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REVIEW

Quercetin-Based Advanced Delivery Systems – From Multimodal Nano-theranostics to Microneedles: a Recent Update on Their Preclinical Studies

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Abstract: Quercetin is a naturally derived flavonoid that has received growing attention for its wide range of pharmacological activities such as strong anticancer, antimicrobial, anti-inflammatory, and antioxidant effects. Its multiple functions and natural bioactivity make it an appealing therapeutic candidate. However, the clinical use of quercetin is still limited by issues like poor water solubility, low bioavailability, fast metabolism, and difficulties in achieving targeted delivery. Recent research has aimed to overcome these challenges through innovative formulation strategies like nanoencapsulation, polymeric carriers, 3D printing, microneedle scaffolds and surface modification. These approaches improve stability, boost bioavailability, and allow for targeted therapeutic effects. Traditional theranostic systems that use nanoparticles, quantum dots, or linked biomolecules have enhanced precision medicine by merging diagnostic imaging methods, such as MRI, PET, and fluorescence, with treatment options like targeted drug delivery and photothermal therapy. Yet, these systems face issues related to biocompatibility, cost, biodegradability, and targeting precision. Platforms based on quercetin are emerging as a promising alternative to tackle these problems. Despite their potential, this area is largely uncharted, and, to our knowledge, no thorough review has focused on quercetin's role in multifunctional theranostic systems. This review offers a systematic look at the design strategies, biomedical uses, and potential for quercetin-based theranostics. We discuss key challenges, such as achieving controlled/stimuli-responsive delivery, validation in higher animal studies, scale-up and to emphasize future directions for evolving quercetin-based platforms as next-generation nano-theranostics.

Keywords: quercetin, theranostics, microneedle, 3D bioprinted, pharmaceuticals, multifunctional

Introduction

In recent times, there has been a significant increase in the utilization of natural bioactive molecules for the management of chronic ailments owing to their low toxicity and environmentally friendly characteristics. Bioactive molecules are naturally occurring molecules that have an effect on living tissues, cells, or biological systems. These molecules play a vital role in regulating physiological functions and can influence health outcomes by interacting with specific molecular targets. Commonly found in foods, plants, and pharmaceuticals, bioactive molecules include flavonoids, alkaloids, peptides, and polyphenols, their therapeutic potential. Due to these properties, bioactive molecules are widely studied for their applications in medicine, nutrition, and drug development.[1]

Quercetin is one such flavonoid, which is a yellow, crystalline substance that is completely insoluble in cold water, soluble in lipids and alcohol, and very slightly soluble in hot water. It is an aglucone or aglycon that gives a variety of flowers their vibrant colours and has no carbohydrate molecules in its structure.[2] It is a natural flavonoid known for its

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wide range of beneficial properties. It has strong antioxidant activity, helping to neutralize free radicals and reduce oxidative stress. Quercetin also exhibits anti-inflammatory effects by modulating inflammatory pathways and cytokines.[3] It has demonstrated antiviral and antimicrobial properties, making it useful in supporting immune function. Additionally, quercetin is associated with cardioprotective,[4] anticancer,[5] and neuroprotective effects,[6] contributing to its potential in managing various chronic diseases. The main limitations include low bioavailability, instability, limited human clinical evidence, dose-dependent toxicity and no testing in vulnerable population respectively.[7]

In order to achieve the fullest therapeutic potential of quercetin, various formulations have been developed and reported in literature. Some of them include microparticles,[8] nanoparticles,[9] electrospun patches,[10] hydrogels,[11] 3D printed scaffolds[12] and many others.[13] The different biomaterials explored in fabricating the quercetin-based formulations include chitosan,[14] PLGA,[15] PCL,[16] mesoporous silica[17] etc, which played a significant role in improving its bioavailability and controlled/sustained release in the region of interests. The integration of quercetin with materials/molecules having diagnostic properties offers a novel approach to theranostic medicine by enabling simultaneous disease detection and treatment. With ongoing research, quercetin-based theranostic platforms could revolutionize biomedical applications, improving patient outcomes across various diseases.

The aim of this review is to summarize all the works done with quercetin for therapy and diagnosis from the year 2020 to 2025. Their properties and applications were reviewed and stated based on the literature. The number of papers indexed in PubMed mentioning quercetin has shown a steady increase over the years. In 2020, there were 5,316 publications on quercetin, which has significantly increased to 10,278 in 2024. As of 2025, the count stands at 4,643, though this number may continue to rise as more papers are published throughout the year. Also, it has been categorized based on disease application and polymer used.

Quercetin Incorporated Nanotherapeutics and Theranostics

Quercetin-loaded nanoparticles are innovative drug delivery systems designed to improve the solubility, stability, and bioavailability of quercetin for biomedical applications. These nanoscale carriers, often made from biocompatible polymers or lipids, enable controlled and targeted release, improving quercetin's therapeutic efficacy in treating inflammation, oxidative stress, and cancer.[18] Their small size allows for enhanced cellular uptake, making them promising candidates for applications in wound healing, neuroprotection, and cardiovascular disease treatment.[19] Wu synthesized quercetin–nicotinamide cocrystals to enhance quercetin's solubility and bioavailability in rats. The co-crystallization improved dissolution rates and nearly quadrupled absorption, likely due to hydrogen bonding between quercetin and nicotinamide, which stabilized the new solid-state form. The pharmacokinetics study in quercetin co-crystal treated rats was reported to have an increased concentration of quercetin co crystal (1.5 μg) in plasma when compared to only quercetin (0.5 μg) making them an ideal strategy for enhancing bioavailability of quercetin.[20] Hao et al fabricated quercetin loaded silk fibroin nanoparticles modified using ZIP-8 (zeolitic imidazolate framework-8) nanoparticles for myocardial infarction. ZIP-8 is used as a carrier or template for the nanoparticle by encapsulating them in its pores. This system facilitated controlled release of quercetin and this mitigates oxidative stress and inflammation through the antioxidative and cardioprotective properties of quercetin, potentially improving cardiac repair, which was evaluated through in vivo study (minimal fibrosis and restored cardiac tissue).[9] Giannouli et al synthesized quercetin loaded PLGA nanoparticles through electro spraying method to enhance the drug loading percentage. This proved to have improved aqueous solubility and stability of quercetin, which thereby can be used for treating atherosclerosis.[21]

In the studies reported by Hao et al and Giannouli et al, the encapsulation efficiency and drug loading efficiency were not quantified, which represents a major limitation of these works. The absence of these parameters makes it difficult to evaluate the actual amount of drug incorporated into the carrier systems and to compare their performance with other delivery platforms. Consequently, the therapeutic relevance and translational potential of the proposed formulations cannot be fully assessed.

Next, in case of quercetin-based theranostic nanoformulations, there are about twenty papers published between 2020 and 2025. Quercetin loaded biomaterials in theranostic application is an upcoming field, and there is no review till date, which systematically describes them. Also, only a few studies have been conducted so far on the combination of quercetin with theranostic agents, highlighting the need for further research in this area. Wei et al studied quercetin

