixation of the tFNA, the drugs associated with the nanocarrier tFNA can be easily released in a sustained release kinetics. Hence, tFNA have been designed for peptide delivery [346]. Also the delivery of the antifibrotic polyphenolic monomer chlorogenic acid with tFNA nanoparticles as delivery system has been described to aid liver regeneration [347]. Another example deals with resveratrol-loaded tFNA to suppress angiogenesis and chronic inflammation in retinopathy [348]. Also Quercetin (Figure 2) has been combined with tFNA in order to mitigate sepsis [349]. To address pulmonary fibrosis, antibacterial tFNAs [350,351] were utilized as delivery vehicles to synthesize a PFD-tFNA (Pt) complex. Using a micronebulizer, Xie et al. achieved quantitative drug delivery to the lungs via inhalation [352]. Taken together,

tFNA as nanocarriers are promising devices that can easily be combined with electrospinning and offer valuable options for the incorporation of antibacterial antioxidants to be released in a controlled manner.

2.7.2. Liposomes

Liposomal formulations for the controlled release of antioxidants have been extensively investigated, primarily due to their ability to enhance penetration through the skin barrier [353]. However, the utility of liposomal carriers (Figure 7) extends beyond dermatological applications. To mitigate neuronal hypoxia-ischemia, and associated mitochondrial dysfunction, miR-9-5p-loaded liposomes were administered in mice. This treatment increased mitochondrial count, normalized mitochondrial membrane potential, and improved Nrf2 activation via the downregulation of Keap1 [335,354]. Another sophisticated study described a multi-component system where the antibacterial enzyme catalase [355], along with PLGA microspheres containing perfluorocarbons, and polypropylene sulfide, were encapsulated into liposomes, and incorporated into a hydrogel [356]. This complex delivery platform facilitated the controlled release of catalase to degrade hydrogen peroxide under hypoxic conditions, while simultaneously releasing oxygen from the perfluorocarbon carriers. Consequently, these liposomes served multiple purposes: delivering a natural enzyme to reduce supraphysiological hydrogen peroxide levels, acting bactericidal, and providing oxygen to restore physiological oxygenation within the tissue [356].

Regarding phenols or terpenes, liposome-based investigations cover quercetin slow release [318], Emodin co-loaded with Geniposide liposome nanocarriers for atherosclerosis treatment [357] or designs for lutein [323].

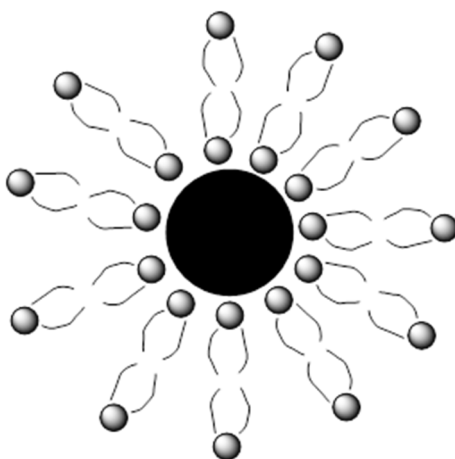


Figure 7. Unilamellar liposomal carrier with an aqueous core for antibacterial antioxidant enzyme delivery, such as catalase.

2.7.3. Zeolites

Another promising delivery platform, particularly for antibacterial antioxidative phenolic compounds, is based on zeolites that exhibit themselves antibacterial properties [358]. These porous aluminosilicates or aluminophosphates occur naturally, although a wide range of synthetic zeolites has also been developed, and characterized [359]. Zeolites can be engineered with microporous, mesoporous, or macroporous structures—a versatility that is exploited for the controlled delivery of therapeutics of varying molecular sizes (Figure 8). The group of antibacterial flavonoids [360], a prominent class of phenolic antioxidants, have been successfully delivered using such zeolite carriers [361]. The interaction between the phenolics, and the zeolites is predominantly mediated by aromatic rings, carboxylic acid groups, but also other functional moieties, such as methoxy, and hydroxyl groups, respectively. Thymol for example has been combined with zeolites in a solvent-free approach, where the antibacterial action of this composite was verified and suggested to be used for the development of antimicrobial biointerfaces for food, home and personal care applications [362]. Furthermore, the combination of zeolites with electrospun PLGA fibers has been reviewed for bone tissue engineering [363].

