European Cells and Materials Vol.57 2026 (pages 1–33) DOI: 10.22203/eCM.v057a01 ISSN 1473-2262

Review

ENGINEERED FLAVONOID NANOCARRIERS FOR TARGETED ONCOTHERAPY AND MULTIMORBIDITY MANAGEMENT

Yanan He[1], Jianye Yang[1], Yuxiang Liu[1], Dan Wang[2], Haimei Li[1], Yatong Ren[1], Zihui Feng[1], Yixuan Yuan[1], Lidan Zhao[1,*] and Wenfang Li[1,*]

[1]School of Life Science and Technology, Shandong Second Medical University, 261053 Weifang, Shandong, China
[2]Department of Physical Education, School of Foundation Medical, Shandong Second Medical University, 261053 Weifang, Shandong, China

Abstract

The prevention and treatment of tumors have become a major public health priority. While surgery and chemoradiotherapy remain the cornerstone of current therapeutic strategies, they are accompanied by notable toxic side effects, which severely compromise patients' quality of life. Flavonoids with precisely characterized molecular structures have demonstrated clinical utility in cancer treatment. Nevertheless, their therapeutic potential is hampered by inherent limitations such as poor aqueous solubility, suboptimal absorption, and chemical instability, ultimately resulting in diminished bioavailability. Recently, the synergistic combination of flavonoid compounds with nanocarrier-based delivery systems has gained prominence as a research focus, owing to its capacity for controlled release of bioactive components and site-specific targeting of tumor tissues. This study examines five flavonoids currently employed in clinical settings, reviewing the latest advancements and future directions in flavonoid-based drug delivery systems (including nanoparticles, hydrogels, and scaffolds) for anticancer applications. Additionally, we review the therapeutic applications of these five flavonoids in other prevalent diseases, proposing novel strategies to overcome the limitations of free drugs and improve therapeutic outcomes in disease management.

Keywords: Flavonoids, nanocarrier delivery systems, tumor-targeted therapy, bioavailability, multidisease therapeutics.

***Address for correspondence**: WenFang Li, School of Life Science and Technology, Shandong Second Medical University, 261053 Weifang, Shandong, China. E-mail: liwenfang@sdsmu.edu.cn; Lidan Zhao, School of Life Science and Technology, Shandong Second Medical University, 261053 Weifang, Shandong, China. E-mail: ldzhao@sdsmu.edu.cn.

Introduction

Malignant tumors have emerged as the leading cause of mortality worldwide, posing a significant threat to global public health. According to the latest estimates from the International Agency for Research on Cancer (IARC), approximately 20 million new cancer cases were diagnosed globally in 2022, with 9.7 million cancer-related deaths reported [1]. Consequently, cancer prevention and treatment remain pivotal public health challenges. Despite advances in clinical research enabling the development of science-driven therapeutic strategies, surgery, radiotherapy, and chemotherapy persist as the primary treatment modalities, each accompanied by inherent drawbacks. Surgical interventions frequently fail to eliminate tumor tissue, leading to a heightened risk of recurrence and metastasis. Additionally, radiotherapy and chemotherapy are accompanied by severe side effects, including immunosuppression, neurotoxicity, gastrointestinal damage, hepatotoxicity, nephrotoxicity, and alopecia [2], all of which significantly diminish patients' quality of life.

Traditional Chinese medicine (TCM) has demonstrated significant efficacy and therapeutic potential in clinical antitumor applications, characterized by low toxicity and enhanced immune function [3–5]. Among the diverse natural compounds identified in TCM formulations, flavonoids have garnered substantial attention due to their broad biological activities, including anti-inflammatory [6], antibacterial [7], antioxidant [8], antiviral [9], antitumor [10,11], and immunomodulatory effects [12–14]. Clinically, flavonoids such as naringin, quercetin, icariin, and puerarin have been applied in the treatment of tumors, diabetes mellitus, cardiovascular diseases, and neurodegenerative disorders [15].

Despite their considerable therapeutic promise, flavonoids are hampered by several intrinsic limitations, including poor aqueous solubility, low absorption efficiency, chemical instability, and rapid metabolic clearance. These factors collectively result in low bioavailability, thereby constraining their broader clinical translation. To overcome these challenges, innovative nanoscale drug de-

livery systems are under intensive investigation. Utilizing biomaterials like tissue-engineered scaffolds, nanoliposomes, polymeric micelles, and nano-microspheres, these systems encapsulate flavonoids to achieve site-specific targeting and controlled release. Consequently, they enhance flavonoid bioactivity, improve delivery precision, and mitigate the off-target toxicity commonly associated with conventional formulations, ultimately augmenting therapeutic efficacy [16–19].

Flavonoid-loaded nanoscale drug delivery systems are under active investigation for tumor therapy. In a previous study, Sun *et al*. [20] developed hyaluronidase-conjugated quercetin liposomes (HQL) as a sophisticated drug delivery system for pancreatic cancer. By degrading hyaluronic acid to remodel the desmoplastic tumor microenvironment, HQL significantly improved nanoparticle penetration and intratumoral accumulation. This platform effectively inhibited cell proliferation, triggered apoptosis, and induced G2/M phase arrest. Furthermore, HQL exhibited potent *in vivo* antitumor efficacy and a favorable safety profile, offering a promising strategy for adjuvant pancreatic cancer therapy . Moreover, nano-flavonoid systems have shown synergistic antitumor activity when combined with radiotherapy or chemotherapy. For example, curcumin-naringenin-loaded dextran-coated magnetic nanoparticles (CUR-NAR-D-MNPs) were used as a chemotherapeutic agent in combination with radiotherapy for the treatment of breast cancer. These nanoparticles promoted reactive oxygen species (ROS) generation to induce apoptosis and inhibited tumor cell proliferation. In combination with radiotherapy, CUR-NAR-D-MNPs significantly suppressed tumor growth by regulating multiple signaling pathways, including p53, p21, TNF, CD44, and ROS [21].

Flavonoid-encapsulated drug delivery systems exhibit enhanced therapeutic performance in non-neoplastic pathologies. For instance, Li *et al*. [22] engineered a multifunctional hydrogel (GSC/PBE@Lut) via sequential photo-crosslinking of gelatin methacryloyl (GelMA) and Cu^{2+}-coordinated alginate crosslinking, which incorporated pH/ROS-dual-responsive luteolin nanoparticles (PBE@Lut). This system not only achieved self-regulated release of copper ions and luteolin but also modulated its mechanical properties to accelerate chronic wound healing. Separately, it was reported that a quercetin-modified $Cu_{2-x}Se$ (CSPQ) nanoparticle could ameliorate sevoflurane-induced neurotoxicity by regulating microglial cell lipid metabolism via the TREM2 signaling pathway. In addition, cell membrane-encapsulated CSPQ (CSPQ@CM) nanoparticles significantly attenuated sevoflurane-induced cognitive impairment and lipidomic dysregulation in murine models. These findings suggested that targeting microglia lipid metabolism to promote neuronal myelin regeneration had great potential in the treatment of neurotoxic and neurodegenerative diseases [23]. Zhang *et al*. [24] developed a biomimetic nanoplatform (HA-RES-OPC-MMP NPs) utilizing resveratrol (RES) and proanthocyanidins (OPC), which featured a hyaluronic acid (HA) core grafted with a matrix metalloproteinase (MMP)-targeting peptide. This nanoformulation exhibited multimodal therapeutic efficacy through potent ROS scavenging, attenuation of NF-κB-mediated inflammatory cascades, and SIRT1-dependent upregulation of circadian rhythm-related genes, thereby enhancing targeted drug delivery to the myocardium following ischemia-reperfusion injury. These findings validate that flavonoid-integrated nanocarrier delivery systems possess substantial therapeutic potential and are positioned to assume pivotal functions in future clinical treatments.

Overall, nano-drug delivery systems effectively circumvent the inherent limitations of free flavonoids, presenting considerable promise for both cancer prevention and the treatment of various diseases. By loading flavonoid-based agents onto these carriers, their pharmacological profiles are substantially enhanced, leading to improved therapeutic outcomes for patients. This study provides a comprehensive overview of flavonoids and their molecular mechanisms in clinical antitumor applications. Additionally, it delineates the current research landscape concerning delivery systems loaded with five clinically relevant flavonoids for cancer treatment and offers insights into future directions for their application in disease management. In contrast to previous studies that have either surveyed a broad spectrum of flavonoids, concentrated on single-type nano-delivery systems, or primarily evaluated antitumor efficacy, this review specifically focuses on five clinically validated flavonoids. It consolidates recent progress in diverse nanocarriers (e.g., nanoparticles, hydrogels, scaffolds) designed to improve flavonoid bioavailability, achieve tumor-specific targeting, and overcome the inherent drawbacks of free flavonoids. Furthermore, this work extends the discussion to their therapeutic potential in other prevalent diseases, thereby providing a comprehensive, multi-disease framework for the optimization of flavonoid-loaded delivery platforms.

Quercetin, naringin, puerarin, rutin, and icariin are uniquely suited as representative candidates for cancer multimorbidity management due to their intrinsic polypharmacological activity across key pathological pathways of cancer, metabolic disorders, cardiovascular diseases, neurodegeneration, and tissue repair. For example, quercetin exerts antitumor effects via JAK2/STAT3 and ROS signaling modulation, while concurrently targeting metabolic and neurodegenerative conditions as well as wound healing via its potent antioxidant, anti-inflammatory, and angiogenic properties [25,26]. Similarly, icariin integrates anticancer activity [27] with capabilities in osteochondral repair [28] and cardiovascular protection [29], directly addressing common comorbidities in cancer patients. Collectively, these flavonoids transcend single-disease targeting paradigms, as their core molecular mechanisms (e.g., ROS

scavenging [30], NF-κB inhibition [31]) intersect with multiple comorbidity-related pathological processes. Nano-delivery platforms are pivotal for translating this polypharmacology into clinical practice by enabling targeted co-delivery, controlled release, and enhanced bioavailability, thereby overcoming the poor solubility and rapid metabolism of free flavonoids. This facilitates the simultaneous delivery to tumor sites and comorbid lesions (e.g., chronic wounds, neurodegenerative foci) [32,33]. This review focuses on these five flavonoids and their associated nano-delivery systems, highlighting their antitumor potential alongside their broader utility in addressing cancer's interconnected comorbidities.

Antitumor Activity of Flavonoids and Clinical Applications for Antitumor Therapy

Antitumor Activities of Flavonoids

Flavonoids manifest their antitumor efficacy by targeting and modulating a diverse array of cellular processes. Pang *et al*. [34] showed that flavonoids could affect tumor cell autophagy, influencing growth, proliferation, apoptosis, necrosis, cell cycle arrest, senescence, migration, invasion, angiogenesis, and drug resistance. Therefore, the modulation of autophagy is regarded as a pivotal therapeutic mechanism of flavonoids in oncology. Additionally, flavonoids inhibit tumor development by regulating the tumor microenvironment (TME) and its dynamic crosstalk with cancer cells, which serves to constrain tumor growth, metastasis, and invasion [35]. Tumor-associated macrophages, which are abundant immune-suppressor cells in the tumor microenvironment, are also modulated by flavonoids to enhance their anticancer activity [36]. Furthermore, microRNAs (miRNAs), key post-transcriptional regulators of gene expression that are frequently dysregulated in malignancies to foster cancer progression and therapy resistance, are also susceptible to modulation by flavonoids [37].

Beyond their direct anticancer activities, flavonoids serve as valuable adjuncts to conventional radiotherapy and chemotherapy by enhancing therapeutic efficacy. Tiwari *et al*. [38] found that flavonoids can function dually as radioprotectants and radiation sensitizers, thereby increasing the sensitivity of tumor cells to radiotherapy and improving treatment outcomes. Besides, flavonoids have been reported to augment the antitumor effects when used in combination with chemotherapeutic agents [39].

Clinical Applications of Flavonoids in Traditional Chinese Medicine

Extensive research has demonstrated that flavonoids combat tumors through multiple pathways, including inducing tumor cell apoptosis, reducing tumor cell proliferation and invasion, inhibiting angiogenesis, reversing multidrug resistance, and enhancing sensitivity to radiotherapy (Fig. 1) [40–43]. The discovery of flavonoids has

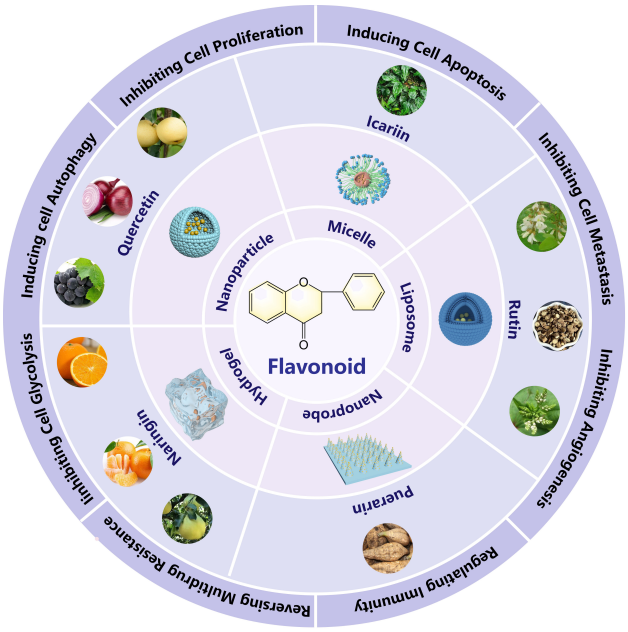

Fig. 1. Flavonoid-based nanodrug carriers for antitumor therapy via modulation of multiple physiological pathways. This figure is edited by Adobe Illustrator 2023 and 3ds Max 2024.

opened new avenues for utilizing TCM in the effective prevention and treatment of tumors. Currently, several flavonoids, such as formononetin, icariin, quercetin, rutin, puerarin, and naringin, are employed in the clinical treatment and prognostic improvement of various cancers. For example, Pueraria Mirifica Isoflavone Capsules containing puerarin have been used to treat breast and endometrial cancers, while Ginseng Astragalus Fuzheng Injection, with quercetin as the primary component, has been combined with chemotherapy to treat gastric, breast, and ovarian cancers (Table 1). However, the antitumor mechanisms of many flavonoids remain under active investigation. Critical challenges still need to be addressed, such as understanding drug toxicology, managing potential side effects, and the prolonged duration of clinical trials. Consequently, the broader clinical translation and large-scale application of many promising flavonoids continue to encounter significant hurdles.

Structural Analysis of Flavonoids and Their Antitumor Activity in Combination With Drug Delivery Systems

Despite their considerable promise in cancer therapy, the clinical translation of flavonoids is significantly hampered by inherent pharmacokinetic drawbacks, including poor aqueous solubility, low stability, and rapid systemic metabolism. To overcome these limitations, integrating flavonoids into advanced drug delivery systems has emerged as a viable strategy. Such systems can markedly enhance flavonoid bioavailability, enable tumor-specific targeted delivery, and allow for controlled drug release tailored to individual therapeutic requirements [18,53].

Table 1. Flavonoid herbal constituents applied to prevent and treat tumor and their clinical applications.