derived carbon dots with red emission as a nano theranostic agent against Alzheimer's β-amyloid (Aβ) protein fibrillogenesis. The quercetin and phenylenediamine derived carbon dots with red emission were synthesized through hydrothermal method and were tested for its inhibition of Aβ fibril protein aggregation, depolarization of neurons and ROS (Reactive oxygen species) scavenging. Also, it was found to have enhanced radical scavenging activity together with inhibition of beta fibril protein aggregation which is a major event in Alzheimer's disease making it a novel theranostic agent for Alzheimer's disease (AD). They also enhance cell viability, extend uptake and presence in AD nematode models, and enable fluorescence imaging in the region of amyloid plaques deposition.[22] R-CDs inherit aromatic structures, phenolic hydroxyl groups, and amino groups from their precursors, quercetin and p-phenylenediamine. These functional groups enable the R-CDs to interact with Aβ species via hydrogen bonding, electrostatic interactions, hydrophobic interactions, and π-π stacking. These interactions allow the R-CDs to effectively target and bind to Aβ plaques, leading to their inhibition and depolymerization. Ma et al studied a dual-modality immune nano-activator based on manganese ions (Mn^{2+}) and quercetin to enhance cyclic GMP-AMP (Guanine mono phosphate-Adenosine mono phosphate) synthase for cancer metallo-immunotherapy. The modified nano-activator showed effective cellular internalisation and enhanced tumor-targeting capability. The method used photothermal effects to accelerate the release of quercetin and manganese ions and cause apoptosis in tumour cells when exposed to near-infrared radiation. Together with quercetin-induced apoptosis, the reactive oxygen species produced by the liberated manganese ions enhanced photothermal-induced DNA damage. Also, quercetin acts as pro-oxidant increasing ROS beyond the threshold that cancer cells can tolerate. Additionally, this DNA damage encouraged the release of cytosolic DNA, which triggered the cGAS-STING (Cyclic GMP-AMP synthase – stimulator of interferon genes) pathway and increased immunological activation.[23] Similarly, Qiu et al developed pH-sensitive alendronate-hyaluronic acid (AHA) graft polymer coated quercetin-loaded manganese phosphate (MnP) nanoparticles as a theranostic agent for lung cancer. The system provides dual therapeutic effects, combining reactive oxygen species (ROS) generation (from Mn^{2+} released from Manganese phosphate catalyze the conversion of intracellular hydrogen peroxide (H_2O_2) (abundant in tumor microenvironments into toxic •OH radicals) and chemo dynamic therapy mediated apoptosis (Mn^{2+}). Additionally, it enables photoacoustic imaging for real-time tumor tracking. Theses nanoparticles are stable at physiological pH, and at acidic tumor environment, it releases quercetin and Mn^{2+} ensuring the release near tumor sites. Mn^{2+} also exhibited MRI (Magnetic Resonance Imaging) signal enhancement for tumour imaging making it a good strategy for clinical diagnosis[24] (Figure 1).

Simon et al analysed quercetin encapsulated copper nanocluster doped hydroxyapatite nanoparticles (Cu-HXNPs) for evaluating the anti-cell proliferative ability in cervical cancer. Doping of hydroxyapatite with copper nanoclusters impart luminescence to the nano system. These nano systems together with quercetin showed cancer cell apoptosis and a drastic change in cell cycle rhythm (cell cycle arrest at G0/G1 phase) indicating their anti-cancer potential. Also, hydroxyapatite is pH sensitive which enable drug release at acidic pH imparting specificity towards cancer environment. Accordingly, the study proposed Cu-HXNPs as a useful nanocarrier for cancer theranostics that can be used for both bioimaging and therapeutic purposes.[25] In another study, Wang et al evaluated croconic acid-based nanoplatform (CCQ) integrating NIR-absorbing croconic acid (an organic synthetic photosensitizer) and quercetin in CaO_2 (calcium dioxide) nanoparticles coated with DSPE-PEG2000 for tumor therapy. The system generates calcium ions and H_2O_2 in the tumor microenvironment, causing mitochondrial apoptosis via calcium overload. Quercetin also reduces heat shock protein expression, making tumors more vulnerable to mild photothermal therapy (~45°C), minimizing damage to healthy tissues.[26] Additionally, inclusion of CaO_2 enables the generation of reactive oxygen species (ROS) in the acidic tumor microenvironment. This chemo dynamic therapy is more effective in the tumor's unique conditions, leading to selective cancer cell damage. Also, CCQ enables photoacoustic imaging-guided therapy and helps to increase temperature in tumor environment even after repeated exposure under NIR light due to its high stability. This multifunctional nanoplatform offers a promising strategy for safe and effective cancer treatment. Jia et al studied explores quercetin-ethylenediamine carbon quantum dots (QECQDs) as a dual-target therapy for intracerebral haemorrhage (ICH). The QECQDs has effectively scavenged reactive oxygen species (ROS), chelated excess iron, and protected neurons from oxidative stress after hemin-induced brain injury. Following intrathecal injection, they accumulate in brain regions affected by ICH, reducing haemorrhage volume, alleviating edema, and improving neurological function. Carbon quantum dots are also

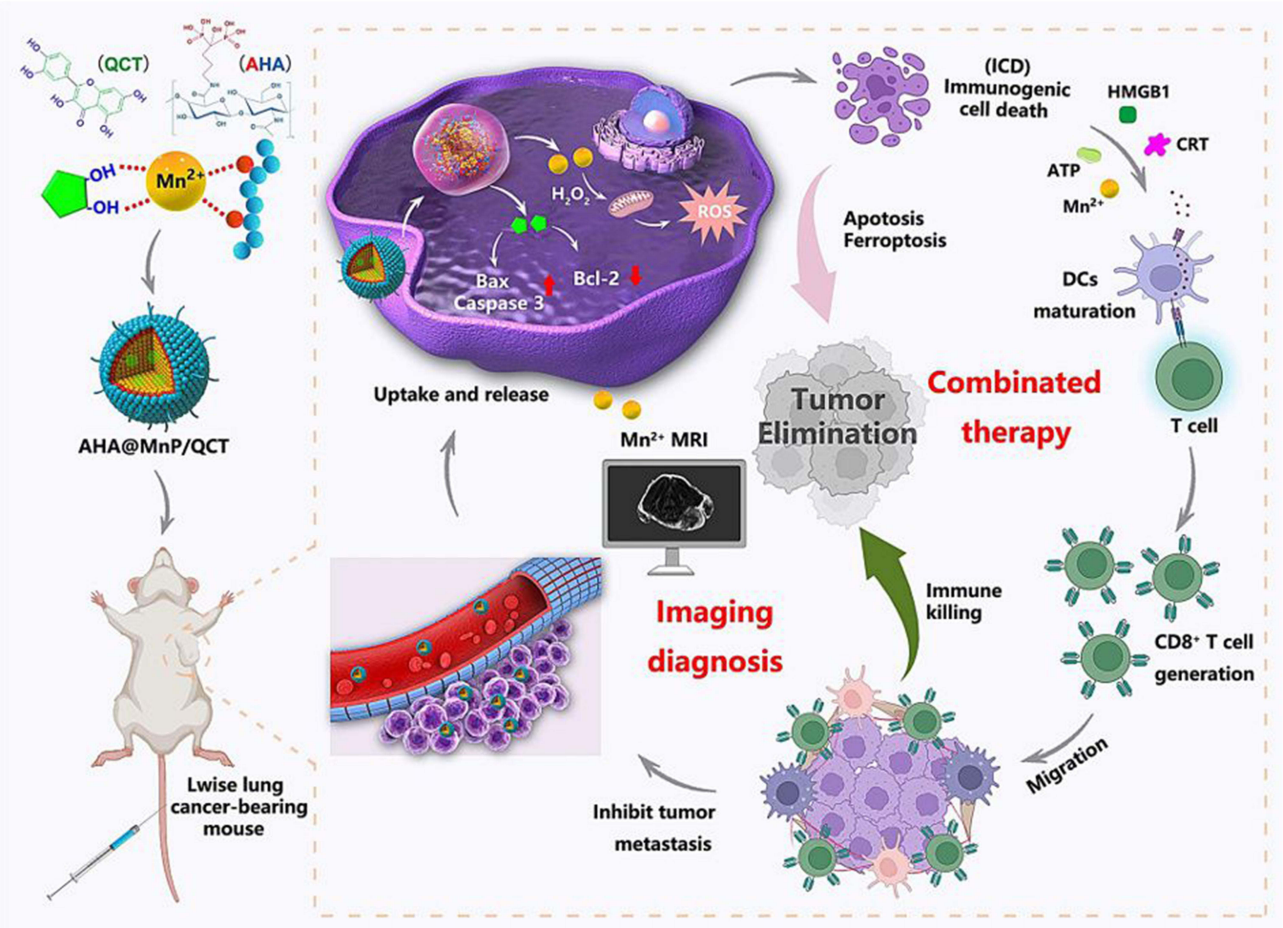

Figure 1 Schematic illustration of quercetin-loaded AHA@MnP nanoparticles displaying a theranostic strategy combining MRI-guided imaging and synergistic cancer therapy. Following tumor uptake, Mn^{2+} mediated imaging enables diagnosis, while quercetin induced ROS generation triggers apoptosis/ferroptosis and immunogenic cell death, leading to immune activation, inhibition of metastasis, and effective tumor elimination.[24]

proven to cross blood–brain barrier, which is also an advantage of using them specific to brain. This research highlights the potential use of quercetin-based nanomaterials in neuroprotection and multi-target therapy for brain injuries, as shown in Figure 2.[27]