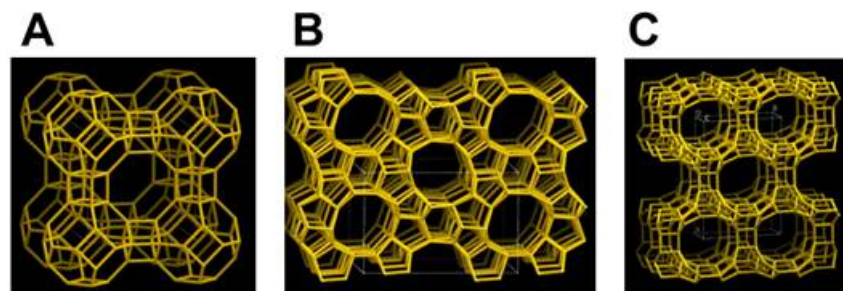


Figure 8. Several zeolite structures underlining the differently sized holes for antibacterial antioxidant drugs to be incorporated, allowing a controlled, and sustained release. Framework **LTA** type (**A**); Framework **MFI** type (**B**), and Framework **USI** type (**C**). All structures were downloaded from the Database of Zeolite Structures (<https://www.iza-structure.org/databases/> accessed on 21 January 2026).

2.8. Metals and Metal Oxides

Nanoporous gold (NPG) was employed as a support for the immobilization, and delivery of catalase [364]. As reported by Wang et al., this configuration exhibited enhanced stability, and excellent enzymatic performance; notably, the surface-bound enzyme retained 78% of its initial activity after 20 consecutive cycles (Figure 9) [364].

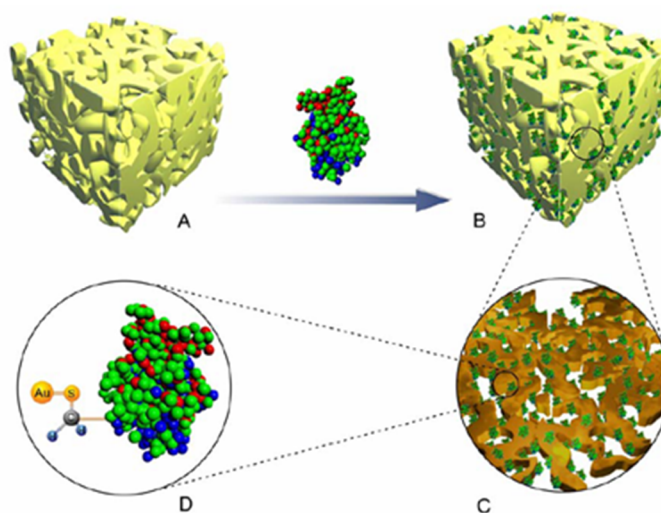


Figure 9. Enzyme immobilized within nanoporous gold; porous gold (**A**), lipase in pores of gold (**B**), magnified image of immobilized lipase in the pores of gold (**C**), and schematic covalent bond of lipase and gold (**D**). Reprinted with permission from [364]. Copyright 2011, Wang et al.

Another class of delivery systems comprises bioactive glasses. For instance, Jebahi et al. developed a bioglass scaffold for the delivery of strontium ions (Sr^{2+}) which were shown to reduce MDA levels while enhancing SOD, CAT, and GPx activities [365]. The material exhibited excellent biocompatibility within the host tissue. Furthermore, the authors evaluated OS biomarkers, and antioxidant profiles during muscle, and skin healing in a rat model; 60 days post-implantation, a significant increase in antioxidant enzyme activities was observed. These findings suggest that Sr^{2+} -releasing bioglass exerts a potent protective effect against ROS in the surrounding soft tissue [365]. Furthermore, strontium ions are reported to be antibacterial [366], and therefore belong to the class of antibacterial antioxidants as well.