Chinese medicine ingredient	Source	Clinical application	Cancer	Reference
Quercetin	√*Pomegranate*, *Panax ginseng*, *Ginkgo biloba*, Acacia rice, Sapindus leaf, Coltsfoot flower, Hawthorn, etc.	※Ginseng Astragalus Fuzheng Injection	Ginseng Astragalus Fuzheng Injection in combination with chemotherapy is used to treat gastric, breast, and ovarian cancers.	[44–46]
Icariin	√Epimedium.	※Shengbai Oral Liquid	Shengbai Oral Liquid can be used to regulate the damage repair such as leukopenia after radiotherapy for tumors.	[47,48]
Rutin	√Rue leaf, Acacia rice, Acacia horn, Ginkgo biloba, Chai hu, Motherwort, etc.	※ Prunella vulgaris L.	Prunella vulgaris L. is used to treat breast cancer.	[49]
Puerarin	√*Pueraria lobata*.	※Pueraria injection	Pueraria injection is used to treat solid cancer.	[50]
Naringin	√*Pomelo*, Grapefruit, Limes, etc.	※Pingxiao Capsules ※Gastrofuchun Tablets	Pingxiao Capsules can be used for the treatment of esophageal cancer, gastrointestinal tract tumors, liver cancer, breast cancer. Gastrofuchun Tablets is used for the treatment of gastric cancer and its postoperative adjuvant therapy.	[51,52]

European Cells and Materials Vol.57 2026 (pages 1–33) DOI: 10.22203/eCM.v057a01

For example, nanoscale drug delivery systems loaded with flavonoids have shown great potential for cancer treatment. Nanomicelles and nanoliposomes carrying apigenin have demonstrated improved targeting efficiency toward colon cancer cells and enhanced antitumor efficacy (Fig. 2**A**) [54]. Peng *et al*. [55] developed a sustained-release composite hydrogel (RKT@gel), which was prepared from tantalum nanoparticles (Ta NPs) doped with a self-assembled hydrogel of raltitrexed chemotherapeutic drug and kaempferol (RK@gel). This RKT@gel system not only functioned as a radiosensitizer but also effectively activated antitumor immunity, offering a novel strategy for the treatment of HCC (Fig. 2**B**). Mi *et al*. [56] developed a PEG-FA@ZIF-8@BAN nano-drug delivery system, where baicalin (BAN) was encapsulated in a folate receptor-responsive carrier (PEG-FA) based on a zeolite imidazolate framework (ZIF-8). This system significantly potentiated the cytotoxic effects of BAN against MCF-7 breast cancer cells. The folic acid-mediated targeting increased nanoparticle uptake by tumor cells, leading to more effective cancer cell elimination and pronounced inhibition of tumor growth in 4T1 mouse models, highlighting its promise as an effective nanomedicine for breast cancer (Fig. 2**C**).

Another study developed nanoparticles composed of luteolin (LUT) encapsulated in poly (propylene sulfide)-polyethylene glycol (PPS-PEG), termed LUT-PPS-NPs. Compared to free luteolin, LUT-PPS-NPs significantly promoted apoptosis in SK-MEL-28 melanoma cells. *In vivo* studies revealed that 14-day treatment with LUT-PPS-NPs significantly suppressed melanoma growth compared to both the control and luteolin-treated groups [57]. Mu *et al*. [58] engineered an innovative Ce@EGCG-based nanoplatform (IR780/Ce@EGCG/APT) through strategic integration of cerium ions and EGCG-derived metal-phenolic frameworks, followed by encapsulation of IR780 and functionalization with AS1411 aptamers. This system demonstrated dual-modality cytotoxicity in breast cancer via Ce^{3+}-mediated Fenton-like ROS generation and photothermally activated mitochondrial targeting of IR780, while EGCG served as a multimodal sensitizer enhancing ferroptosis-photothermal combinational efficacy (Fig. 2**D**). Another reported strategy involved a carrier-free, self-assembled nanoparticle (IMCN) formed from indocyanine green, copper ions, and the chemopreventive flavonoid Morusin (Mor). Mor induced cytoplasmic vacuolization and mitochondrial oxidative stress in tumor cells, enabling effective ablation. This nanoassembly demonstrated significant in vivo tumor growth suppression with high biosafety and biocompatibility, representing an advancement in anticancer therapeutic design (Fig. 2**E**) [59]. In addition, another study developed a nanoengineered Cu-EGCG platform that integrateschemodynamic therapy (CDT), photothermal therapy (PTT), and photodynamic therapy (PDT) for dual tumor-microbe eradication. This triple-therapeutic system addressed refractory tumors characterized by acidic and high-glutathione microenvironments while concurrently combatting post-surgical resistant infections (Fig. 2**F**) [60].

Currently, the integration of flavonoids with drug delivery systems is primarily achieved through three principal strategies, as illustrated in Fig. 3: (1) Encapsulation within nanocarriers, such as liposomes or exosomes; (2) Complexation with polymeric matrices (e.g., polylactic acid, polyhydroxyalkanoates, polyvinylpyridinium chloride), which are subsequently incorporated into carriers such as nanoparticles, electrospinning or micelles; and (3) Conjugation to hydrogel or scaffold networks via covalent linkages (e.g., via Schiff bases) or non-covalent interactions (e.g., hydrogen bonds or van der Waals forces).

The general preparation workflows for these flavonoid-loaded delivery systems are summarized in Fig. 4. (1) Phospholipids and cholesterol are dissolved in anhydrous ethanol, followed by dropwise addition of flavonoid solution. After that, the mixed solution is subjected to spin evaporation to remove the organic solvent, triggering self-assembly into large flavonoid-coated liposomes. Subsequently, the particle size is homogenized by ultrasonication. Alternatively, flavonoid-coated nanoparticles can be prepared by spinning and sonication after dissolving flavonoids and polymers in organic solvents (Fig. 4**A**). (2) The flavonoid-polymer composite was prepared by co-dissolving flavonoids and amphiphilic polymers in an organic phase, which was gradually introduced into an aqueous phase via controlled dropwise addition to generate an oil-in-water emulsion. The emulsion was subjected to rotary evaporation to remove the organic solvent and ultimately promoted micelle formation by ultrasonication (Fig. 4**B**). (3) Flavonoid-incorporated electrospun fibers are fabricated by homogenously dissolving flavonoids with polymeric or natural matrices in an organic solvent system. Ultrasonication-assisted dispersion is implemented to optimize flavonoid distribution uniformity, followed by electrospinning at an applied voltage of 10-20 kV using an electrospinning machine (Fig. 4**C**). (4) Upon co-dissolution of flavonoids with polymeric or natural matrices in a homogeneous solvent system, flavonoid-functionalized drug delivery platforms (bioactive hydrogels, composite scaffolds, and nanoprobes) are engineered via 3D printing, precision molding, and microfluidic templating techniques (Fig. 4**D**).

Quercetin-loaded Delivery Systems for Enhanced Antitumor Activity and Improved Wound Healing

Quercetin ($C_{15}H_{10}O_7$, Fig. 5**A**), a flavonol in *Panax quinquefolius*/*Ginkgo biloba*/*Sophora japonica*, exhibits a characteristic C-ring 3-hydroxy-4-keto group and 5/7- (A-ring) /3’/4’-hydroxyls in the B-ring. These structural features are fundamental to its biological activity and its ability to bind to nanocarriers [61]. Structure-activity relationship (SAR) analysis indicates that B-ring 3’,4’-ortho-

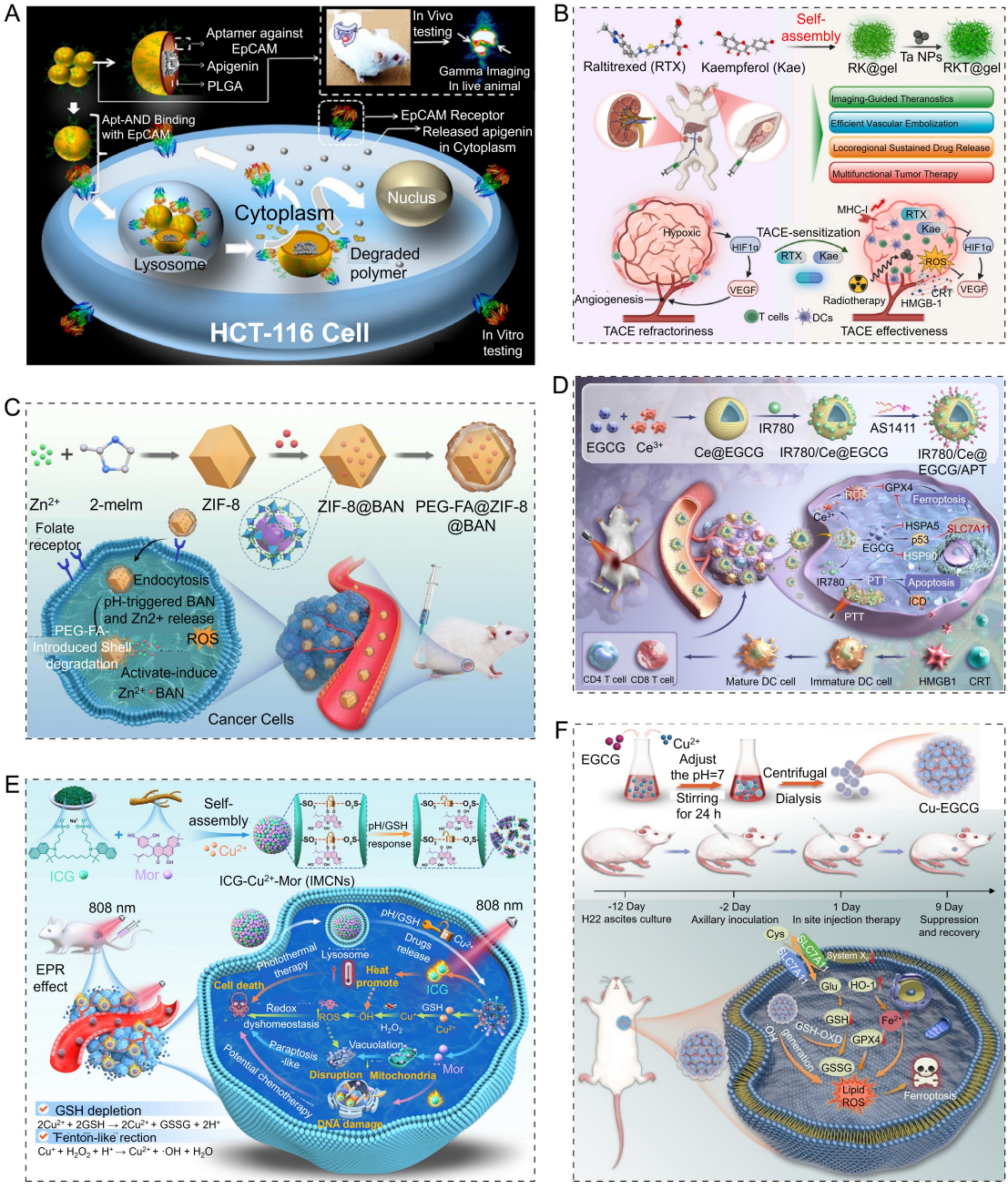

Fig. 2. Antitumor activity of nanoscale drug delivery systems loaded with flavonoids. (**A**) Nanoparticles loaded with apigenin significantly reduced tumor size in a mouse model of colon cancer. Adapted and reprinted from [54]. Copyright © 2023 Elsevier. (**B**) RKT@gel could efficiently treat HCC by enhancing radiotherapy sensitivity and enhancing anti-tumor immunoactivation. Adapted and reprinted from [55]. Copyright © 2025 Elsevier. (**C**) Schematic diagram of the preparation of PEG-FA@ZIF-8@BAN and folate receptor-mediated responsive drug delivery system for effective antitumor therapy. Adapted and reprinted from [56]. Copyright © 2021 Dove Medical Press Ltd. (**D**) Schematic of the preparation and mechanisms of synergistic therapy of IR780/Ce@EGCG/APT. Adapted and reprinted from [58]. Copyright © 2024 Elsevier. (**E**) Schematic diagram of self-assembled IMCN nanoparticles with pH/GSH response and their application in multimodal synergistic tumor therapy. Adapted and reprinted from [59]. Copyright © 2024 Elsevier. (**F**) Schematic diagram of the preparation and the antitumor mechanisms of Cu-EGCG. Adapted and reprinted from [60]. Copyright © 2024 Elsevier.

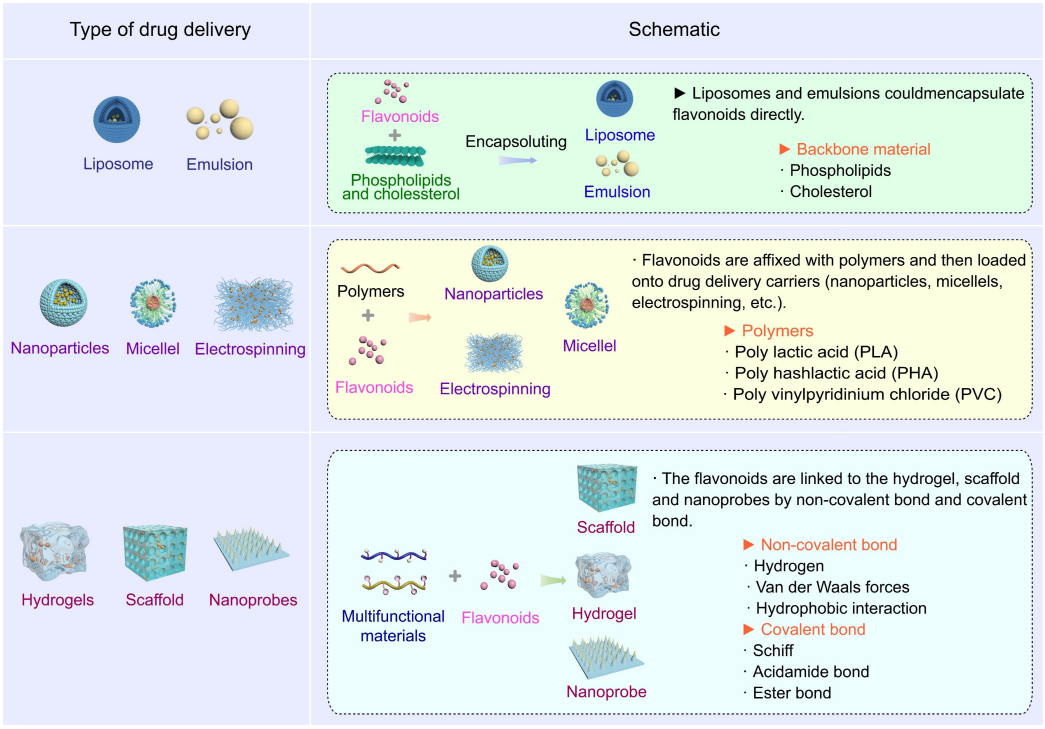

Fig. 3. The three primary methods for flavonoid-based drug delivery systems. This figure is edited by Adobe Illustrator 2023 and 3ds Max 2024.

dihydroxyls are critical for antioxidant activity and Fe^{3+} chelation. Meanwhile, the 3-hydroxy-4-keto group in the C ring mediates its binding affinity to the JAK2/STAT3 signaling pathway, which is pivotal for its antitumor effects. For nanonization, the hydroxyl groups of quercetin can form hydrogen bonds with nanocarriers, while the hydrophobic moieties of the A- and B-rings can embed into the hydrophobic core of carriers. This dual interaction balances hydrophilicity and hydrophobicity, thereby enhancing the water solubility of quercetin. Clinically, quercetin has been utilized in the treatment of various conditions, including non-alcoholic fatty liver disease [62], disc degeneration [63], type II diabetes, and Alzheimer's disease [64]. Additionally, as a key component of Ginseng Astragali Fuzheng Liquid, quercetin has been employed as an adjuvant therapy in clinical treatments for gastric, lung, breast, and ovarian cancers.