Song et al evaluated the theranostic effect of quercetin encapsulated in polydopamine nanorings in liver tumor. This study introduces hollow magnetic vortex nanorings (HMVNp) with polydopamine coating, loaded with quercetin (Q) for dual-mode thermal therapy (magnetothermal + photothermal). HMVNp exhibits enhanced heat generation (SAR = 1441 W/g), thereby improved the quercetin release under tumor acidity, due to the responsive pH potential of polydopamine and superior MRI and PAI (Photo acoustic imaging) contrast (~62% higher R2 value) property of the magnetic nanorings. The combination of dual-mode therapy and quercetin significantly reduces tumor growth and prevents metastasis *under* in vivo, confirming HMVNp/quercetin as a promising theranostic nanoplatform (Figure 3).[28]

In another study, Mishra et al developed folic acid-conjugated magnetic mesoporous silica nanoparticles (FA-FE-SBA15QN) loaded with quercetin as a theranostic agent for colorectal cancer. The nanoparticles enable pH-sensitive drug release, triggering mitochondrial-dependent apoptosis via a redox-regulated signalling pathway. They activate tumor suppression, and inhibit heat shock protein-27 (HSP-27) to promote apoptosis. Additionally, in vivo treatment with the particles showed effective targeting and diagnosis at target site using MRI due to the presence of Fe_3O_4 making it a successful treatment strategy for cancer.[29] Li et al evaluated the effect of Quercetin loaded Melanin-Collagen Nanoparticles (MNP-QUE-COL) for liver fibrosis.[30] Quercetin downregulates TGF-β1 and downstream Smad2/3 phosphorylation, reducing collagen I/III and fibronectin expression. Also, Quercetin increases matrix metalloproteinases

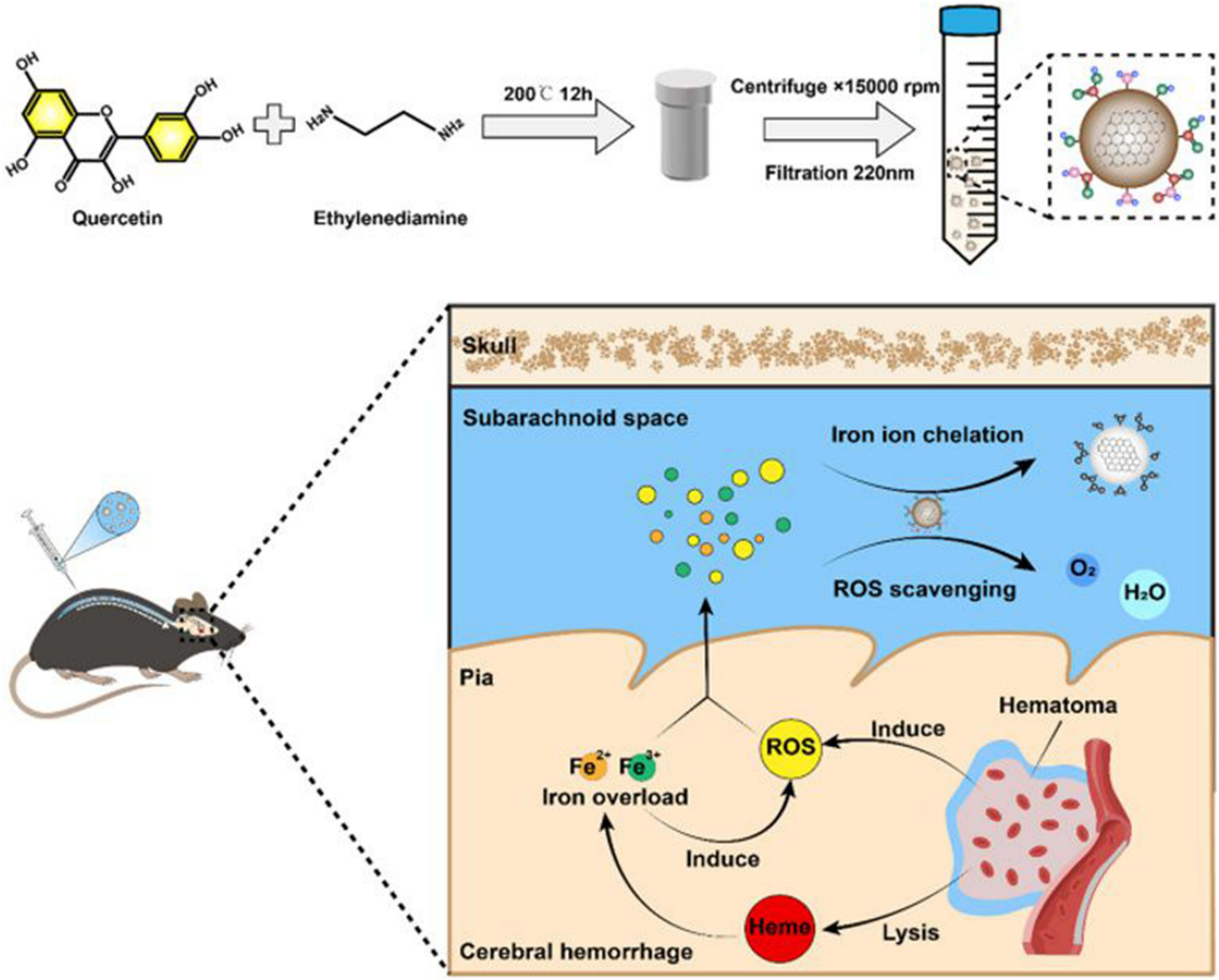

Figure 2 Schematic representation of the synthesis of quercetin loaded nanoparticles and their administration in an intracerebral hemorrhage model. The nanoparticles act by chelating excess iron ions and scavenging reactive oxygen species in the subarachnoid space, thereby reducing oxidative stress, hematoma progression, and secondary brain injury. Reproduced with permission from.[27]

(MMPs) like MMP-2 and MMP-9, which directly degrade ECM proteins (Extra cellular membrane). Simultaneously, quercetin and MNP improved the capacity to eliminate ROS and successfully controlled macrophage polarisation to M2 (anti-inflammatory). Additionally, MNP-quercetin-COL demonstrated outstanding dual-modality imaging capabilities in PAI and MRI, allowing for real-time, non-invasive monitoring of the treatment effect. Crucially, there was no discernible cellular cytotoxicity or haemolysis and the nanoparticles showed strong biocompatibility.

Despite their promising outcomes, these studies have several limitations that should be acknowledged. Key formulation parameters such as scale-up feasibility, batch-to-batch reproducibility, and stability under physiological and storage conditions are insufficiently addressed. Furthermore, although MRI- and PAI-based theranostic capabilities are demonstrated, direct comparisons with existing clinically approved contrast agents and standardized quantitative imaging metrics are largely lacking, restricting assessment of their true translational advantage. In addition to the above mentioned studies, there are a few other similar studies reported based on MRI imaging-based theranostics,[31–33] which are listed in Table 1.

Quercetin Incorporated Electrospun Patch

Electrospun scaffolds offer a high surface area-to-volume ratio, which enhances cell attachment and nutrient exchange crucial for tissue engineering. Their structure closely mimics the native extracellular matrix, promoting better cell