Several metal hydrides can release hydrogen upon reaction with water, whereby the evolved H_2 gas is antibacterial [299], and neutralizes reactive oxygen species (ROS) [367]. For instance, MgH_2 was evaluated in the context of peritoneal adhesions—a fibrotic response typically driven by persistent inflammation. It was demonstrated that the reaction of MgH_2 with water, yielding Mg^{2+} , OH^- , and $\text{H}_2(\text{g})$, mitigates inflammatory dysregulation, reduces OS, and effectively prevents the formation of peritoneal adhesions in rat models [368]. Beyond its anti-adhesive properties, MgH_2 was found to suppress M1 macrophage polarization while promoting a shift towards the M2 phenotype. Thus, while direct delivery of hydrogen gas may represent a challenge, the application as metal hydride offers opportunities for easy application.

Zero-valent metals like gold offer a slow release option for phenolic compounds, by adsorption via the hydroxy group of the phenol [369]. While the metal is oxidized—for example by ROS, the attached phenol is reduced and released from the surface, acting as antibacterial antioxidant. Polyphenolic compounds have also been reported to be adsorbed on zero-valent iron—with the option to be released under OS [370].

3. Conclusions & Outlook

While the phenolic and terpenic compounds hold great promise in the dawn of the antibiotic resistance crisis, concerns about their potential toxicity at high concentrations are not to be neglected. Further testing will require careful evaluation for acceptable concentration ranges, where toxicity to host cells and tissues are minimal, but the antibacterial, as well as antioxidant, activity will be retained. In this regard, the evaluated concentrations across the identified microbiological studies varied greatly. This can be accounted for by the use of different assays for assessment of the antibacterial activity. While microbroth dilution assays usually evaluated substances in the range of micrograms, agar disc diffusion assays more frequently evaluated the substances in the range of milligrams. When considering testing the antibacterial potential of phenolic and terpenic compounds incorporated into electrospun fiber meshes, different assay types, such as microbroth dilution, adhesion and biofilm formation assays as well as agar disc diffusion assays might be used. Further complexity for antibacterial testing arises when the electrospun fiber meshes are intended to dissolve over time [371]. In this particular scenario, careful planning and assay development will need to occur, taking into account various variables such as the dissolution time, contact time to bacteria, efficacy read out and time frame, just to name a few. Great potential lies in the development and standardization of such assay types.

In addition, the selection of the bacteria is of great importance. While certain types of IAI, such as orthopedic hip and knee as well as tendon ligament rupture repair infections, are predominantly caused by Gram-positive, aerobic and facultative aerobic bacteria [372], orthopedic shoulder and jaw bone infections are predominantly caused by either strictly anaerobic bacteria or polymicrobial biofilms involving the presence of anaerobic bacteria [373,374]. While the phenolic compounds were reported to have antibacterial efficacy across a broad spectrum of Gram-positive as well as -negative bacteria, there was no activity against strictly anaerobic bacteria, irrespective of Gram typification, observable. While there is no clear answer as to why strictly anaerobic bacteria seem to be tolerant or even resistant towards phenolic substances, one of the major hypotheses to be drawn from the collected data suggests that the phenolic substances predominantly cause OS within the bacterial cells, and this OS then causes the plethora of cellular effects described. For this process, oxygen is required in order to form reactive oxygen species such as H_2O_2 or ROS [375]. This could potentially explain why strictly anaerobic bacteria, which grow in niches with microaerophilic conditions, show tolerance or even resistance towards certain phenolic substances. Another hypothesis for the absence of any substantial effect of phenolic substances against strictly anaerobic bacteria is the expression of phenol degrading enzymes by those bacteria [376,377]. Future strategies should also focus on circumventing this challenge, potentially through the combination of either multiple phenolic substances, combination with additives that might render them active in an anerobic environment or their combination with antibiotics.