Nanoparticle-loaded Quercetin for Enhanced Antitumor Applications

Numerous studies have shown that combining quercetin with drug delivery systems enhances its bioavailability and bioactivity, yielding superior clinical outcomes, particularly in cancer treatment [65–67]. Li *et al.* [68] developed a multifunctional photothermal/immunotherapeutic nanoparticle (QFN) capable of releasing quercetin upon near-infrared (NIR) irradiation. This controlled release inhibited the phosphorylation of JAK2 and STAT3, leading to reduced programmed death ligand 1 (PD-L1) expression in tumor cells and remodeling of the extracellular matrix (ECM) by downregulating α-SMA^{+} fibroblasts (Fig. 5**Ba**). Concurrently, quercetin enhanced T-cell infiltration and activation within the tumor microenvironment, thereby modulating the immunosuppressive landscape. Furthermore, QFN treatment promoted long-term antitumor immune memory, which effectively reduced tumor metastasis and recurrence in murine models (Fig. 5**Bb–c**) [67]. A previous study demonstrated that self-assembled quercetin-Fe^{3+} nanoparticles (Qu-Fe NPs) could synergize low-temperature photothermal therapy (LTPTT) with NIR light. Following cellular internalization, quercetin released from Qu-Fe NPs inhibited heat shock protein 70 expression and activated LTPTT. Additionally, Qu-Fe NPs depleted excessive glutathione (GSH) in cancer cells, increasing their sensitivity to ROS. The concomitant release of quercetin further induced apoptosis and inhibited the growth of 4T1 tumor cells [68]. Moreover, a quercetin nanosuspension (QUR-NPs) was fabricated via micro-precipitation and high-pressure homogenization using mPEG-DCA as a stabilizer. QUR-NPs significantly improved the antitumor efficacy and immune modulation in tumor-bearing mice compared to free quercetin solutions, highlighting its potential as a novel delivery platform for combined tumor therapy and immunoregulation [69].

Chen *et al.* [70] developed RGD-MSN/QR/shTERT nanoparticles for the co-delivery of quercetin and shTERT. This nanosystem induces ovarian cancer cell apoptosis via

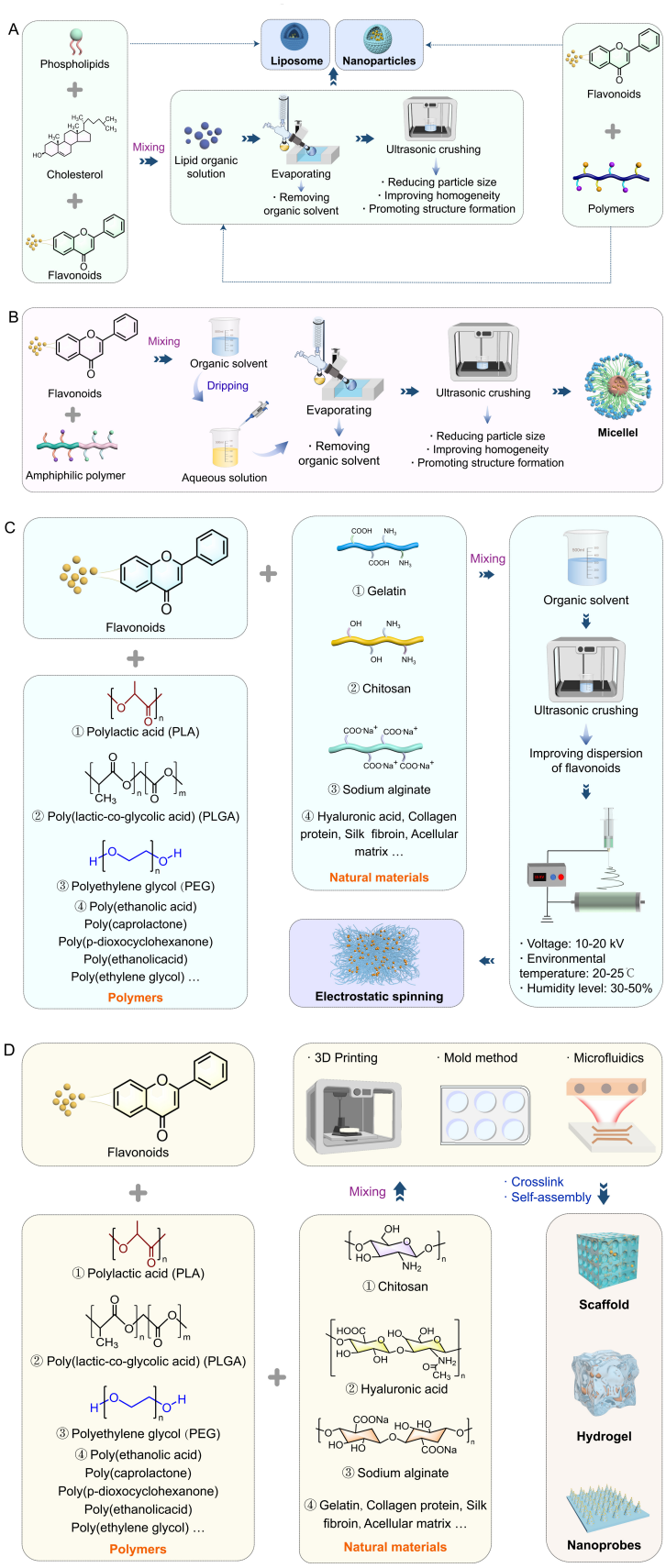

Fig. 4. Preparation processes for the four flavonoid drug delivery system approaches. (**A**) Schematic diagram of the preparation process of flavonoids encapsulated within liposomes and nanoparticles; (**B**) Schematic of the preparation process of the micelle loaded with flavonoids; (**C**) Schematic representation of the preparation process of the electrostatic spinning loaded with flavonoids; (**D**) Schematic representation of the preparation process of the hydrogel, scaffold, and nanoprobe loaded with flavonoids. This figure is edited by Adobe Illustrator 2023 and 3ds Max 2024.

the p53/Bax signaling pathway and exhibits superior tumor-targeting and antitumor efficacy. Consequently, it represents a promising therapeutic strategy for the management of ovarian cancer. In another study, a multifunctional therapeutic nanoparticle (CCQ) was successfully engineered by integrating CaO_2-loaded crotonic acid-based molecules with quercetin (Qu), followed by encapsulation within DSPE-PEG2000. This design aimed to achieve synergistic mitochondrial metabolic inhibition via calcium overload combined with mild photothermal therapy (PTT). Upon accumulation in the tumor microenvironment, CCQ produced abundant H_2O_2 and calcium ions, disrupting intracellular calcium homeostasis and triggering mitochondrial apoptosis. Concurrently, quercetin released from CCQ suppressed the expression of heat shock proteins (Hsps) during PTT, effectively mitigating tumor thermotolerance while sparing adjacent healthy tissues. This CR organic molecule-based nanotherapeutic platform exhibited synergistic antitumor efficacy with photothermal therapy, achieving tumor ablation within a biosafe thermal range [71].

Hydrogel-based quercetin delivery for enhanced antitumor applications

A previous study demonstrated that a synthesized Fe_2O_3/Starch/Polyvinyl alcohol (Fe_2O_3/S/PVA) nanocarrier-incorporated hydrogel encapsulating quercetin was demonstrated as a potential nano-anticancer agent targeting liver cancer. This Fe_2O_3/S/PVA nanocarrier exhibited high encapsulation efficiency (86.5%) and drug loading efficiency (47%) for quercetin. The system effectively targeted HepG2 liver cancer cells and induced cell apoptosis [72]. Another study developed a local drug delivery system, Qu@PM@Gel, consisting of quercetin-loaded polymer micelles within an F127 hydrogel matrix for breast cancer treatment. The encapsulation of quercetin into polyethylene glycol-based micelles improved its distribution homogeneity and stability within the hydrogel, thereby enhancing compatibility with F127 hydrogels. This system inhibited 4T1 cell proliferation by inducing apoptosis and reducing cellular activity [73].

A NIR-responsive hybrid liposome/hydrogel platform (QD Lipo/ICG/LAgel) was developed by co-loading quercetin (QUE) and doxorubicin (DOX) into liposomes (QD Lipo), which were then co-encapsulated with indocyanine green (ICG) within a low-melting-point agarose hydrogel (LAgel). This system enables localized, on-demand chemo-photothermal combination therapy for retinoblastoma. Specifically, QUE enhances therapeutic efficacy by modulating the epithelial-mesenchymal transition (EMT) and inhibiting heat shock protein (HSP) expression to overcome drug resistance. By reducing the frequency of invasive injections, this platform offers a novel strategy for treating retinoblastoma and complex ocular malignancies [74]. Jia *et al.* [75] fabricated an intelligent hydrogel (Que@TA-Fe@PNAGA) by encapsulating quercetin (Que)-loaded tannin-iron (TA-Fe) nanoparticles within poly(N-acryloylglycylglycine) amine (PNAGA) matrices. This platform was designed to dually enhance the efficacy of mild PTT for postoperative skin cancer while mitigating photothermal-associated inflammatory responses. Upon NIR irradiation, NIR-responsive hydrogen bond dissociation triggered a controlled gel-sol transition, enabling the spatiotemporal release of therapeutic Que@TA-Fe nanoparticles. The released nanoparticles inhibited the expression of Hsp proteins in tumor cells by generating ROS and entered the inflammatory cells to release TA and Que. Consequently, the Que@TA-Fe@PNAGA hydrogel demonstrated dual therapeutic efficacy in achieving tumor ablation and preventing photothermal-induced damage to surrounding healthy tissues, offering a novel strategy for postoperative photothermal treatment of skin cancer (Fig. 5**C**).

The therapeutic potential of quercetin-loaded hydrogels extends to challenging malignancies such as triple-negative breast cancer (TNBC). Li *et al.* [76] developed an injectable DNA hydrogel (Q-5FDHG) via a novel DNA amplification reaction, comprising a 5-fluorouracil (5-FU)-based scaffold embedded with Que. Que remodels the immunosuppressive tumor microenvironment by inhibiting CCL2 secretion and tumor-associated macrophage recruitment, while 5-FU suppresses tumor proliferation and induces immunogenic cell death with minimal systemic toxicity. This synergistic approach enhances chemoimmunotherapy efficacy against TNBC, effectively inhibiting primary tumor growth and lung metastasis through a safe and translatable strategy.

Additionally, quercetin-loaded hydrogels have demonstrated significant cytotoxicity through the modulation of epigenetic pathways. Abbaszadeh *et al.* [77] developed a quercetin-loaded chitosan-based nanohydrogel (ChiNH/Q) using chitosan and tripolyphosphate (TPP) via ionic gelation. This ChiNH/Q system exhibited antitumor effects by regulating DNA methylation and showed strong antibacterial activity against Gram-positive bacteria and *Candida albicans*, suggesting its potential as a nanomedicine for cancer therapy with inherent anti-infective properties.

Other Strategies for Quercetin-loaded Nanodrug Delivery Systems

Advancing beyond single-agent delivery, researchers have engineered a TEM-responsive hybrid organosilica micellar system (ZnPP@FQOS), designated ZnPP@FQOS, for the co-encapsulation of a zinc protoporphyrin photosensitizer (ZnPP). This dual-drug nanoplatform demonstrated potent therapeutic efficacy against fibroblast-rich tumors while concurrently activating systemic antitumor immunity. Significantly, ZnPP@FQOS exhibited a synergistic effect in enhancing anti-PD-L1-based immunotherapy, showing particular promise for the treatment of

highly immunosuppressive pancreatic cancer. The therapeutic superiority of ZnPP@FQOS was achieved through laser-activated photodynamic reprogramming of cancer-associated fibroblasts (CAFs), which initiated multimodal ROS amplification cascades. This photonic modulation simultaneously triggered apoptotic pathways, suppressed HO-1-mediated antioxidant defenses, and enabled substantial generation of singlet oxygen ($^1O2$), collectively driving potent tumor eradication. This study provides new insights for designing nanomedicines to treat tumors (Fig. 5**D**) [78].

Quercetin-loaded Delivery Systems for Improved Wound Healing

Emerging evidence has indicated that quercetin exhibits potent wound-healing bioactivity through multimodal therapeutic actions [79]. Delivery systems loaded with quercetin can amplify this regenerative capacity by harnessing its inherent antimicrobial, anti-inflammatory, and antioxidant effects. To this end, researchers have developed a polysaccharide-based self-healing hydrogel wound dressing, designated CPP@PDA/Que3, by incorporating quercetin and polydopamine nanoparticles into a carboxymethyl chitosan matrix. The CPP@PDA/Que3 hydrogel exhibited significant antioxidant and antimicrobial properties due to the combination of quercetin and NIR-induced photothermolysis. This multifunctional system effectively reduced oxidative stress and promoted angiogenesis, thereby accelerating the transition from inflammation to wound healing. Furthermore, its thermoresponsive injectability enabled form a protective barrier at wound sites, which facilitated rapid hemostasis and suppression of inflammation. Collectively, this hydrogel presents a novel strategy to advance the clinical management of bacterial-infected wounds [80].

In another study, quercetin-loaded hollow mesoporous cerium dioxide nanoparticles were synthesized and subsequently incorporated into a light-cured, double cross-linked hydrogel, yielding a composite designated HQu@BC. The HQu@BC hydrogel could be injected into the flap site to activate macrophage reprogramming to maintain local ROS homeostasis and reduce inflammation. The quercetin-loaded hydrogel exhibited a combination of antimicrobial, antioxidant, anti-microbial, and pro-healing properties, providing a novel therapeutic strategy to enhance the success rate of skin flap surgery (Fig. 5**E**) [81].

In addition, demonstrates beneficial effects in promoting the healing of diabetic skin wounds. Liu *et al.* [82] prepared a novel swollen hydrogel (QL@MAB) loaded with quercetin and the antibiotic levofloxacin using methyl acrylate (MA) and (3-acrylamidophenyl) boronic acid (AAPBA). The QL@MAB hydrogel accelerated drug release in a hyperglycemic wound microenvironment due to the cleavage of boronate ester bonds and the consequent exposure of diffusion channels. Furthermore, QL@MAB promoted wound debridement and re-epithelialization in diabetic mice, as well as angiogenesis, hair follicle regeneration, and extracellular matrix remodeling (Fig. 5**F**).

Quercetin demonstrates enhanced bioavailability and therapeutic efficacy when incorporated into diverse delivery systems such as nanoparticles and hydrogels, a benefit largely attributable to its structural features encompassing polyhydroxyl groups and a hydrophobic aromatic ring. Notably, significant advancements have been achieved utilizing quercetin-based delivery platforms in fields including antitumor therapy and wound healing. In contrast, naringin, a dihydroflavonoid glycoside, is characterized by a saturated C2-C3 bond within its C-ring and the presence of a rutinose moiety. These distinct structural attributes play a pivotal role in balancing solubility and enabling targeted release, which are critical considerations in the design of its delivery systems, as will be elaborated in the following sections.

Naringin-loaded Delivery Systems for Enhanced Antitumor Activity and Improved Wound Healing

Naringin ($C_{27}H_{32}O_{14}$, Fig. 6**A**), a dihydroflavonoid glycoside abundant in citrus fruits, is characterized by a saturated C2-C3 bond within its C-ring, hydroxyl groups located on the A- and B-rings, and a 7-linked rutinose moiety [83]. The dihydroflavonoid backbone of naringin contributes to its enhanced metabolic stability, while the hydroxyl groups on the A/B rings are instrumental in mediating its anti-inflammatory and antitumor activities. During nanonization, the hydrophilic rutinose moiety serves to improve aqueous solubility, albeit at the potential cost of introducing steric hindrance. Conversely, the hydrophobic aglycone component readily interacts with lipid-based nanocarriers. This interplay between hydrophilic and hydrophobic structural elements is key to balancing solubility and bioavailability, thereby enabling effective nanoformulation. This compound exhibits a broad spectrum of pharmacological activities, including anti-inflammatory, antiviral, anticancer, anti-mutagenic, anti-allergic, and hepatoprotective effects, and shows utility in the management of diabetes [84]. Furthermore, it demonstrates capabilities in lowering blood cholesterol levels, inhibiting thrombus formation, and enhancing local microcirculation and nutrient delivery, which underpins its application in the prevention and treatment of cardiovascular and cerebrovascular diseases [85]. Currently, naringin-based formulations, such as Gastrofuchun Tablets and Pingxiao Capsules, are used in the clinical treatment of tumors [51,52].