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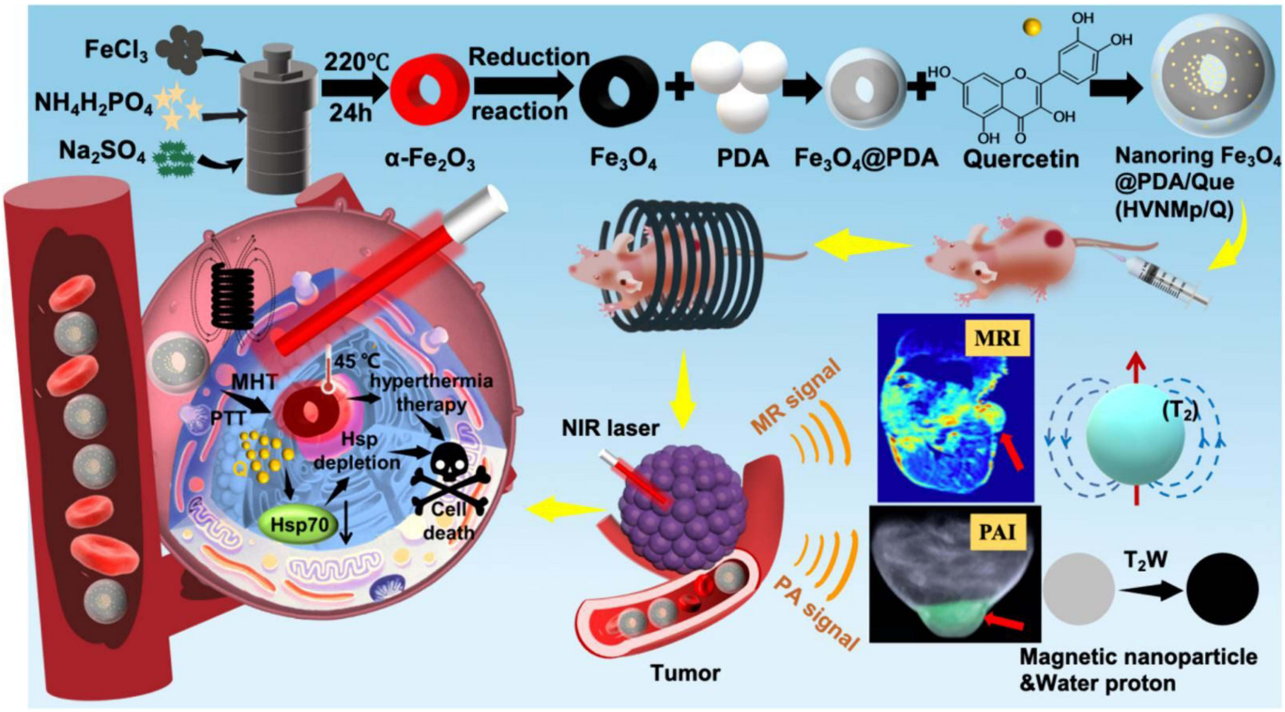

Figure 3 Illustration of the synthesis of quercetin-loaded Fe_3O_4@PDA nanorings and their application as a theranostic platform for cancer treatment. Upon NIR laser irradiation, the system enables magnetic hyperthermia and photothermal therapy while simultaneously providing MRI and photoacoustic imaging for real-time tumor diagnosis and treatment monitoring.[28] Copyright [2025] [Manli Song, Junying Cheng].

proliferation and tissue regeneration. Additionally, the fibre diameter and scaffold architecture can be precisely controlled to suit-specific applications. These scaffolds also allow incorporation of bioactive molecules for targeted therapeutic effects.[34] Similarly, in another study, Viscusi et al have fabricated quercetin-loaded polycaprolactone-polyvinylpyrrolidone electrospun membranes for drug delivery applications. It was found that upon adding quercetin, the conductivity of the material has increased thus causing the change in the electrospinning jet's whipping action thereby producing thinner fibres. Conductive surfaces can attract and organize proteins like fibronectin and vitronectin from the surrounding medium. These proteins mediate cell adhesion and cells stick to surfaces where adhesion proteins are present and well-aligned.[16] This could be due to charge transfer between the OH group of the quercetin and ketone bond of the PCL and PVP. Quercetin release from the nanofibers in PBS and pH 3 media showed tunable drug release up to 7 days. The release profiles reached a plateau at approximately 50 h, with cumulative release of 82% in PBS and 71% at pH 3. Owing to quercetin's susceptibility to photo-oxidation, UV exposure significantly reduced release efficiency, decreasing from 82% in non-irradiated samples to 57% after 10 h of UV treatment. Thus, making it a great biomaterial sustained release of the drugs in various biomedical applications.

Quercetin Incorporated Hydrogels

Hydrogels are biomaterials that offer biocompatibility, tunable properties, and the ability to encapsulate drugs or cells for biomedical applications. Their ability to transform from liquid to solid at body temperature makes them highly effective for minimally invasive treatments. Xing et al developed polysaccharide (chitosan (CS) and sodium alginate (Alg)) based injectable hydrogel (PECE) loaded with quercetin for wound healing. The hydrogel (PECE) is stabilised by a combination of electrostatic and Schiff base processes, and quercetin was loaded by hydrogen-binding interactions with CS and Alg. With the help of the many hydroxyl, carboxyl, and aldehyde groups, PECE was able to adhere firmly to the skin's surface and preserve wound hydration.[35] Similarly, Zawani et al studied quercetin containing gelastin-elastin injectable hydrogel for cutaneous application (Figure 4) and observed that WVTR of the hydrogel helped in moisture retention without dehydration of the wound, absorb wound exudates, ROS reduction and biocompatible making it

Table 1 Table Showing Recent Advancements in Quercetin-Based Nanoparticle Theranostic Formulations

SL No	Theranostic Agent used	In vitro/ex vivo	Imaging Modality	Application	Reference
1	Quercetin derived carbon dots with red emission	In vitro *and* In vivo	Fluorescence (NIR) imaging	• (×) Alzheimer's β-amyloid fibrillogenesis • ROS (↓) • A beta protein degradation	[22]
2	Copper nano clusters	In vitro	Fluorescence imaging using confocal microscope	• (↓) glutathione in tumor region • T cell activation • ROS (↑)	[25]
3	Croconic acid-based nanoplatform	In vivo	Photoacoustic imaging (PAI)	Photothermal therapy for cancer • (↑) ROS • (×) heat shock proteins during PTT	[26]
4	Manganese phosphate nanoparticles	In vivo	MRI	ROS generation and chemodynamic therapy mediated apoptosis • (↑) ROS generation • (↑) lung cancer cell death	[24]
5	Magnetic mesoporous silica nanoparticles	In vivo	Micro CT	• Tumor (↓) • (↑) mitochondrial-dependent apoptosis • Theranostic property through MRI imaging	[29]
6	Manganese chloride tetrahydrate	In vivo	NIR imaging	• Tumor targeting • Cellular internalization • Photothermal effects • Cancer cell apoptosis	[23]
7	Ethylenediamine carbon quantum dots	In vivo	MRI	• (↓) oxidative stress • ROS (↓) • (↑) cerebral blood flow • (↓) neuronal death • Theranostic property	[27]
8	Hollow magnetic vortex nanorings	In vivo	MRI/PAI	• Magnetic and photothermal therapy • (↓) tumor growth • Metastasis (×)	[28]

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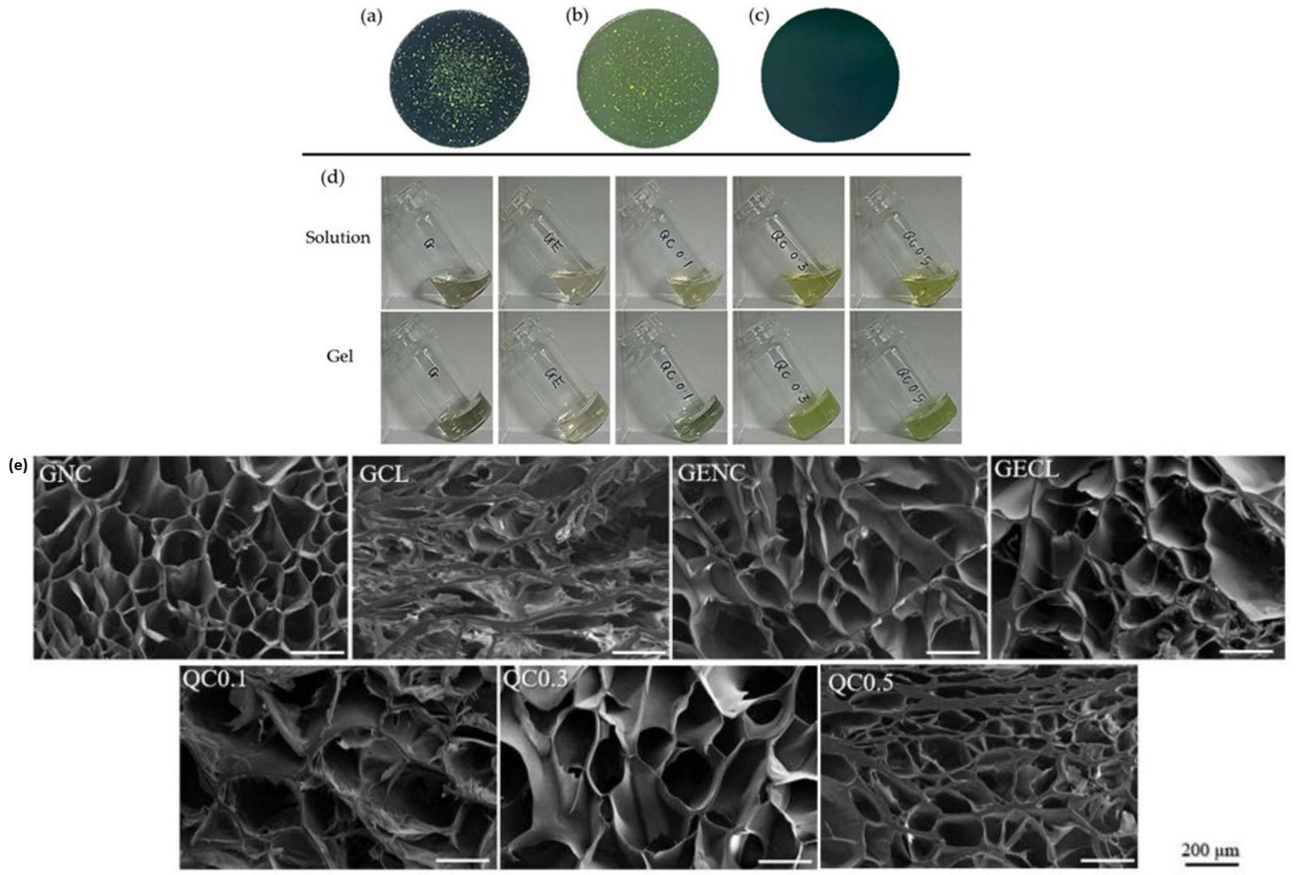