Assessment of electrospun fiber meshes with incorporated antibacterial compounds should also be tested in combination with antibiotics. In the case where electrospun material will be implanted during a revision surgery because of an ongoing infection, antibiotics will be present in the host system [378–380]. Hence, it will be crucial to investigate the potential effect of the phenolic substance loaded electrospun fiber meshes in combination with antibiotics. In case where additive or even synergistic effects could be observed, this might allow for the reduction of the concentration of phenolic substances required to be incorporated. In turn, this might favor the balance between maintaining an antibacterial effects, while minimizing potential host cellular and tissue toxicity.

Concerning the antioxidative character of phenolic and terpenic compounds, this remains largely unexplored for the cell types involved in regeneration and healing of tissue associated with the skeletal apparatus, such as osteoblasts, osteocytes, tenocytes or specialized fibroblasts such as periodontal ligament fibroblasts. Given that ROS play a dual role in wound healing, and fibrosis [26]—where low levels are essential for signaling, but high concentrations associated with inflammation lead to fibrosis, scarring, and inferior tissue quality—antibacterial ROS-regulating biomaterials have emerged as a novel research field [381,382]. These systems utilize multi-phase, multi-drug, and multi-dynamic delivery mechanisms to meet the spatiotemporal requirements of the healing process. Consequently, moving beyond the single- or dual-drug vehicles discussed previously, next-generation systems incorporating multiple inhibitors with distinct release dynamics are envisioned to address complex clinical needs, such as bone repair [383] and tendon regeneration [384].

Ideally, next-generation antibacterial ROS-regulating biomaterials should be capable of sensing physiological ROS thresholds during wound healing, allowing them to distinguish between basal signaling levels,

and excessive, pathological concentrations. Currently, most antioxidant systems focus primarily on ROS clearance without accounting for the necessity of terminating scavenging once redox homeostasis is restored. Consequently, future biomaterials should not only facilitate the sophisticated release of various antibacterial antioxidants but also function as sensors that cease delivery when ROS levels are low. These systems would inherently provide a redox feedback loop, halting antioxidant release until triggered again by an aberrant spike in ROS—enabling a truly on-demand therapeutic response.

To develop effective redox-responsive delivery systems, it is essential to define the physiological, and pathological ROS thresholds of the target tissues. ROS levels, and production rates vary by orders of magnitude across different environments, such as blood [385], bone marrow [386], skin [387], and musculoskeletal tissues [388,389]. Consequently, the sensitivity of antioxidant platforms must be tailored to these specific sites. For instance, a ROS-responsive hydrogel was successfully utilized in a rat periodontitis model, where it enabled the “on-demand” delivery of gallic acid based on fluctuating local ROS concentrations [390].

In this context, phenylborate esters have been engineered to respond to moderate hydrogen peroxide concentrations [391], whereas cysteine-coordinated metal centers function as redox switches to mitigate high ROS levels [392]. Integrating these moieties with varying sensitivities into sophisticated, redox-responsive carriers via electrospinning will pave the way for effective clinical applications aimed at controlling fibrotic progression and simultaneously avoid any infections.

Supplementary Materials

The additional data and information can be downloaded at: <https://media.sciltp.com/articles/others/2609101729297033/AAM-26050037-SI.pdf>. Figure S1: PRISMA flowchart of the literature search conducted.

Author Contributions

T.A.S.: Writing—review & editing, writing—original draft, conceptualization. G.K.: Writing—review & editing, writing—original draft. J.B.: Writing—review & editing, writing—original draft, conceptualization. All authors have read and agreed to the published version of the manuscript.

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Use of AI and AI-Assisted Technologies

No AI tools were utilized for this paper.

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