Nanoparticle-encapsulated Naringin for Enhanced Antitumor Applications

Naringin-loaded nanocarriers have demonstrated efficacy against cancer, inflammation, neurodegeneration, and various other diseases [86]. For instance, naringin-loaded solid lipid nanoparticles (NRG-SLNs) have been shown to effectively treat aflatoxin B1 (AFB1)-induced hepato-

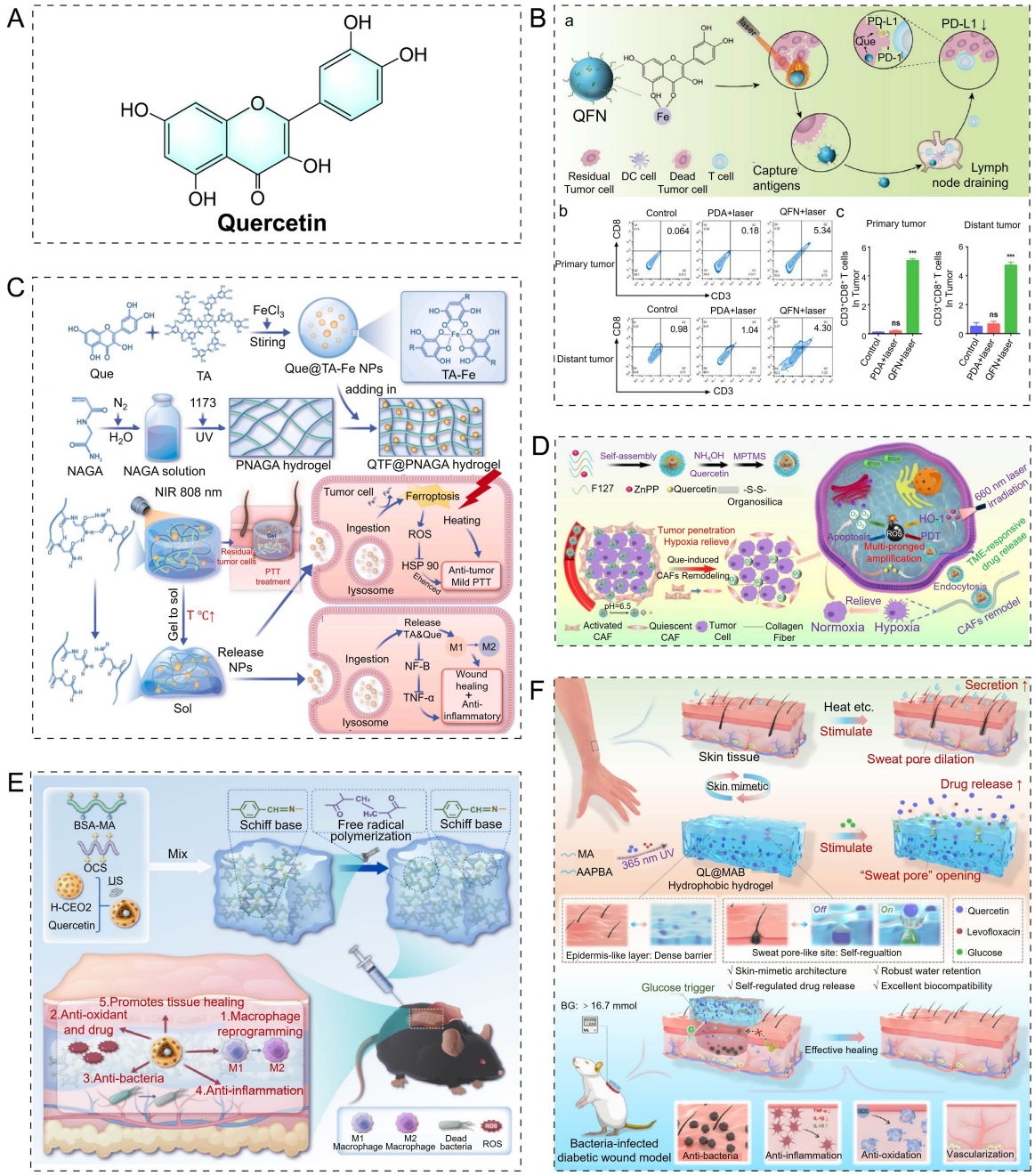

Fig. 5. Nanoscale drug-delivery systems loaded with quercetin for tumor treatment. (**A**) Structural formula of quercetin. (**B**) QFN can synergize with photothermal therapy to treat tumors. (**a**) Schematic diagram illustrating how QFN enhances photothermal and immunotherapeutic efficacy for antitumor effects. (**b–c**) Analysis of $CD8^+$ T cells in the primary tumor and the distant tumor at 10 days post laser irradiation. Adapted and reprinted from [67]. Copyright © 2022 Elsevier. (**C**) Schematic diagram of the preparation and therapeutic mechanism of Que@TA-Fe@PNAGA for the treatment of skin cancer. Adapted and reprinted from [75]. Copyright © 2025 Elsevier. (**D**) Schematic diagram of the preparation and therapeutic mechanism of ZnPP@FQOS for the treatment of fibroblast-rich tumors. Adapted and reprinted from [78]. Copyright © 2025 Springer Nature. (**E**) Schematic diagram of the preparation of HQu@BC hydrogel and its potential application in Subcutaneous of the flap. Adapted and reprinted from [81]. Copyright © 2024 Elsevier. (**F**) Schematic diagram of a dermatomimetic multitubular hydrophobic hydrogel (QL@MAB) for diabetic wound treatment. Adapted and reprinted from [82]. Copyright © 2025 Wiley-VCH Verlag GmbH.

cellular carcinoma (HCC). Specifically, NRG-SLNs promote apoptosis in HCC cells by upregulating caspase-3 expression and significantly reducing the levels of vascular endothelial growth factor-C (VEGF-C), thereby inhibiting HCC invasion and migration [87]. Additionally, Yang *et al*. [88] developed a novel naringin (NG)-loaded zinc oxide (ZnO)-3-carboxyphenylboronic acid (PBA) nanoparticle system immobilized on titanium substrates (Ti-ZnO-PBA-NG). Following osteosarcoma resection, naringin and Zn^{2+} were released from the functionalized titanium substrates under acidic conditions caused by bacterial infection or the Warburg effect in osteosarcoma. This release induced osteosarcoma cell apoptosis through the generation of ROS and activation of the ROS/ERK signaling pathway. Furthermore, ROS accumulation also inhibited bacterial growth. These findings suggest that Ti-ZnO-PBA-NG represents a promising nanocarrier for drug delivery, with potential applications in large bone repair and reconstruction after osteosarcoma resection (Fig. 6**B**).

Previous research has demonstrated that dextrin (Dx) serves as an excellent nanocarrier for naringin (Nar). A Nar-Dx-NCs nanocomplex was synthesized from dextrin using an emulsion cross-linking technique with glyoxal as the cross-linker. This nanocomplex significantly enhanced naringin's anticancer efficacy against lung cancer by reducing diethylnitrosamine (DEN)/2-acetylaminofluorene (2AAF)-induced lung carcinogenesis through multiple mechanisms, including the inhibition of oxidative stress and inflammation, induction of apoptosis, and suppression of tumor cell proliferation [89]. Additionally, Ge *et al*. [90] developed a metal-organic framework (MOF) as a nanocarrier to encapsulate naringin. They selected a non-toxic iron (III)-based MOF, MIL-101(Fe), to create the naringin@MIL-101 drug carrier. This carrier not only exhibited antimicrobial properties but also enhanced T-cell growth by stimulating IL-2 expression, which further aided in cancer cell destruction. The antimicrobial, anticancer, and immune-enhancing activities of naringin@MIL-101 render it a versatile therapeutic agent for cancer treatment and postoperative recovery.

Naringin can be combined with other drugs to enhance its anti-tumor activity. For instance, a nanoparticle encapsulating boswellic acid, curcumin, and naringin, produced via nanoprecipitation, has demonstrated anti-cancer potential by inhibiting the proliferation of human HepG2 cells [91]. Secerli *et al*. [92] developed nanoparticles composed of poly (methyl methacrylate) (PMMA) coated with either berberine or naringin, which proved effective for colon cancer treatment. These berberine or naringin-coated PMMA nanoparticles significantly induced apoptosis in colon cancer cells. Additionally, naringin-loaded nanoparticles can mitigate the side effects of chemotherapy drugs. Long-term chemotherapy with oxaliplatin is known to cause brain damage in cancer patients. To address this, naringin-loaded chitosan nanoparticles, prepared via an ionic gelation method, have been administered nasally to effectively alleviate chemotherapy-induced neurotoxicity. Naringin released from these nanoparticles exerts neuroprotective effects by modulating the cGAS/STING and HMGB1/RAGE/TLR2/MYD88 pathways. Thus, naringin-loaded chitosan nanoparticles hold promise as a therapeutic candidate for clinical trials in chemotherapy patients [93].

Naringin-loaded Hydrogels for Enhanced Antitumor Therapy

A pH/magnetic-sensitive hydrogel, composed of pineapple peel carboxymethyl cellulose (PCMC), regenerated nanofibrillated cellulose (rPPNc), and polyvinyl alcohol (PVA), and doped with Fe_3O_4, demonstrates efficient encapsulation and controlled release of naringin. This composite hydrogel represents a promising candidate for drug nano-delivery systems aimed at effective cancer treatment [94]. Additionally, a nanohybrid hydrogel incorporating zinc oxide nanoparticles (ZNPs) and naringin showed significant potential for skin cancer therapy. This system was synthesized by cross-linking L-cysteine (CYS)-modified chitosan (CH-CYS) with dialdehyde cellulose (DAC). The hydrogel exhibited notable antibacterial activity against Staphylococcus aureus and Trichophyton rubrum. Moreover, the cytotoxicity of naringin delivered by this nanohybrid hydrogel against A431 cancer cells was doubled compared to free naringin (Fig. 6**C**) [95].

Naringin Encapsulation in Nano-emulsions for Enhanced Antitumor Therapy

Said-Elbahr *et al*. [96]developed a translucent lipid-based nano-emulsion co-encapsulating naringin and celecoxib, constituting an innovative nebulized drug delivery system for lung cancer treatment. This nano-emulsion demonstrated enhanced targeting capabilities and significant cytotoxicity against lung cancer cell lines *in vitro*. However, the effectiveness of this novel nebulized delivery system in animal models of lung cancer remains to be confirmed. In a separate study, a nanostructured lipid carrier encapsulating naringin (NCNLC) was prepared using ultrasonic melt emulsification with coix seed oil (CSO) as the liquid lipid. The NCNLC exhibited excellent naringin release properties and effectively inhibited the proliferation while inducing apoptosis of HepG2 cells *in vitro*. Additionally, the combination of naringin with CSO upregulated the expression of IL-6 and IL-10 in hormonal mice. These findings suggest that NCNLC represents a promising platform for the effective co-delivery of therapeutic agents in tumor immunotherapy (Fig. 6**D**) [97].

Naringin-loaded Delivery Systems for Improved Wound Healing

Naringin has been shown to possess wound-healing properties [98], as evidenced by the development of polyvinylpyrrolidone (PVP) films loaded with naringin and

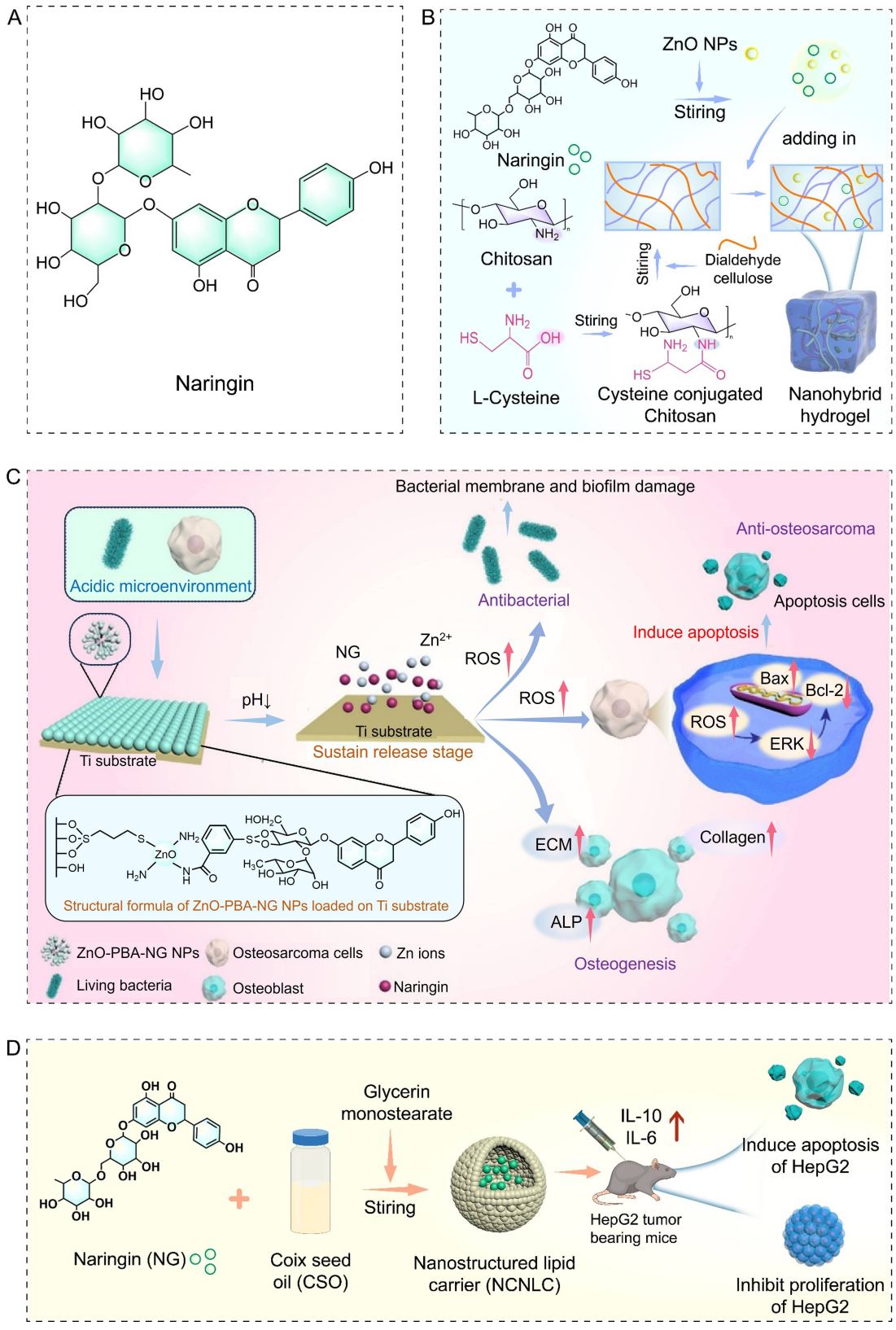

Fig. 6. Naringin-loaded hydrogels and nanoparticles for tumor treatment. (**A**) Chemical structure of naringin. (**B**) Schematic representation of the preparation and multifunctional properties of ZnO-PBA-NG nanoparticles, including antibacterial, apoptosis-inducing, and osteoblast proliferation-promoting activities. (**C**) Schematic diagram illustrating the preparation and drug release process of a nanohybrid hydrogel loaded with naringin and ZnO nanoparticles. (**D**) NCNLC carrier's capability to inhibit HepG2 cell proliferation, induce apoptosis, and enhance immunotherapy efficacy. This figure is edited by Adobe Illustrator 2023 and 3ds Max 2024.