Figure 4 Visual assessment of quercetin-loaded gelatin–elastin hydrogels prepared using different solvents and their corresponding gelation behavior. (**a**–**c**) Images under visible light depicting quercetin dispersion in hydrogels prepared using different solvents: (**a**) Milli-Q water, (**b**) 90% ethanol, and (**c**) dimethyl sulfoxide (DMSO). (**d**) Vial inversion test demonstrating the sol–gel transition of hybrid hydrogels at room temperature. The images depict the change from liquid to gel state across different formulations prepared with varying genipin concentrations. (G- Gelastin, GE – Gelastin -Elastin, QC – Quercetin embedded gelastin-elastin solution). (**e**) Scanning electron microscopy images interconnected porous structures for cross-sectional morphology of the hybrid gelatin hydrogels. Reproduced with permission from.[36]

a promising material for wound healing application.[36] A major limitation of the reported study is the absence of drug release profile data, which is a critical parameter for evaluating the suitability of the system for wound-healing applications. Additionally, the degradation behaviour was not comprehensively analyzed, as the comparison was performed only between samples; a more informative assessment would involve time-dependent degradation profiles across different samples to better understand material performance.

Yu et al developed a quercetin loaded injectable hydrogel for cartilage regeneration. Sodium alginate/bioactive glass/agarose hydrogel loaded with quercetin were used to maintain chondrocyte phenotype due to ECM like environment in 3D structure, inhibits ECM degradation and reduces inflammatory response.[37]

From the authors' perspective, the key barriers for clinical translation of such hydrogel scaffolds include sterilization, as conventional methods (eg., autoclaving or gamma irradiation) may alter network structure, crosslink density, and drug stability, necessitating careful selection and validation of mild sterilization approaches. Mechanical integrity remains another challenge, since hydrogels may exhibit reduced strength or deformation under physiological handling and wound-site stresses, requiring optimization of crosslinking and formulation. In addition, long-term storage stability is a limitation, as hydrogels are susceptible to dehydration, microbial contamination, and changes in physicochemical properties over time, highlighting the need for suitable packaging and storage conditions to ensure consistent performance prior to clinical use.

Quercetin Incorporated 3D Printed Scaffolds

Quercetin-loaded 3D-printed scaffolds are advanced biomaterials designed for tissue engineering and regenerative medicine. These scaffolds, fabricated using biocompatible polymers through 3D printing, offer precise structural control, ensuring optimal mechanical strength and degradation rates. Their potential applications include wound healing, bone regeneration, and drug delivery, making them a promising innovation in biomedical research. Toulou et al developed quercetin loaded PCL-based 3D printed scaffold for bone tissue engineering. The incorporation of quercetin increased M1/M2 macrophage polarisation thereby regulating the immune response. Also, quercetin enhances osteogenesis and mineralization in vivo.[38] Huang et al studied the effect of quercetin containing 3D printed mesoporous calcium-based polycaprolactone scaffolds for differentiation of mesenchymal stem cells (MSC) to osteogenic lineage and the results presented that quercetin had a positive impact in calcium deposition and cytoskeletal network alignment on the first day of culture similar to the native tissue in vitro (Figure 5). Also, the in vitro effects of the scaffold in mineralization were also analysed through alizarin staining and found to have pink to dark red transition due to matrix deposition, and formation of calcium mineral nodules.[39]

In theranostic aspect, only one article was found from the year 2020–2025 which was done by Luo. They evaluated the effect of quercetin containing MXene modified 3D printed scaffold containing collagen (C), silk fibroin (S) and quercetin (Q) for the reconstruction of oral wound using photothermal therapy (PTT). In vivo experiments showed MXene (M) scaffold containing collagen– silk–quercetin was able to inhibit tumor growth by the photothermal activity in the NIR region (Near-Infrared Region) and quercetin reduced the heat resistance of cancer cells to obtain a more efficient effect of PTT when compared to only CS and CSQ group. Also under irradiation, the quercetin release from the scaffold increased from 10% to 75% making it an efficient system to

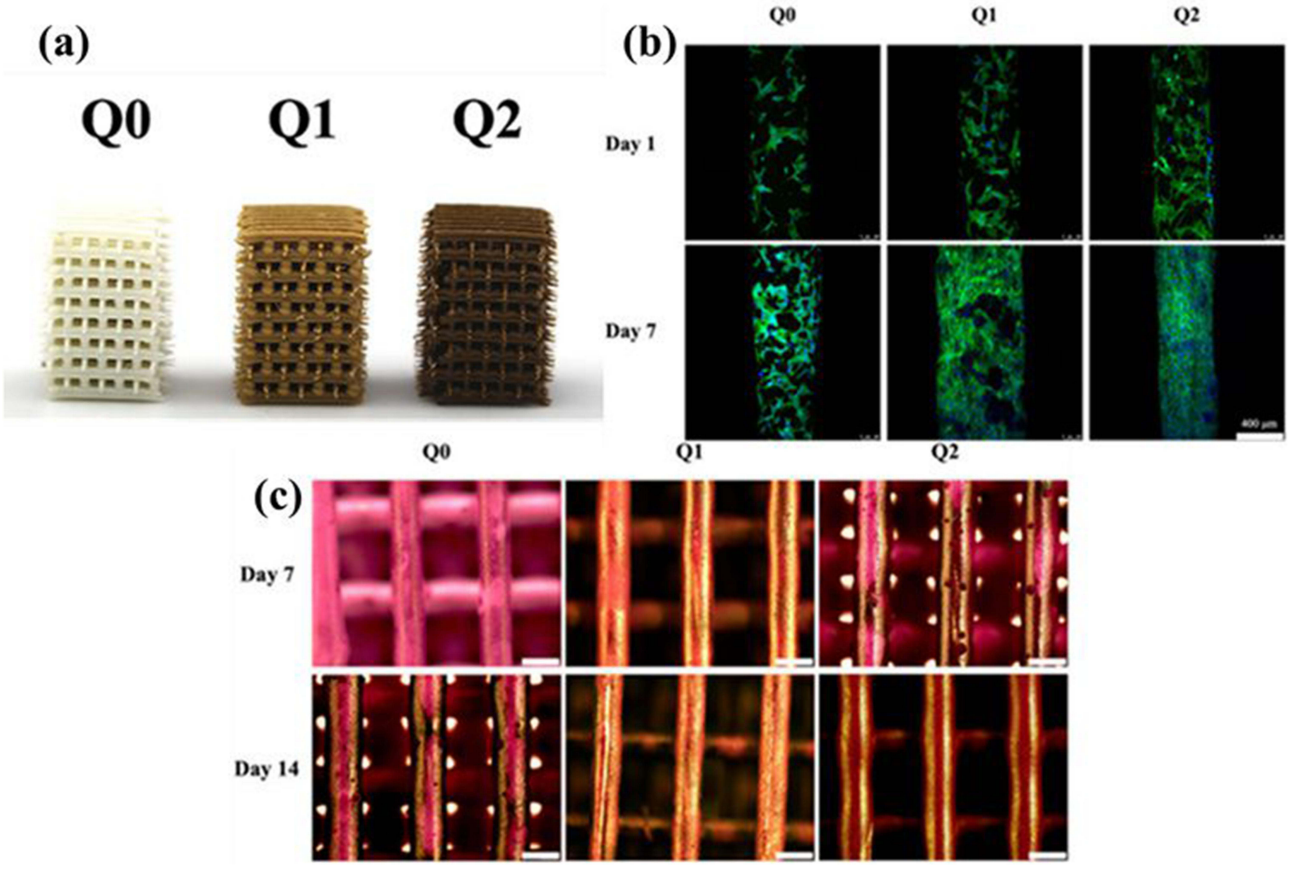

Figure 5 (**a**) The photographs of the 3D-printed scaffold, (**b**) The proliferation of MSCs cultured on Q0 (concentration of quercetin 0%), Q1 (low concentration of quercetin 0.1%), and Q2 (high concentration of quercetin 0.5%) scaffolds for 1st and 7th day. The F-actin filaments (green) and nuclei (blue) staining. Alizarin red staining for day 7 and day 14 (**c**). The scale bar is 400 μm. Reproduced with permission from.[39]

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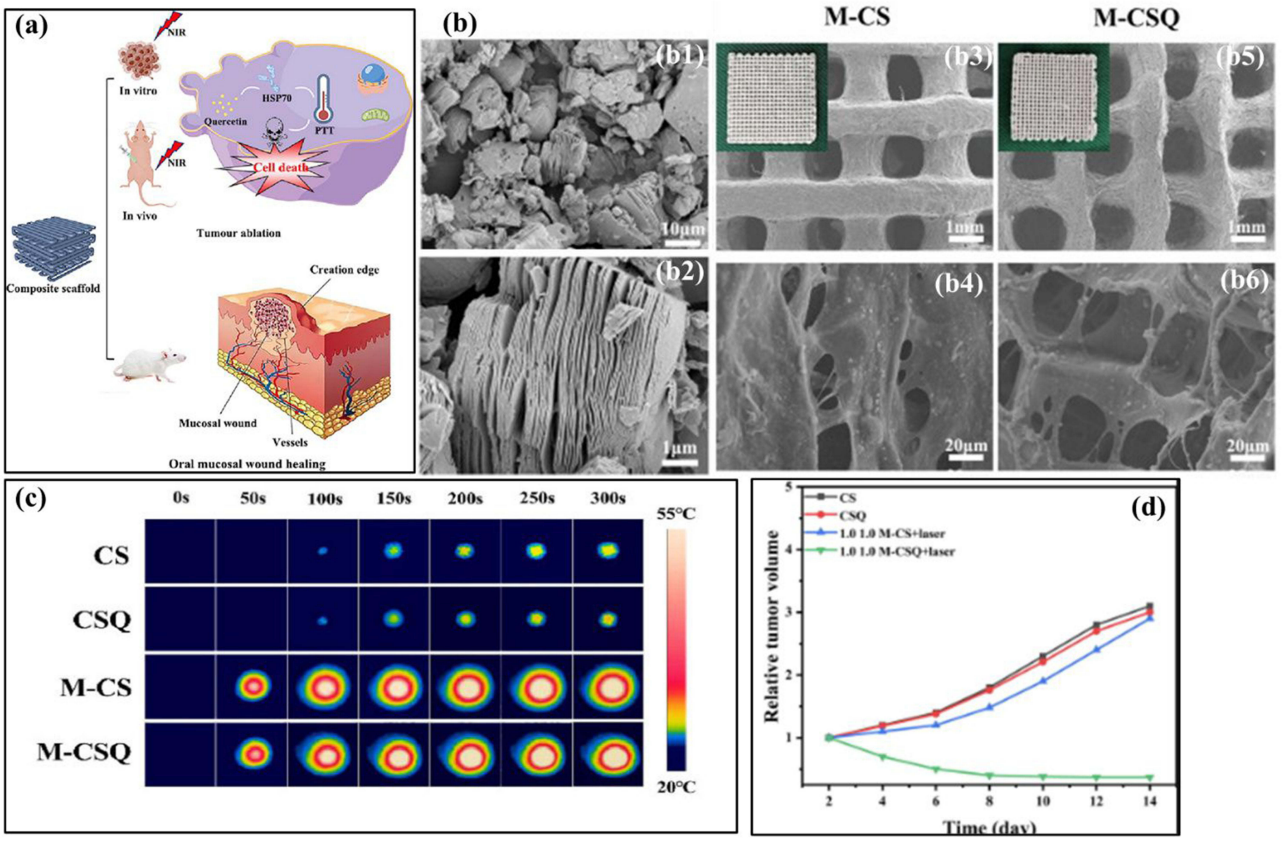

Figure 6 (**a**) Preparation scheme of 3D printed MXene incorporated scaffolds for PTT in oral mucosal wound. (**b1-b2**) SEM images of Ti_3C_2 MXene multilayer nanosheets; SEM images of M-CS (**b3-b4**) and M-CSQ (b5-b6). (**c**) Real-time thermograms of CS, CSQ, M-CS, and M-CSQ scaffolds. (**d**) Relative tumor volume change curves after treatment with different scaffolds over 14 days. Reproduced with permission from.[40]

release the drug at targeted site (Figure 6).[40] Since there are no other available literature in quercetin based theranostic agents for scaffolds, the future scope relies on scaffold based theranostics for various biomedical applications.

Quercetin Incorporated Microneedles

The oral route is the most common method for delivering phytochemicals due to patient convenience, adherence, and cost-effectiveness. However, poor water solubility, high lipophilicity, and instability in the gastrointestinal tract limit their oral bioavailability. These challenges have driven interest in intra/transdermal delivery methods. Microneedles (MNs) offer a promising alternative by painlessly penetrating the skin to deliver compounds directly to the dermal layer for improved absorption. When combined with nanoparticles (NPs), MNs enhance drug stability, enable sustained release, and improve the overall effectiveness of phytochemical therapies.[41] Zhang et al evaluated the effect of androgenic alopecia (AGA) based on quercetin/zinc/copper (ZCQ) dual-doped mesoporous silica nanocomposite embedded gelatin – hyaluronate - alginate microneedle patch and found enhancement of hair growth by inhibiting pathophysiological processes of AGA in testosterone-induced model. In vivo models showed proofs for inhibition of androgen, inflammation and upregulation of follicle regeneration. However, pharmacokinetics and pharmacodynamic studies remain unperformed and a limitation to the study (Figure 7).[17] Other works on recent advancements in quercetin loaded biomaterials are also listed in Table 2.

The Future Prospectives

Quercetin-loaded biomaterials represent a promising approach to overcoming the limitations of quercetin, such as poor solubility, bioavailability, and stability. By integrating quercetin into advanced biomaterials, researchers have developed