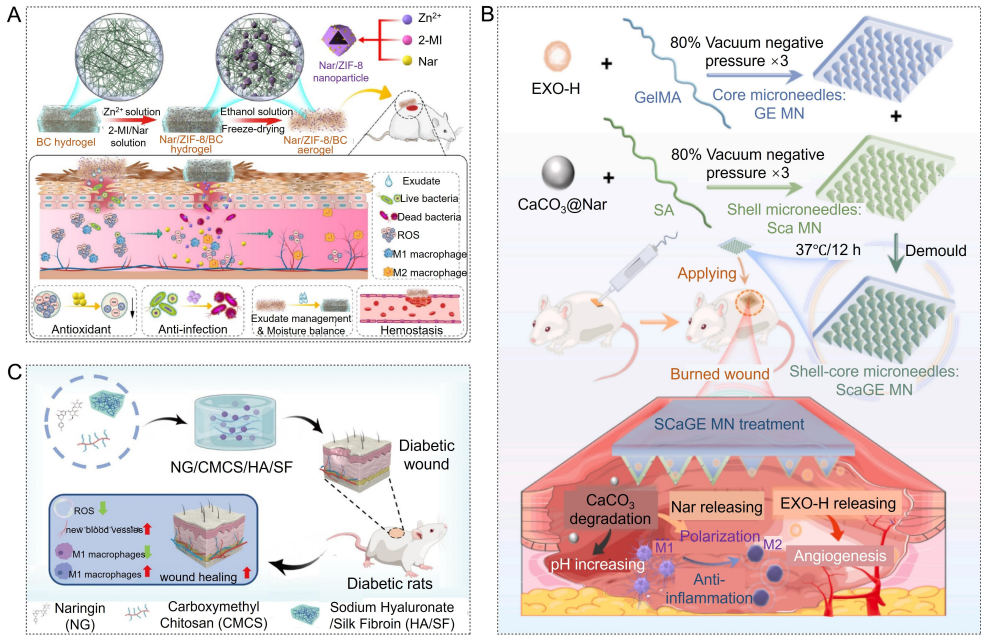

Fig. 7. Naringin-loaded hydrogels and microneedles for wound healing. (**A**) Nar/ZIF-8/BC sponges showed excellent antimicrobial, antioxidant, and anti-inflammatory properties, effectively promoting diabetic wound healing. Adapted and reprinted from [100]. Copyright © 2025 American Chemical Society. (**B**) $CaCO_3$@Nar microneedle could effectively treat burned skin healing by reducing local inflammation, removing excess reactive oxygen species, and enhancing angiogenic capacity. Adapted and reprinted from [101]. Copyright © 2024 Elsevier. (**C**) The NG/CMCS/HA/SF scaffold was effective in promoting diabetic wound healing by promoting angiogenesis and antioxidants. Adapted and reprinted from [102]. Copyright © 2024 Elsevier.

silver nanoparticles (AgNPs) via gamma-ray irradiation. These composite films exhibit pH-responsive properties, favorable drug release kinetics, and potent antibacterial activity against E. coli and S. aureus. Consequently, they demonstrate significant potential as advanced wound dressings for clinical skin regeneration [99]. In another study, a multifunctional sponge was fabricated by a zeolitic imidazolate framework-8/bacterial cellulose (ZIF-8/BC) matrix loaded with the Nar. This Nar/ZIF-8/BC sponge demonstrated excellent mechanical strength and antimicrobial efficacy. Notably, the pH-responsive properties of ZIF-8 enabled the sponge to release Nar in response to the microenvironment of diabetic foot ulcers (DFUs). Importantly, Nar exerted angiogenic promotion alongside antioxidant and anti-inflammatory effects, thereby accelerating infected wound regeneration in diabetic rat models (Fig. 7**A**) [100].

Chen *et al.* [101] developed a bilayer lamellar microneedle system. Its lower layer encapsulated hypoxia-inducible exosomes (EXO-H) from HUVECs within a gelatin methacrylate (GelMA) matrix, and the upper layer incorporated sodium alginate (SA) embedded with naringin-loaded $CaCO_3$ nanoparticles ($CaCO_3$@Nar). Upon application to thermal burn sites, $CaCO_3$@Nar degraded in the wound interstitial fluid, enabling sustained naringin release to counteract inflammation and oxidative stress. Meanwhile, the delivered EXO-H robustly enhanced HUVEC migration, proliferation, and angiogenesis, facilitating scarless tissue regeneration. This work establishes a multimodal therapeutic platform for clinical burn management (Fig. 7**B**). Separately, Yang *et al.* [102] engineered a multifunctional composite scaffold comprising naringin/carboxymethyl chitosan/sodium hyaluronate/silk fibroin (NG/CMCS/HA/SF). This scaffold exhibited potent anti-inflammatory, antioxidant, and pro-angiogenic activities. It effectively accelerated diabetic wound healing, demonstrating therapeutic outcomes with direct clinical relevance and highlighting its promise as a translatable strategy for managing chronic wounds (Fig. 7**C**).

Naringin, a dihydroflavonoid glycoside, offers a valuable model for studying flavonoid delivery systems due to its structural duality, comprising both a hydrophilic glycoside and a hydrophobic aglycone. This unique architecture underpins its utility in tumor-responsive delivery and chronic wound repair applications. Puerarin, an isoflavone C-glycoside, is characterized by a planar isoflavone backbone and a C8-glucose moiety, which confers notable phytoestrogenic activity. The design strategies for their respective delivery systems and the mechanisms for enhancing therapeutic efficacy are discussed in the following sections.

Antitumor Activity and Improved Wound Healing of Puerarin and Its Enhanced Efficacy Through Drug Delivery Systems

Puerarin ($C_{21}H_{20}O_9$, Fig. 8**A**), an isoflavone C-glycoside from *Pueraria lobata*, exhibits a planar

isoflavone backbone with 5/7-hydroxyls in the A-ring and a 4'-hydroxyl in the B-ring, coupled with a C8-glucose moiety [103]. This structural configuration enables it to bind estrogen receptors, thereby modulating STAT3 signaling and conferring cardiovascular, antitumor, and immunomodulatory effects. During nanonization, the glucose hydroxyls form hydrogen bonds with hydrophilic carriers, while the hydrophobic aglycone embeds into carrier cores, balancing hydrophilicity and hydrophobicity to optimize encapsulation and controlled-release performance. Puerarin demonstrates potent antioxidant, anti-inflammatory, antitumor, analgesic, cardiovascular protective, immunomodulatory, and neuroprotective activities [104]. Clinically, it has been utilized to treat various conditions, including cardiovascular and cerebrovascular diseases, osteoarthritis, cancer, Parkinson's disease, Alzheimer's disease, diabetes, and kidney disease [105]. Currently, *Pueraria Mirifica* isoflavone capsules are primarily used in the treatment of breast and endometrial cancers.

Puerarin-loaded Nanoparticles for Enhanced Antitumor Therapy

Puerarin-loaded nanoparticles have demonstrated significant therapeutic efficacy for diverse tumor types. Xu *et al*. [106]developed a novel puerarin nanoparticle formulation (nanoPue) to enhance its solubility and bioavailability. The mesenchymal microenvironment associated with nanoparticle treatment facilitated deeper penetration of nanoPue into tumor parenchyma, thereby enhancing the chemotherapeutic efficacy of nano-paclitaxel in a triple-negative breast cancer (TNBC) model. Furthermore, nanoPue treatment markedly improved the tumor immune microenvironment in TNBC models, increasing the therapeutic efficacy of α-PD-L1. In another study, puerarin-loaded sodium alginate microspheres demonstrated potent antitumor effects against colorectal cancer. These microspheres, prepared using the latex-endocoagulation method, significantly reduced inflammatory responses by downregulating pro-carcinogenic cytokines. Additionally, the microspheres induced epithelial-mesenchymal transition in colitis-associated colorectal cancer models, leading to reduced tumorigenesis and metastasis [107].

Puerarin can also be co-loaded with chemotherapeutic drugs in nanocarriers to enhance antitumor activity. For example, poly-puerarin nanoparticles (PPue-NPs), prepared via nanoprecipitation, were co-loaded with paclitaxel (PTX) to create an effective drug delivery platform (PPue@PTX NPs) for colon cancer treatment. PPue@PTX NPs exhibited rapid cellular uptake by CT26 cells and prolonged tumor retention *in vivo*, significantly enhancing their therapeutic potential. Additionally, they induced apoptosis in CT26 cells, as evidenced by H&E and TUNEL staining, indicating more serious tumor-cell damage compared to PBS and PPue NPs groups. Thus, PPue@PTX NP offered a promising platform for colon cancer therapy [108]. Another study found that nanoparticles co-loaded with puerarin (PRN) and 5-fluorouracil (5-FU) were effective against lung cancer. These nanoparticles (PRN-5FU NPs), composed of polyethylene glycol-polylactic acid (PEG-PLGA) and dioleylphosphatidylserine (DOPA), were prepared using an oil-water solvent evaporation technique, which improved the encapsulation efficiency of both drugs. PRN-5FU NPs significantly induced apoptosis in human lung carcinoma cells (HEL-299 and A549 cells) compared to either PRN NPs or 5-FU NPs alone, highlighting their potential as a dual-drug delivery system for lung cancer treatment [109].

Puerarin-loaded Hydrogels for Enhanced Antitumor Therapy

A self-assembled nanofiber hydrogel (CP@Au@DC_AC50), incorporating the gene-targeting drug DC_AC50 and puerarin, has shown potential for treating uveal melanoma via intraocular injection. This hydrogel system exhibited a synergistic response to low-intensity near-infrared (NIR) light, enabling PTT (Fig. 8**Ba**). The inclusion of gold nanorods enhanced the mechanical strength of the hydrogel, facilitating both PTT and a thermosensitive gel-to-sol phase transition in response to NIR light, which allowed for controlled release of DC_AC50 on demand (Fig. 8**Bb**). Histological analysis using H&E and Ki67 staining demonstrated that CP@Au@DC_AC50 effectively killed tumor cells without damaging surrounding healthy tissues, owing to the combined mild PTT and gene-targeted therapy (Fig. 8**Bc**). This NIR-triggered gene therapy/PTT/antimicrobial treatment platform offers a promising strategy for multifunctional therapy in intraocular tumors [110]. In another study, Liu *et al.* [50] developed a geraniol-based injectable hydrogel (Puerarin@PEGel) that responded to hydrogen peroxide (H_2O_2) for targeting solid tumors. This hydrogel, composed of poly (ethylene glycol) dimethacrylate (PEGDMA) and ferrous chloride ($FeCl_2$), formed within one minute when exposed to an optimal $H_2O_2/FeCl_2$ ratio, whereas no gelation occurred in the absence of H_2O_2 (Fig. 8**Ca**). Scanning electron microscopy (SEM) revealed a porous network structure in both PEGel and Puerarin@PEG gel (Fig. 8**Cb**). The hydrogel enhanced tumor infiltration and the efficacy of epidermal growth factor receptor (HER1)-targeted HER1-CAR-NK cells after intravenous administration. As a result, Puerarin@PEGel significantly improved tumor suppression in HER1-overexpressing MDA-MB-468 and NCI-H23 xenograft mouse models, with minimal side effects (Fig. 8**Cc**). It also reversed tumor hypoxia and immunosuppression, enhancing the therapeutic potential of HER1-CAR-NK cells by promoting tumor vasculature normalization.

Improvement of Wound Healing of Puerarin-loaded Drug Delivery System

Accumulating evidence has established the significant role of puerarin in enhancing tissue repair processes [111–113]. For diabetic wound management, Wan *et al.* [114] developed an injectable hyaluronic acid–silanol hydrogel (AP@HA-Si InjGel) loaded with arginine and puerarin. This hydrogel possesses favorable biocompatibility and antioxidant properties, effectively modulating macrophage polarization toward the pro-healing M2 phenotype. By accelerating wound closure and promoting both collagen deposition and neovascularization, this system significantly enhances diabetic wound healing, offering a comprehensive and promising therapeutic strategy for managing chronic diabetic ulcers.

Recent investigation demonstrated that puerarin self-assembled into a nanofibrous architecture interpenetrating with Ga^{3+}-coordinated silk fibroin networks through electrostatic-driven supramolecular organization. The resulting hydrogel exhibited excellent mechanical strength, biocompatibility, and bacteriostatic effect. Mechanistically, the controlled release of Ga^{3+} ions synergized with puerarin to confer dual hemostatic potency and antioxidant properties, thereby facilitating wound healing. This integrated therapeutic system establishes a novel biomaterial paradigm for clinical management of infected chronic wounds (Fig. 8**D**) [115]. A previous study reported a ROS-responsive hydrogel consisting of silk fibroin methacrylate (SFMA), modified collagen type III (rCol3MA), and lipid nanoparticles (LNPs). This hydrogel enabled sustained release of antimicrobial peptides (AMP) and puerarin (PUE), demonstrating potent bactericidal activity alongside coordinated regulation of inflammatory cascades and vascular homeostasis, highlighting its significant value in diabetic wound repair [116]. In addition, Chen *et al.* [117] accelerated the self-assembly of chitosan (CS) and puerarin (PUE) by introducing mechanical forces to form CS@PUE(C@P) hydrogels. The synergistic antimicrobial and immunomodulatory properties of C@P hydrogel effectively eradicated skin wound bacteria and reduced inflammation, ensuring anti-infective effects and promoting wound healing (Fig. 8**E**).

The delivery systems for puerarin are designed to overcome its inherent poor lipid membrane permeability, a challenge addressed by its balanced molecular structure featuring both a hydrophilic C-glycoside and a hydrophobic aglycone moiety. This structural characteristic enables its effective application in diverse areas such as antitumor combination therapy and diabetic wound healing. Rutin, classified as a flavonol glycoside, exhibits a complex molecular architecture that confers a broad spectrum of biological activities, including antioxidant, antitumor, and anti-Alzheimer's disease properties. The advanced delivery strategies developed for rutin will be elaborated in the following section.

Rutin and Its Enhanced Antitumor and Treatment of Alzheimer's Disease Activity Through Advanced Delivery Systems

Rutin ($C_{27}H_{30}O_{16}$, Fig. 9**A**), a flavonol glycoside found in *Ruta graveolens*, *Ginkgo biloba*, and *Bupleurum chinense*, contains hydroxyl groups in the A/B/C-rings and a 3-linked rutinose moiety [118]. Specifically, the B-ring 3',4'-ortho-dihydroxyls exhibit ROS scavenging activity and inhibit Aβ fibrillogenesis, while the C-ring 3-hydroxy-4-keto group binds to GLUT and ULK1, mediating tumor targeting and autophagy. During nanonization, the hydroxyl groups form hydrogen bonds with carriers, and the hydrophobic backbones embed into carrier cores. The steric hindrance caused by the rutinose moiety is mitigated through carrier design, enhancing nanonization compatibility. Extensive Studies have shown that rutin exhibits antioxidant [119], antiallergic, antiviral, antitumor, anti-inflammatory, and metabolism-boosting properties [120]. Additionally, rutin shows promise in treating conditions such as Alzheimer's disease [121], anxiety disorders [122], and various cancers. Rutin has been found to inhibit the growth of several cancer types, including breast, liver, lung, and colorectal cancers [123]. Its antitumor mechanisms involve inhibiting cell proliferation, inducing apoptosis or autophagy, and preventing angiogenesis and metastasis [124]. Clinically, a rutin-based oral solution, Xia Ku Cao, also known as Prunella vulgaris L. [125], has been used for thyroid tumor treatment.

Nanoparticle-loaded Rutin for Enhanced Antitumor Applications

Free rutin is rapidly absorbed by the human body but is primarily metabolized and broken down by the liver, leading to limited antitumor efficacy. To address this issue, Pandian *et al.* [126] developed solid lipid nanoparticles (SLNs) encapsulating rutin using oil-in-water microemulsion technology. The encapsulated rutin showed enhanced release from SLNs under acidic conditions (pH 5.5), enabling them to penetrate the blood-brain barrier and effectively target brain tumors. However, further *in vivo* animal studies are needed to fully evaluate the risks and benefits of SLN-based delivery systems. Additionally, chitosan nanoparticles (rCNPs) synthesized via ionic gelation and loaded with rutin have been shown to be effective against liver cancer. The antitumor activity of rCNPs is linked to the activation of Unc-51-like autophagy-activated kinase (ULK1)-mediated autophagy and nuclear factor-κB (NF-κB) signaling in Hep3B cells [127].