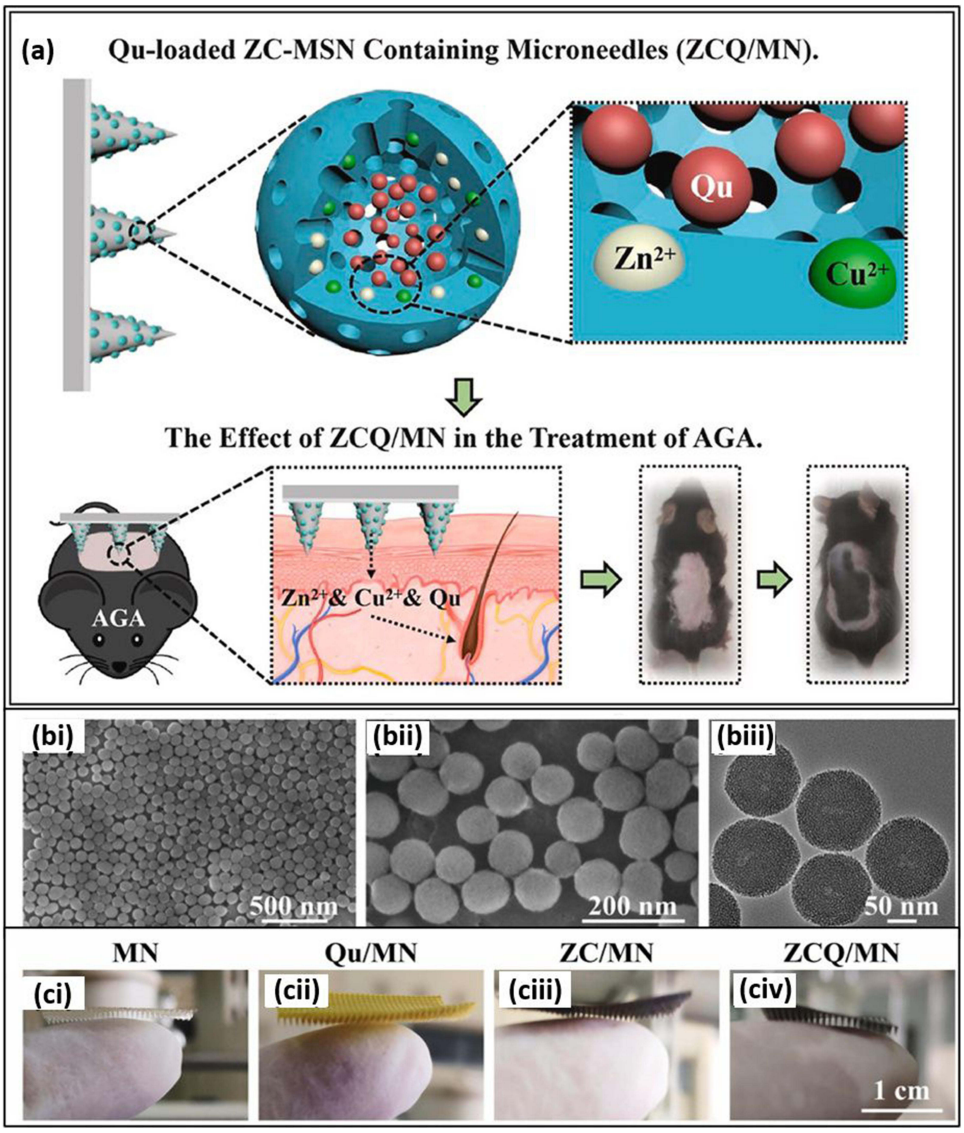

Figure 7 (**a**) Schematic representation of quercetin-loaded ZC-MSN–incorporated microneedles (ZCQ/MN), illustrating nanoparticle composition, drug loading, and transdermal delivery for the treatment of androgenetic alopecia. (**bi, bii**) SEM images and TEM image (**biii**) showing the morphology and porous structure of Zn/Cu co-doped mesoporous silica nanoparticles (ZC-MSN). (**ci-civ**) The ZCQ formulation is embedded into a microneedle mold with gelatin, alginate and hyaluronate, vacuumed for 2 hours to ensure mold filling, and dried at 45 °C for 72 hours. Reproduced with permission from.[17]

effective drug delivery systems that enhance its therapeutic potential. These biomaterials have demonstrated significant antioxidant, anti-inflammatory, anticancer, wound healing, and bone regeneration properties. Additionally, theranostic applications have emerged, enabling simultaneous diagnosis and treatment in conditions such as cancer. Various delivery platforms, including hydrogels, nanoparticles, microneedles, and scaffolds, have been explored to improve targeted and controlled release of quercetin, minimizing side effects and maximizing efficacy. Currently, only a few lipid-based quercetin products (eg., liposomal or micelle formulations) are commercially available, with just two widely recognized examples on the market. This indicates that the area is still in its early stages of development, and widespread commercialization of advanced quercetin nano- or lipid-based formulations has not yet emerged. Despite promising advancements, several challenges and opportunities remain (Figure 8) in the field of quercetin-loaded biomaterials such as (i) development of smart biomaterials for controlled and targeted delivery on response to stimuli (eg., pH, temperature, light or using conjugation with ligands and antibodies) (ii) personalized medicine such as siRNA, mRNA and exosomes (iii) further validation of in vivo experiments in higher animals are warranted for pharmacokinetics study and theranostic imaging validation (iv) scale

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Table 2 Table Showing Recent Advancements in Quercetin Loaded Biomaterials

SL No	Formulation Type	Polymer Used	In vitro/in vivo	Application	Reference
1	Microspheres	Inulin and chitosan in alginate	In vitro	Drug delivery to colon • (↑) encapsulation efficiency • Delivered 80% quercetin to colon • Microspheres delayed release of quercetin under fecal microbiota degradation	[42]
2	Nanoparticles	Chitosan	In vivo	Treatment for cardiotoxicity • (↓) cadiac serum enzyme • ROS (↓) • Sustained release • Cardio-protection	[43]
3	Nanoparticles	Alginate/chitosan	In vivo	Wound healing • Sustained drug release • ROS (↓) • Inflammation (↓) • (↑) re-epithelialization and collagen formation	[44]
4	Nanoparticles	Silk	In vitro and In vivo	Myocardial infarction • Sustained drug release • (↑) blood parameters as that of healthy control in vivo	[9]
5	Hydrogel	Gelatin/carbopol	In vivo	Wound healing • ROS (↓) • Inflammation (↓) • (↑) re-epithelialization and collagen formation	[45]
6	Scaffolds containing liposomes	Chitosan-PLGA	Ex vivo using goat mucosa	Oral Lesions • Anti-bacterial property • Cell migration property in vitro • Sustained drug release	[15]
7	Bio-polymeric foaming beads	Gelatin-Alginate	In vitro	Tissue regeneration • Controlled release • Antioxidant property (↑) • Anti-inflammatory property (↑) • (↑) cell proliferation	[46]
8	Micelles	PVCL–PVA–PEG	In vitro and ex vivo	Antitumor therapy • Anti-tumor activity • (×) angiogenesis • (×)PI3K/Akt/VEGF pathway	[47]
9	Nanoformulation	Cyclodextrin	In vitro and in vivo	Colorectal cancer • (↑) ROS production • (↑) retension time in circulation • Cancer cell apoptosis	[48]

10	Nanoparticle	Alginate/chitosan	In vitro	Anti-bacterial • Sustained drug release	[49]
11	Liposomes	L-α-phosphatidylcholine, 1,2-distearoyl-sn-glycero -3-phosphoethanolamine-N-[methoxy(polyethylene glycol)-2000]	In vitro and In vivo	Ischemia and Reperfusion Injury • pro inflammatory cytokines (↓) • Ani-inflammatory potential • (↑) recovery	[50]
12	Nanoparticle	Chitosan/halloysite/graphitic-carbon nitride	In vitro	Breast cancer • Sustained drug release • Ph responsiveness • (↑) ROS production • Stability due to graphitic-carbon nitride	[51]
13	Nanoparticle	Poly (lactic-co-glycolic acid)	In vitro	Macrophage Polarization chronic kidney disease • Regulate macrophage polarization (↑) • (↑) tissue remodeling and regeneration	[52]
14	Nanoparticle	Mesoporous silica nanoparticles	In vitro	Lung cancer • ROS (↑) • Apoptosis (↑)	[53]
15	Nanoparticle	PLGA	In vitro	Hypoxia-Reoxygenation Injury • Protects the cells from hypoxia • ROS (↓)	[54]
16	Nanoparticle system coated onto the surface of the catheter	Poly (lactic-co-glycolic acid) and Eudragit RL 100	In vitro	Angioplasty balloon • Balloons coated with antiproliferative agents reduce vessel re-narrowing, or restenosis after surgical intervention • Sustained drug release	[55]
17	Nanoparticles	Gallium-modified gelatin	In vitro	Wound healing • ROS (↓) • Anti-inflammatory potential (↑) • (↑) re-epithelialization and collagen formation	[56]
18	Nanoparticles	Solid lipid	In vivo	Bio mimic tear film and enhance drug delivery • Sustained drug release	[57]
19	Nanoparticles	Chitosan	In vivo	Doxorubicin induced cardiotoxicity • (↓) cell death • (↓) oxidative stress	[43]
20	Nanoparticles	PLGA	In vivo	Hypoxia-reoxygenation injury • (↓) ROS • (↓) Calcium overload • (↓) inflammation • (↓) apoptosis	[54]

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Table 2 (Continued).