Beyond its role as a ligand for glucose transporter proteins (GLUTs), which are overexpressed in various malignancies, rutin can also exhibit photothermal effects upon chelation with metal ions. A previous study demonstrated the efficacy of rutin-coated ultrasmall manganese oxide nanoparticles (Ru/MnO_2 NPs) in treating hepatocellular carcinoma. Ru/MnO_2 NPs enabled precise magnetic reso-

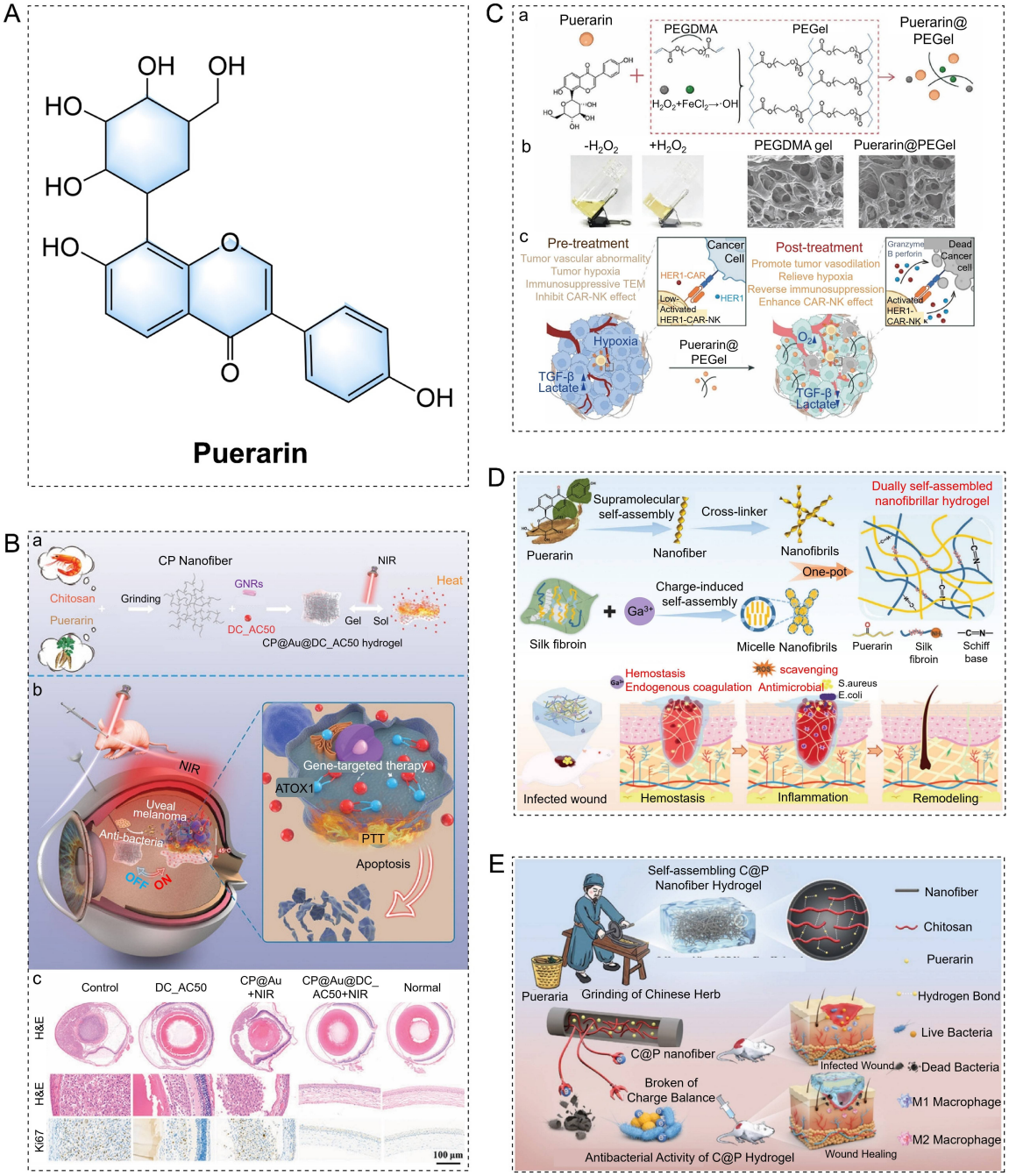

Fig. 8. Nanoscale puerarin-loaded drug delivery systems for tumor treatment. (**A**) Chemical structure of puerarin. (**B**) CP@Au@DC_AC50 for melanoma treatment. (**a**) Schematic diagram of CP@Au@DC_AC50 preparation; (**b**) Mechanism of action for CP@Au@DC_AC50; (**c**) Inhibition of melanoma UM cell proliferation by CP@Au@DC_AC50 combined with NIR light, as shown by H&E and Ki67 staining. Adapted and reprinted from [110]. Copyright © 2021 Wiley-VCH Verlag GmbH. (**C**) Puerarin@PEGel for immunotherapy enhancement: (**a**) Preparation process of Puerarin@PEGel; (**b**) Macro- and micro-appearance of Puerarin@PEGel hydrogel; (**c**) Mechanism of action for Puerarin@PEGel hydrogel in tumor therapy. Adapted and reprinted from [50]. Copyright © 2024 Wiley-VCH Verlag GmbH. (**D**) Schematic illustration of the preparation of nanofibrillar hydrogel and the promotion of the healing mechanism of infected wounds. Adapted and reprinted from [115]. Copyright © 2024 Wiley-VCH Verlag GmbH. (**E**) Schematic diagram of the preparation process and the promotion of wound healing of C@P hydrogel. Adapted and reprinted from [117]. Copyright © 2022 Wiley-VCH Verlag GmbH.

nance imaging (MRI) and tumor ablation in H22 hepatocellular carcinoma models, owing to their excellent biocompatibility, stability, photothermal efficiency, and tumor-targeting properties (Fig. 9**B**) [128]. Additionally, Paudel *et al*. [129] developed liquid crystal nanoparticles (LCNs) encapsulating rutin, which effectively induced apoptosis and inhibited the proliferation and metastasis of NSCLC cells. Furthermore, a novel nanoparticle formulation co-encapsulating rutin and quercetin has been reported. This system effectively penetrated tumor cells, releasing both flavonoids and mediating antitumor effects by inhibiting cell proliferation, inducing apoptosis or autophagy, and suppressing angiogenesis and metastasis [67].

Hydrogel-based Rutin Delivery for Enhanced Antitumor Therapy

A novel rutin-loaded nanogel has been developed as a potential therapeutic approach for HCC. The chitosan/poly (acrylic acid) nanogels (CANs) were synthesized using radiation, with rutin being loaded onto the CANs via hydrogen bonding. Rutin-loaded CANs induced apoptosis in HCC cells by upregulating the expression of pro-apoptotic proteins Caspase 3 and Bax, while downregulating the expression of the anti-apoptotic protein Bcl-2. The biological activities of rutin-loaded CANs, including anti-proliferative, anti-angiogenic, and pro-apoptotic effects, were significantly enhanced compared to free rutin [130]. Additionally, a hydrogel based on polyvinyl alcohol (PVA) and dialdehyde cellulose (DAC), loaded with anticancer drugs, demonstrated a promising therapeutic effect against lung cancer. In this study, three drugs (ibuprofen, rutin, and phenanthriplatin) were incorporated into the PVA/DAC hydrogel to evaluate their inhibitory effects on A549 lung cancer cells. The results indicated that phenanthriplatin had the best release profile from the hydrogel, making PVA/DAC more effective for antitumor therapy [131].

Other Strategies for Rutin-loaded Nanodrug Delivery Systems

Rutin can be incorporated into nanocarriers through various methods to enhance its antitumor effects. Li *et al*. [132] developed pH-responsive astragalus polysaccharide-based (ACR) micelles for the targeted delivery of rutin. Rutin was conjugated with carboxyphenylboronic acid (CPBA) via EDC/NHS coupling and subsequently esterified with astragalus polysaccharide. These ACR micelles facilitate stimuli-responsive drug release within the acidic tumor microenvironment, effectively inhibiting matrix metalloproteinases and downregulating PD-L1 expression. By remodeling the immunosuppressive landscape, this synergistic strategy significantly bolsters anti-melanoma immunotherapy, offering a robust platform for delivering TCM-derived active components. In another study, a novel fibrous material loaded with quercetin and rutin was designed for local cervical tumor therapy and wound dressing. The material was prepared through co-electrospinning and bi-electrospinning using cellulose acetate (CA), water-soluble polyether, and polyethylene glycol (PEG). The rutin-containing fibers exhibited strong antioxidant activity and induced apoptosis in HeLa cells, showing potent cytotoxicity [133].

In addition, a Fe (III)-RH/PVP nanoprobe, loaded with rutin and Fe^{3+}, was developed for use with NIR light to enhance antitumor effects (Fig. 9**C**). This ultrasmall nanoprobe was intravenously injected and actively targeted tumor cells. Upon uptake, the nanoprobe released rutin and Fe^{3+}, which activated peroxidase enzymes, generating free radicals and oxygen to induce ferroptosis and apoptosis in tumor cells [134]. Furthermore, Zhang *et al*. [135] developed a GLUT1-targeted polymetallic coordination nanopolymer (RCPM), utilizing rutin as a multifunctional skeleton to chelate Fe, V, and Pt ions. RCPM could significantly reverse chemoresistance by triggering Fenton reaction-mediated ferroptosis and downregulating ERCC1, GSH, and ATP to impair DNA repair and cisplatin inactivation. Furthermore, its favorable photothermal performance and rapid renal clearance ensure excellent biosafety, representing a promising rutin-integrated multimodal platform to combat lung cancer. Lu *et al*. [136] engineered a hierarchical nanoarchitecture (Ru/CCDs-PTX@ZIF) through coordination-driven integration of carbon quantum dots (CCDs) within ZIF-8 frameworks, co-encapsulating paclitaxel and rutin. Leveraging GLUT receptor-mediated endocytosis, the CCDs-based single-atom nanoenzymes released from Ru/CCDs-PTX@ZIF demonstrated superior POD activity. The phenolic hydroxyl moieties on CCDs enabled the reduction of Fe^{3+} to Fe^{2+}, which subsequently initiated Fenton chemistry to produce abundant hydroxyl radicals, inducing a free-radical-dependent cell cycle blockade. Besides, Ru/CCDs-PTX@ZIF nanocomposite orchestrated tumor-specific cytotoxicity and migration inhibition (Fig. 9**D**).

Treatment of Alzheimer's Disease of Rutin-loaded Drug Delivery System

Accumulating evidence underscores the potential of rutin as a multifactorial therapeutic agent for Alzheimer's disease (AD), primarily by suppressing amyloid-β (Aβ) fibrillogenesis and mitigating neuroinflammatory pathways [121,137]. To harness this potential, Ouyang *et al*. [138] engineered a DNA nanoflower (DF)-based delivery system (Rutin@DF-miR-124/RVG29) designed for the cerebral restoration of miR-124, a microRNA deficient in AD pathogenesis. Rutin was co-encapsulated within the DFs via intercalation into double-stranded DNA, while RVG29 peptide functionalization conferred BBB-penetrating ability and neuronal targeting. This design enabled a synergistic action where rutin and miR-124 jointly inhibited Aβ production, offering an effective therapeutic strategy for AD (Fig. 9**E**). Furthermore, innovative nanomedicines

employing dual-targeted layered double hydroxide (LDH) nanoparticles were developed. These nanoparticles facilitated the co-delivery of rutin with siRNAs against key AD-related enzymes (BACE1 or GSK3β). In P301S transgenic AD mice, this combinatorial regimen potently inhibited Aβ aggregation, modulated glial cell function to alleviate neuroinflammation, and synergistically rescued memory and cognitive impairments, presenting a novel paradigm for confronting the multifactorial complexity of AD (Fig. 9**F**) [139].

Research on rutin underscores the significance of "structure-targeted delivery" for flavonoid glycosides, enabling effective tumor and neuroprotective delivery (e.g., blood-brain barrier penetration). Icariin, characterized by an 8-isopentenyl group and multiple hydroxyl substitutions, demonstrates enhanced lipophilicity and membrane permeability, alongside osteochondral repair and antitumor activities. The development of targeted delivery systems for Icariin is discussed below.

Antitumor Potential and Osteochondral Repair of Icariin Enhanced by Targeted Delivery Systems

Icariin ($C_{33}H_{40}O_{15}$, Fig. 10**A**), an 8-isopentenyl flavonoid glycoside derived from *Epimedium*, contains hydroxyl groups in the A/B/C-rings, an 8-isopentenyl group in the A-ring, and a 7-linked glucose-rhamnose moiety [140]. The 8-isopentenyl group contributes to enhanced lipophilicity and membrane permeability. The hydroxyl groups on the B/C-ring are implicated in promoting osteogenic differentiation and inducing apoptosis. During nanonization, the 7-glycoside hydroxyls form hydrogen bonds with hydrophilic carriers, whereas the isopentenyl and aromatic moieties embed into hydrophobic carrier phases. Furthermore, the multiple hydroxyl groups enable metal ionresponsive release properties, thereby improving the overall efficiency of nanonization. Icariin has been shown to enhance cardiovascular and cerebrovascular blood flow, promote hematopoietic function, and improve immune function and bone metabolism. Additionally, it exhibits kidney-tonifying, aphrodisiac, anti-aging, and antitumor properties [141]. Numerous studies have demonstrated its effectiveness in tumor prevention and treatment [142–144]. Icariin-based medications, such as Weidakang Oral Liquid, Shengbai Oral Liquid, and Icariin Soft Capsules, are currently used in clinical antitumor therapies.

Nanoparticle-loaded Icariin for Enhanced Antitumor Therapy

A novel biomimetic nanoparticle system, icariin-loaded red blood cell membrane nanoparticles (iRINPs), was developed by incorporating red blood cell membranes (RBCMs) functionalized with the tumor-penetrating peptide iRGD (cRGDKGPDC). The iRINPs enhanced both the solubility and tumor penetration of icariin. Annexin-V-FITC/PI assay results showed that iRINPs significantly induced apoptosis in A549 cells. Furthermore, the iRGD peptide notably improved the targeting ability of iRINPs toward A549 cells. iRINPs exerted antitumor effects by inhibiting the migration, proliferation, and invasion of A549 cells, while also inducing apoptosis. As a result, iRINPs hold potential for precise lung cancer treatment [145]. In another study, Gao *et al.* [146] developed a novel microsphere, ICT-CMC-CD59sp, using carboxymethyl chitosan (CMC) and a cell differentiation antigen 59-specific ligand peptide (CD59sp) via an emulsion cross-linking method. Icariin (ICT) was encapsulated within the microspheres, which delivered the drug into cells through receptor-mediated endocytosis. Guided by CD59sp, ICT-CMC-CD59sp specifically targeted oral squamous cell carcinoma (OSCC) cells, activating the complement system to form a membrane attack complex, leading to OSCC tumor cell lysis. Additionally, ICT-CMC-CD59sp activated the caspase protease family, inducing apoptosis in OSCC cells.

Other Strategies for Icariin-loaded Nanodrug Delivery Systems in Antitumor Therapy

Conventional surgical resection of osteosarcoma often leaves residual tumor cells, leading to metastasis and bone tissue defects. To address this, Liu *et al.* [147] developed a novel coaxial fibrous membrane made of gelatin and poly (lactic acid) (PLA), with a shell layer containing adriamycin-loaded hydroxyapatite nanoparticles (DOX@nHAp) and a core layer of icariin. This fibrous membrane not only promoted osteogenic mineralization but also inhibited cancer cell proliferation. It showed good compatibility with mouse embryonic osteoblast precursor cells and strong inhibitory effects on human osteosarcoma cells. Thus, the dual drug-loaded nHAp/gelatin/PLA membranes with controlled release of DOX and icariin present a promising solution for osteosarcoma postoperative repair, combining anticancer and bone regeneration properties (Fig. 10**B**). Xiong *et al.* [148] developed porous PLGA microspheres for the inhalable co-delivery of icariin and miR-23b to treat metastatic lung cancer. Optimized for lung deposition and retention via appropriate aerodynamic diameters and sustained release, these biocompatible microspheres effectively suppress tumor progression and pulmonary metastasis. Their therapeutic efficacy is driven by the induction of apoptosis and G1-phase arrest, alongside the inhibition of cancer cell proliferation, migration, and invasion, highlighting the system's potential as a safe platform for localized chemo-gene combination therapy. CD44, a receptor overexpressed in many solid tumors, plays a critical role in tumor growth, while biotin (Bio) receptors are highly expressed in various malignancies due to the increased need for proliferation. A self-assembled nanomicelle (Bio-oHA-Hyd-FA) targeting multiple tumor cell receptors was developed, loaded with both icariin and curcumin. The micelle was formed using oligomeric hyaluronic acid (oHA), folic acid (FA), and Bio,

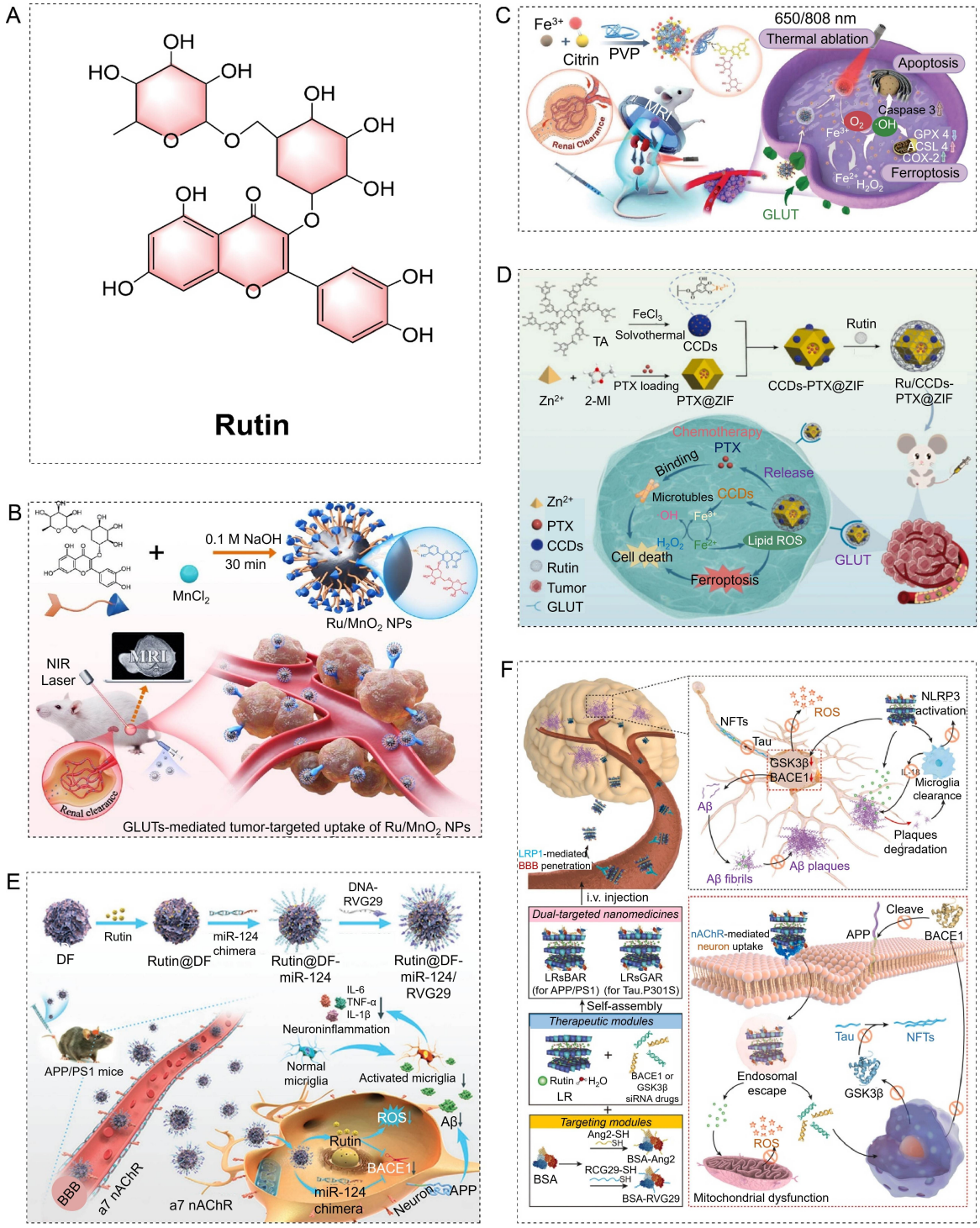

Fig. 9. Rutin-loaded nanoscale drug delivery systems for tumor treatment. (**A**) Chemical structure of rutin. (**B**) Schematic diagram of Ru/MnO_2 NP preparation and GLUT-mediated tumor targeting in hepatocellular carcinoma. Adapted and reprinted from [128]. Copyright © 2024 Elsevier. (**C**) Fe (III)-RH/PVP nanoprobes with NIR light for antitumor therapy. Rutin and Fe^{3+} release from Fe (III)-RH/PVP nanoprobes activate peroxidase, generating free radicals and oxygen, resulting in significant tumor growth inhibition in mice. Adapted and reprinted from [134]. Copyright © 2022 Wiley-VCH Verlag GmbH. (**D**) Ru/CCDs-PTX@ZIF effectively inhibited breast tumor development by inducing cell cycle arrest, targeted killing, and inhibiting migration in breast cancer cells. Adapted and reprinted from [136]. Copyright © 2024 Elsevier. (**E**) Rutin@DF-miR-124/RVG29 could cross the blood-brain barrier and effectively inhibit the production of amyloid β in neurons for the treatment of Alzheimer's disease. Adapted and reprinted from [138]. Copyright © 2022 Wiley-VCH Verlag GmbH. (**F**) Schematic diagram of the mechanism of LRsAR nanomedicine therapy for Alzheimer's disease. Adapted and reprinted from [139]. Copyright © 2023 Elsevier.

stabilized by a hydrazone bond (Hyd) between FA and HA. The Bio-oHA-Hyd-FA nanomicelle was pH-responsive, releasing higher concentrations of icariin and curcumin in acidic conditions typical of tumors. Importantly, it effectively inhibited tumor cell growth and invasion by binding to the FA/HA/Bio receptors on the tumor cell surface, making it a promising multi-targeted, pH-sensitive nanomicelle for tumor therapy (Fig. 10**C**) [149].

Repairment of Osteochondral Damage of the Icariin-loaded Drug Delivery System

Icariin (ICA) demonstrates potent osteoregenerative efficacy in bone defect repair [150,151]. Li *et al*. [152] developed a sophisticated photopolymerizable composite hydrogel. The hydrogel was engineered through the synthesis of gelatin methacryloyl (GelMA) integrated with interleukin-10 (IL-10)-functionalized heparin-modified hyaluronic acid (HA). Icariin was delivered via poly(dl-lactide-co-glycolide) (PLGA)-HA nanoparticles loaded into this matrix. This design enabled the sustained release of ICA, which potently triggered osteogenic differentiation of bone marrow mesenchymal stem cells (BMSCs). Remarkably, in a rat model of severe cranial bone defects, the co-delivery of IL-10 and ICA from the composite hydrogel demonstrated a synergistic enhancement of bone remodeling (Fig. 10**D**).

Osteoarthritis (OA) is currently one of the most common chronic disabling diseases worldwide. To address this challenge, a mussel-inspired multifunctional hydrogel system was engineered. This system integrated chitosan, β-glycerophosphate disodium salt hydrate (β-GP), and dialdehyde-functionalized polyethylene glycol (DF-PEG) to encapsulate bone marrow mesenchymal stem cell (BMSC)-derived exosomes (Exos), which were pre-loaded with epimedium glycosides (Fig. 10**Ea–b**). SEM revealed that the hydrogel possessed a reticulated porous internal structure (Fig. 10**Ec**). Furthermore, the multifunctional hydrogel exhibited thermosensitivity (Fig. 10**Ed**), self-healing capacity, and adhesive properties, enabling its retention within the joint cavity post-injection. Within this system, ICA stimulated chondrocyte proliferation and migration, thereby facilitating cartilage regeneration in osteoarthritis therapy [153].

In another study, a temperature-responsive bone restorative scaffold (PTG/PHA) was successfully fabricated. This scaffold was constructed from a shape memory terpolymer poly (lactic acid)-trimethylene carbonate-hydroxyacetic acid (PLAG-TMC-GA) and a composite of dopamine-modified nanohydroxyapatite (PHA), which collectively enhanced its biocompatibility, hydrophilicity, and mechanical strength. Besides, a sodium alginate (SA) hydrogel loaded with Icariin was encapsulated onto the scaffold surface. This design aimed to promote osteoblast growth and differentiation through the synergistic interaction between the drug and the scaffold matrix. Both *in vivo* and *in vitro* experiments showed that this icariin-composite scaffold synergy could significantly enhance the repair of bone defects [154]. Wu *et al*. [155] fabricated ICA prodrug-like microspheres (ICA@GM) using ICA coupled to gelatin methacryloyl via a microfluidic system. Monocyte-targeted IL-4 mRNA-LNPs were subsequently engineered and incorporated into the injectable microspheres (mRNA-ICA@GM) by electrostatic and hydrogen bonding interactions. Upon implantation into bone defects, the mRNA-ICA@GM system not only reversed the local inflammatory milieu but also inhibited the formation of monocyte-derived osteoclasts, thereby accelerating bone repair. This combinatorial delivery system proposes a promising therapeutic strategy for bone repair.

Summary and Prospects

In recent years, the incidence and mortality rates of cancer have exhibited a sustained upward trend, engendering heightened public concern regarding health issues. This has concomitantly spurred increased investments in fundamental research and clinical applications aimed at tumor prevention and treatment. However, the intricate mechanisms governing tumor development and drug resistance pose substantial challenges to the development of novel therapeutic agents. Conventional cancer treatment modalities, including surgery, radiotherapy, and chemotherapy, are still plagued by high rates of recurrence and substantial side effects. Thus, there is a critical need for the development of anti-tumor drugs that offer high targeting efficacy, minimal side effects, reduced non-specific toxicity, and enhanced safety profiles.

Chinese herbal medicine has demonstrated substantial contributions to human health by providing therapeutic benefits characterized by minimal or low toxicity, effective tumor cell cytotoxicity, and enhancement of overall immune function. Within the diverse components of TCM, some flavonoids with well-defined molecular structures have emerged as promising candidates for anti-tumor therapy. These bioactive compounds exhibit multifaceted mechanisms, including inhibition of tumor cell proliferation, induction of apoptosis and autophagy, and suppression of angiogenesis and cell migration (Fig. 11). Notably, several flavonoids, such as quercetin, icariin, rutin, puerarin, and naringin, have been clinically applied in the treatment of various cancers, including breast, lung, liver, colorectal, thyroid, esophageal, and gastric cancers [44,47,49–52].

Currently, nano-drug delivery systems hold significant promise in tumor therapy. Research has shown that metallic nanoparticles loaded with therapeutic agents can be effectively integrated with photothermal therapy, targeted drug delivery, sensing, and imaging, thereby emerging as pivotal tools in cancer treatment [16]. Additionally, surface-engineered nanoparticles have been shown to modulate immune activity and selectively target various immune cells, consequently enhancing the tumor-specific

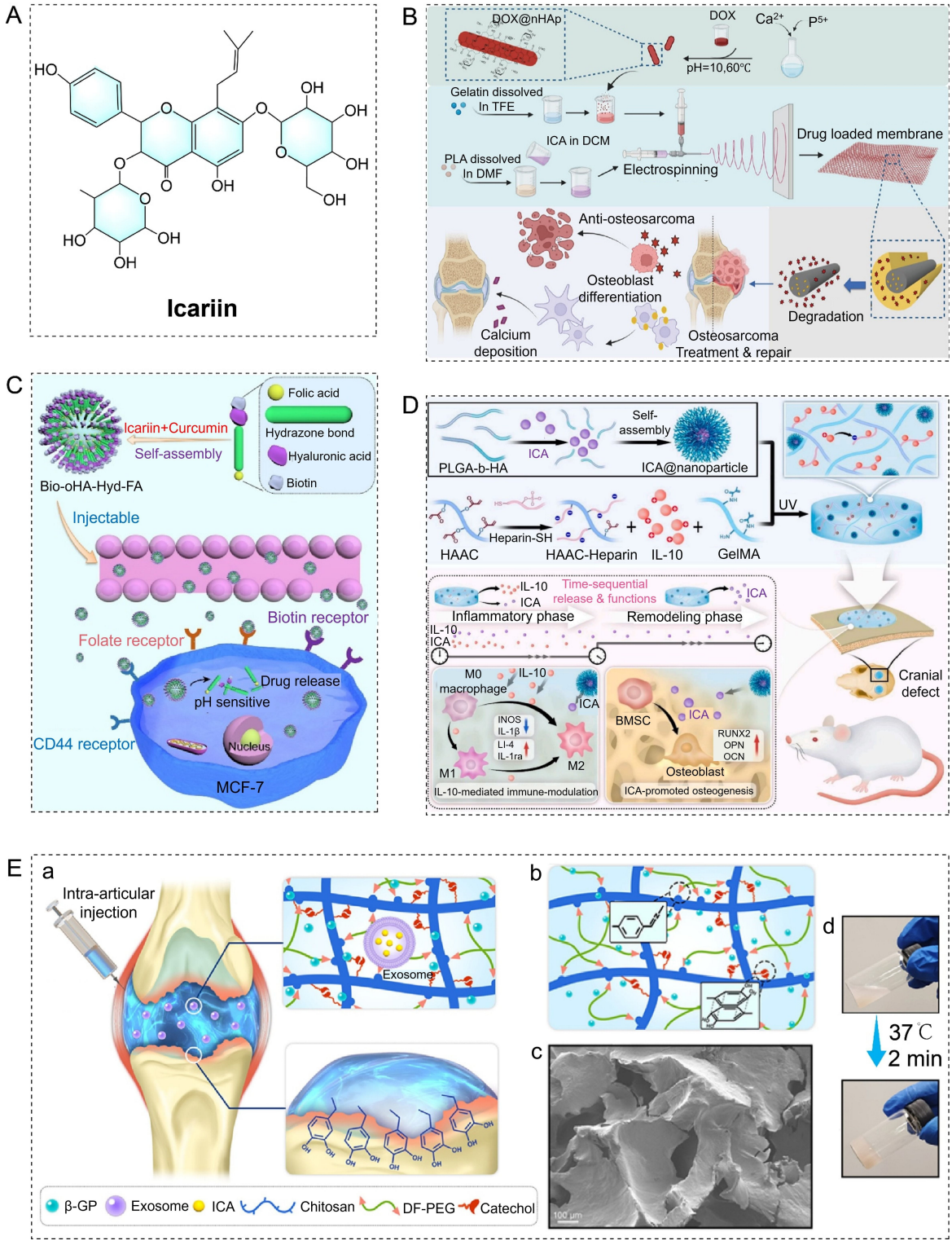

Fig. 10. Nanoscale drug-carrying system loaded with icariin for tumor treatment. (**A**) Chemical structure of icariin. (**B**) Gelatin/poly (lactic acid) coaxial fiber membrane coated with icariin and Adriamycin promoted osteogenic mineralization and inhibited proliferation of human osteosarcoma cells. Adapted and reprinted from [147]. Copyright © 2023 Elsevier. (**C**) The anti-tumor mechanism of Bio-oHA-Hyd-FA nanomicelle. This figure is edited by Adobe Illustrator 2023 and 3ds Max 2024. (**D**) Hydrogel coated with ICA-PLGA-HA nanoparticles could effectively repair bone defects. Adapted and reprinted from [152]. Copyright © 2024 Elsevier. (**E**) Schematic diagram of characterization and mechanism of ICA@Exos loaded hydrogel for the treatment of OA. (**a**) Schematic of ICA@Exos-loaded hydrogel system for the cartilage repair and regeneration in OA treatment; (**b**) The structural schematic diagram of hydrogels; (**c**) The SEM images of internal structure of hydrogels; (**d**) The temperature sensitivity of hydrogels. Adapted and reprinted from [153]. Copyright © 2023 Elsevier.