SL No	Formulation Type	Polymer Used	In vitro/in vivo	Application	Reference
21	Liposomes	-	In vitro and In vivo	Antitumor therapy • (↓) cell proliferation • Cell cycle arrest • (↑) ROS	[58]
22	Nanocrystal	Nicotinamide	In vivo	Enhanced bioavailability	[20]
23	Electrospun membranes	Polycaprolactone-polyvinylpyrrolidone	In vitro	Wound healing • Hemostasis • Inflammation (↓) • (↑) proliferation	[59]
24	Electrospun patch	Polycaprolactone/gelatin	In vivo	Wound healing • (↑) epithelialization • (↑) Angiogenesis • Fibroblast migration	[60]
25	Electrospun patch	PLGA	In vivo	Wound healing • Collagen deposition • Inflammation (↓) • (↑) proliferation	[61]
26	Electrospun patch	Zein	In vivo	Streptozotocin-Induced Diabetes • ROS (↓) • Inflammation (↓)	[10]
27	Injectable Hydrogel	Gelastin	In vitro	Wound healing • Inflammation (↓) • (↑) proliferation	[36]
28	Bio-conjugate	Chitosan	In vitro and In vivo	Osteoporosis • (↑) bone regeneration • (↑) bone calcification and callus formation • (×) Osteoclast activity	[62]
29	Hydrogels	Sodium Alginate and Cellulose	Ex Vivo Skin Permeation Experiments	Topical Application • (↑) adhesiveness	[63]
30	Nanocochleates gel	Carbopol 940	In vitro	Breast cancer therapy • Proliferation (↓) • Angiogenesis (↓) • Oxidative stress (↑)	[64]

31	Hydrogel	Chitosan/Gamma Alumina/Graphene Quantum Dots	In vitro	Lung cancer • Proliferation (↓) • Angiogenesis (↓) • Oxidative stress (↑)	[65]
32	Hydrogel	Gelatin/chitosan	In vitro	Osteogenesis • ALP (↓) • (↓) mineralization	[66]
33	Inhalable nanogel	Alginate	In vitro and In vivo	Acute lung injury • Alveolar damage (↓) • Endothelial function (↑) • Inflammation (↓)	[67]
34	Hydrogel	Gelatin/Polyvinyl Alcohol/Titanium Dioxide Nanocomposite	In vitro	Cancer • Angiogenesis (↓) Oxidative stress (↑)	[68]
35	Injectable hydrogel	Bio-glass	In vivo	Periodontal bone defects • Inflammation (↓) • Osteoclast activation (↓) • Matrix degradation (↓)	[69]
36	Nanogels	Folic–gelatin–pluronic P123	In vitro and In vivo	Chemotherapy • DNA damage • Cell-cycle arrest • Apoptosis	[70]
37	Hydrogel	Poly vinyl alcohol- alginate	In vitro	Antiinflammation • ROS (↓) • Inflammation (↓)	[71]
38	Hydrogel	Basil Seed Gum/Chitosan	In vitro	Bone Tissue Engineering • Angiogenesis (↑) • Cell adhesion (↑) • Bone regeneration (↑)	[11]
39	Brushite calcium phosphate cement	Soybean phosphatidylcholine (SPC) phospholipid	In vivo	Orthopedics	[72]
40	Microarray patches	Polyvinyl alcohol, polyvinylpyrrolidone	In vitro	Anti-inflammation • Cytokine (↓) • ROS (↓) • (↓) edema	[73]
41	Microneedles	Polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol (Soluplus)	Ex vivo	Transdermal delivery. • Sustained drug release	[73]

(*Continued*)

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Table 2 (Continued).

SL No	Formulation Type	Polymer Used	In vitro/in vivo	Application	Reference
42	Microneedle	GelMa	In vitro *and* In vivo	Wound healing • ROS (↓) • Inflammation (↓) • (↑) Re-epithelialization and collagen formation	[74]
43	Scaffolds	Alginate-chitosan	In vitro	Dental regeneration • Angiogenesis (↑) • ECM formation (↑) • Inflammation (↓)	[75]
44	Scaffold	Gelatin/tragacanth/ nano-hydroxyapatite	In vitro	Osteogenic activity • Collagen synthesis • Wnt/β-catenin activation • BMP signaling	[76]
45	Scaffold	Collagen/chitosan/SiO_2	In vitro	Antioxidant • ROS (↓)	[77]
46	Membranes	Chitosan/gelatin	In vitro and In vivo	Anti-bacterial • Protein synthesis (×) • DNA/RNA damage	[78]
47	3D printed scaffolds	Calcium phosphate nanospheres	In vitro	Bone repair • Inflammation (↓) • Bone remodeling • Angiogenesis (↓)	[12]
48	Nanocomposite	MXene with zinc-based metal-organic frameworks and chitosan	In vivo	MCF-7 breast cancer • 98% drug release on irradiation • Apoptosis (↑) • Renal stress (↓)	[79]
49	Nanoparticles	Silver and gold	In vitro	Antioxidant activity • ROS scavenging (↑) • Oxidative stress (↓)	[80]
50	Nanoparticles	Gold	In vitro	Photothermal therapy • Apoptosis (↑) • ROS (↑) • Reduced-toxicity	[81]

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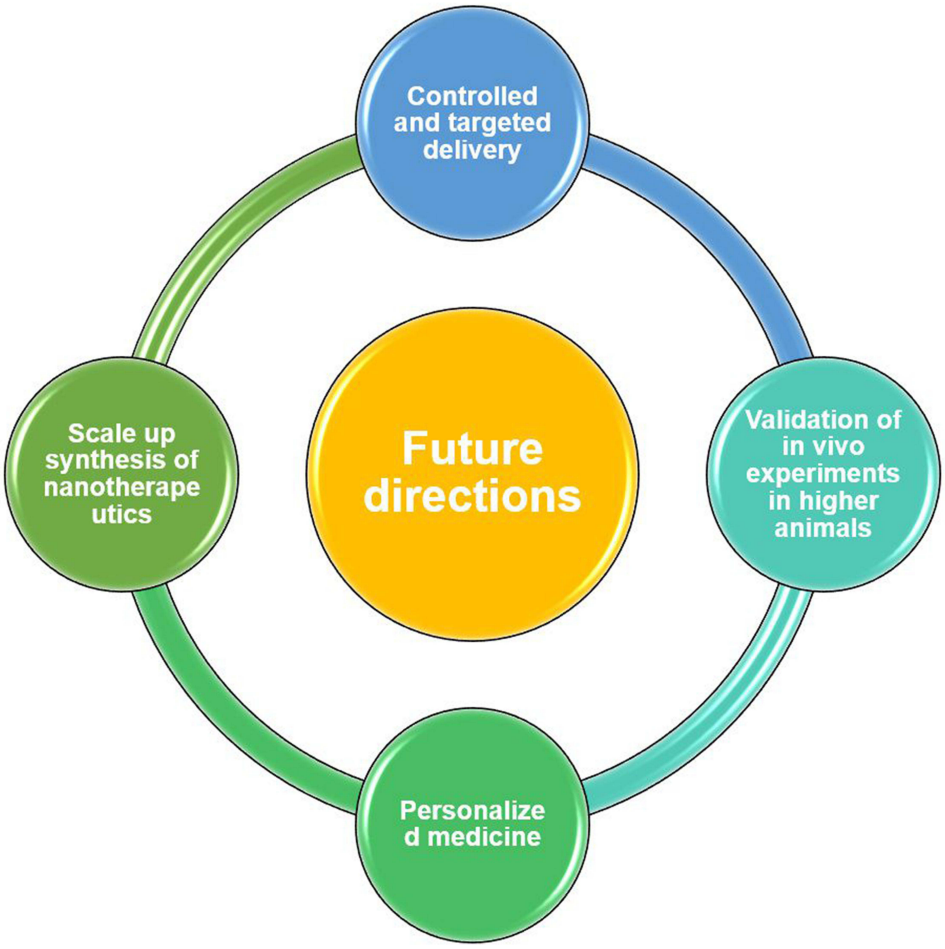

Figure 8 Schematic representation of future directions of quercetin incorporated biomaterials.

up of nanotherapeutics should also be validated. These advancements can be novel upcoming areas for research in the area of quercetin-based diagnostic nanoparticle in the treatment of cancers, neurodegenerative diseases, cardiovascular therapy, and autoimmune disorders. Future studies should investigate the integration of quercetin into theranostic platforms combining diagnostic imaging and therapy to enable real-time monitoring of biodistribution, therapeutic response, and disease progression. Also, the regulatory obstacles that hinders the product development which has to be effectively rectified include (i) lack of large-scale clinical trials hinder market approval, (ii) Variability in natural sources makes standardization and GMP compliance challenging and (iii) Apart from preclinical evidence, long-term safety data in humans are limited.

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Disclosure

The authors declare no conflict of interest.

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