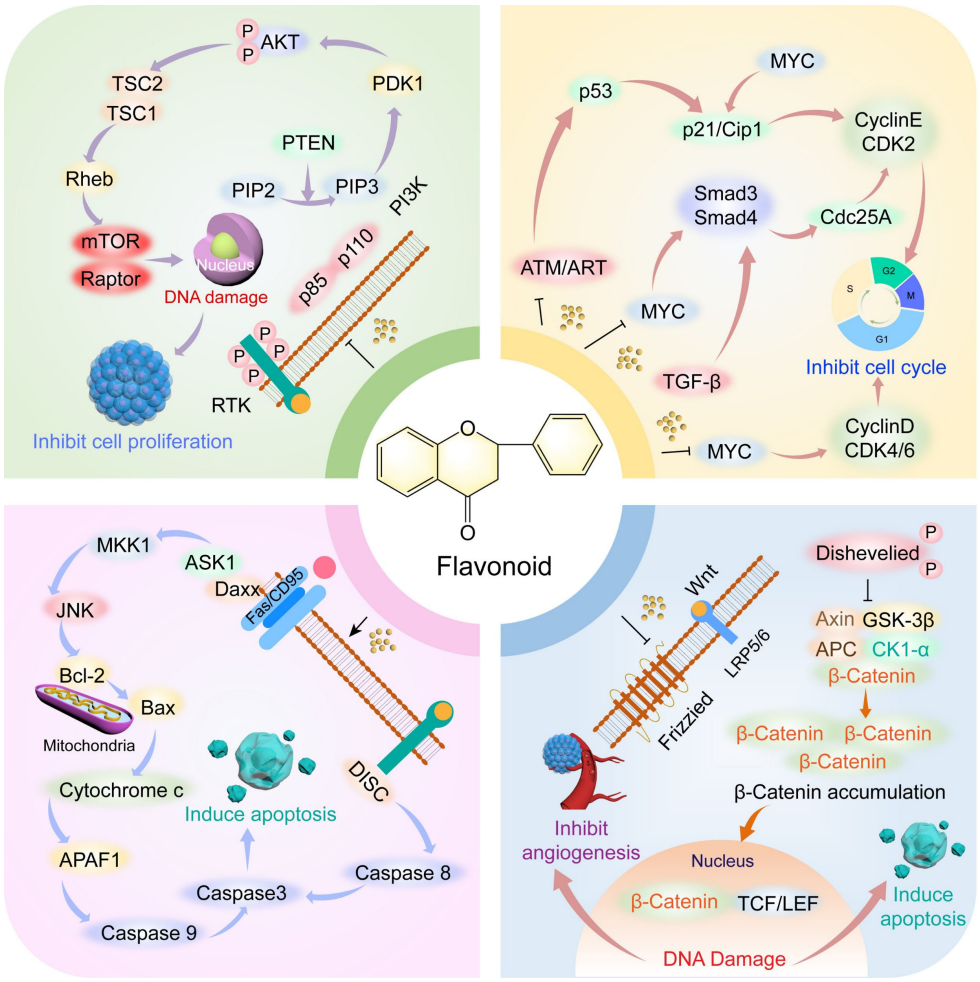

Fig. 11. Schematic diagram illustrating the anti-tumor molecular mechanisms of flavonoids. This figure is edited by Adobe Illustrator 2023 and 3ds Max 2024.

immune response and improving outcomes in cancer immunotherapy [156]. Additionally, nanoscale drug carriers confer significant advantages, including protection against drug degradation, efficient intracellular delivery, and controlled sustained release profiles, all of which contribute to enhanced therapeutic efficacy [157].

Beyond their well-documented efficacy in oncology, flavonoids exhibit pleiotropic therapeutic effects across multiple pathological conditions. These include promoting wound healing through extracellular matrix remodeling, repairing osteochondral defects via osteochondrogenic differentiation potentiation, and synergistically modulating neurodegenerative/metabolic/cardiocerebrovascular diseases by targeted mechanisms such as Aβ clearance enhancement, insulin signaling potentiation, and endothelial nitric oxide synthase activation [158–160].

The development of novel drug delivery systems that combine flavonoid components with nanotechnology holds promise for overcoming the limitations inherent to free drug administration. In this study, we systematically review five clinically relevant flavonoids, elucidating their anti-tumor mechanisms and exploring their applications within nano-delivery platforms for the treatment of tumors and other prevalent diseases (Table 2). Innovative delivery modalities, such as nanoparticles and hydrogel systems, facilitate sustained release of flavonoid therapeutics and enable precise targeting of tumor sites or defective lesions, offering efficient, safe, and targeted therapeutic strategies for disease management [161–163].

Quercetin, naringin, puerarin, rutin, and icariin serve as foundational molecules for cancer multimorbidity management due to their ability to modulate overlapping pathological pathways across cancer, metabolic disorders, cardiovascular diseases, neurodegeneration, and tissue repair. Collectively, their polypharmacological activity addresses comorbidities, such as post-surgical wounds and metabolic dysfunction [162], that complicate cancer care. Nano-delivery systems amplify this therapeutic potential via "one-system-multiple-targets" strategies, thereby overcoming the limitations of free flavonoids (poor solubility and rapid metabolism) to enable co-delivery to tumors and comorbid lesions (e.g., chronic wounds [167]) and synergistic regulation of shared pathways (e.g., ROS homeostasis [168]).

Table 2. Comparative summary of representative flavonoids and their antitumor nanocarrier delivery systems.

Flavonoid	Carrier types	Diseases	Routes of administration	Key mechanisms	Limitations	Reference
Quercetin	Nanoparticles, Hydrogels, Micelles, Nanoprobes.	Tumors (Breast cancer, Liver cancer, Skin cancer, Brain cancer, etc.), Wound healing, Bacterial infection.	Intravenous injection, local administration.	Stimulus-responsive release, synergizes with therapies, induces tumor cell death, wound-healing.	The system is confined to in vitro and animal (murine/rabbit/zebrafish/ goat/dog) model studies.	[61]
Naringin	Nanoparticles, Hydrogels, Scaffolds, Microneedles.	Tumors (Liver cancer, Osteosarcoma, Lung cancer, Colorectal cancer), Wound healing, Diabetic wounds.	Intravenous injection, local implantation.	Stimulus-responsive release, inhibits tumor progression, pro-healing properties.	The system is confined to in vitro and animal (murine/rabbit/pig/ guinea pig) model studies.	[164]
Puerarin	Nanoparticles, Hydrogels, Microspheres, Micelles.	Tumors (Triple-negative breast cancer TNBC, Colorectal cancer, Lung cancer, etc.), Wound healing, Diabetic wounds.	Intravenous injection, local implantation.	Synergizes with chemo/immunotherapy, induces apoptosis, vascular normalization.	The system is confined to in vitro and animal (murine/rabbit/ monkey/pig) model studies.	[165]
Rutin	Nanoparticles, Hydrogels, Nanofibers, Nanoprobes.	Tumors (Brain cancer, Liver cancer, Non-small cell lung cancer, Glioblastoma, Breast cancer etc.), Alzheimer's disease.	Intravenous injection, local administration.	BBB penetration, stimulus-responsive release, induces tumor cell death, neuroprotective activity.	The system is confined to in vitro and animal (murine/rabbit/zebrafish/ goat/dog) model studies.	[67]
Icariin	Nanoparticles, Hydrogels, Microspheres, Scaffolds, Fibrous membranes, Micelles.	Tumors (Lung cancer, Oral squamous cell carcinoma, Osteosarcoma, Pancreatic cancer etc.), Bone defects, Osteoarthritis.	Intravenous injection, local implantation.	Tumor targeting, induces apoptosis, osteochondral regeneration.	The system is confined to in vitro and animal (murine/rabbit/goat/pig) model studies.	[166]

In addition, key clinical translation challenges include optimizing nanocarrier biocompatibility, enhancing tissue-specific targeting precision, resolving pharmacokinetic conflicts, and validating long-term safety in multimorbid patients. Future research endeavors should prioritize the development of multifunctional nano-platforms, exemplified by dual-responsive release systems and multi-ligand targeting strategies, alongside preclinical validation in animal models of cancer with comorbidities (e.g., cancer coupled with postoperative wound healing [167]). This review underscores the pivotal role of these flavonoids and nano-delivery technologies in advancing holistic cancer care for patients with coexisting diseases.

Flavonoid-nanocarrier conjugates exhibit shared commonalities in targeting mechanisms, release patterns, and synergistic effects, alongside consistent nanocarrier compatibility features. For targeting, a universal dual-targeting modality is formed by passive tumor accumulation via the enhanced permeability and retention (EPR) effect and active targeting through folic acid/transferrin ligand modifications. Flavonoid release is predominantly governed by TME-responsive triggers (pH, redox, or enzyme activity), enabling controlled and sustained release across delivery systems. Synergistically, nanocarriers address inherent limitations of free flavonoids (e.g., poor solubility, bioavailability, and degradation susceptibility [16]), while flavonoids enhance carrier biocompatibility, reduce off-target toxicity, and synergize with carriers to modulate tumor pathways (e.g., JAK2/STAT3 signaling, caspase activation) [169]. Regarding compatibility, flavonoid-nanocarrier conjugation relies on hydrophilic-hydrophobic matching: hydrophobic aglycones are embedded in carrier cores, whereas hydrophilic glycosylated flavonoids form hydrogen bonds or electrostatic interactions. Additionally, nanocarriers with hydroxyl or amino groups demonstrate superior compatibility and drug-loading efficiency.

Nano-delivery systems represent a promising strategy to overcome the inherent physicochemical limitations of flavonoids and expand their clinical applicability in disease treatment. However, the therapeutic efficacy of these systems hinges critically on the rational selection and modification of carrier materials, coupled with precise control over preparation processes. Consequently, synergistic optimization of both material properties and processing parameters is imperative to address current delivery challenges. Natural polymers emerge as ideal carrier matrices owing to their optimal balance of biocompatibility, biodegradability, and drug-loading capacity. For instance, sodium alginate facilitates flavonoid encapsulation and sustained release through calcium ion-mediated crosslinking [170]. Chitosan facilitates pH-sensitive drug release in the tumor microenvironment via its amino functional groups [171]. Hyaluronic acid can selectively target CD44 receptors, which are frequently overexpressed on tumor cells. Further performance enhancement can be achieved through chemical modifications such as quaternization or β-cyclodextrin grafting. Additionally, PEGylated liposomes and functionalized polymeric nanoparticles demonstrate improved targeting precision and stimulus-responsive behavior. Advanced preparation techniques, including microfluidic processing and supercritical fluid technologies, enable precise control over particle size distribution and enhance biocompatibility. These innovations collectively contribute to improved flavonoid solubility, prolonged circulatory stability, and enhanced therapeutic efficacy.

Despite their promising efficacy in tumor therapy and inflammatory bowel disease management, flavonoid nano-delivery systems still face multiple challenges. Future research should prioritize multi-responsive carrier design and combined therapy optimization to advance clinical translation. In terms of multi-responsive carrier design, the focus should be on the integrated construction of "precise recognition-intelligent response-controlled drug release" to develop novel carriers that integrate multiple stimulus-responsive mechanisms. For example, pH/redox dual-responsive systems can achieve tumor-specific delivery [172], enzyme/temperature-responsive hydrogels enhance local retention [173,174], and photosensitive carriers enable spatiotemporal release precision [175]. With respect to the optimization of combined therapy strategies, leveraging the multi-target biological activities of flavonoids, synergistic delivery schemes should be designed. First, co-loading flavonoids with chemotherapeutic agents such as doxorubicin or paclitaxel on nanocarriers can be implemented. Flavonoids sensitize tumors by inhibiting P-glycoprotein-mediated multidrug resistance, thereby reducing chemotherapy dosage and side effects. Second, bionic carriers co-delivering flavonoids with PD-1 antibodies and CpG oligonucleotides can be employed. Here, flavonoids activate anti-tumor immunity through immunomodulatory activity, while carrier-targeted delivery enables dual regulation of immune cells and tumor cells. Third, co-delivering flavonoids with siRNA and miRNA offers a promising approach. Flavonoids optimize the gene therapy microenvironment through anti-inflammatory and antioxidant effects, while gene silencing downregulates resistance and inflammatory factors, achieving synergistic enhancement between chemotherapy and gene therapy. Additionally, integrating AI-assisted carrier screening and 3D printing of personalized drug delivery systems can accelerate clinical translation.

Conclusions

This review summarizes the anti-tumor mechanisms and nano-delivery applications of five clinically relevant flavonoids, clarifying the structure-activity-nanocarrier correlations and core characteristics of flavonoid-based delivery systems. These systems encompass targeted delivery, stimulus-responsive release, and synergistic therapeutic effects. The study highlights the potential of multi-

responsive carriers and optimized combination therapies to enhance clinical translation. However, it also identifies limitations in scalable preparation and standardized biocompatibility evaluation. Future research should prioritize precise nanoformulation regulation and personalized delivery strategies. This work provides key insights for the rational design of tumor-targeting flavonoid-based nanomedicines.

List of Abbreviations

AAPBA, (3-acrylamidophenyl) boronic acid; AD, Alzheimer's disease; AFB1, aflatoxin B1; ALP, alkaline phosphatase; AMP, antimicrobial peptides; APP, amyloid precursor protein; Aβ, amyloid-β; BACE1, β-site amyloid precursor protein cleaving enzyme 1; β-GP, β-glycerophosphate disodium salt hydrate; BMSC, bone marrow mesenchymal stem cell; CAF, cancer-associated fibroblast; CDK, Cyclin-dependent kinase; CMC, carboxymethyl cellulose; CS, chitosan; CSO, coix seed oil; CDT, chemodynamic therapy; DAC, dialdehyde cellulose; DCMC, oxidized carboxymethyl cellulose; DISC, death-inducing signaling complex; DOX, doxorubicin; DOPA, dioleylphosphatidylserine; DSPE-PEG2000, 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[methoxy (polyethylene glycol)-2000]; DF-PEG, dialdehyde-functionalized polyethylene glycol; DFUs, diabetic foot ulcers; ECM, extracellular matrix; EGFR, epidermal growth factor receptor; EMT, epithelial-mesenchymal transition; ERK, extracellular regulated protein kinases; FA, folic acid; GelMA, gelatin methacryloyl; GQD, graphene quantum dot; HA, hyaluronic acid; HAp, hydroxyapatite; Hsp, heat shock protein; HUVEC, human umbilical vein endothelial cell; LCN, liquid crystal nanoparticle; LDH, layered double hydroxide; LNP, lipid nanoparticle; LTPTT, low-temperature photothermal therapy; MA, methyl acrylate; MMP, matrix metalloproteinase; mPEG-DCA, methoxy polyethylene glycol-dichloroacetic acid; NF-κB, nuclear factor kappa-B; NIR, near-infrared; NSCLC, non-small cell lung cancer; OSCC, oral squamous cell carcinoma; P-gp, P-glycoprotein; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand 1; PDK1, 3-phosphoinositide-dependent protein kinase 1; PDT, photodynamic therapy; PLA, polylactic acid; PLAG-TMC-GA, poly (lactic acid)-trimethylene carbonate-hydroxyacetic acid; PLGA, Poly (lactic-co-glycolic acid); PHA, polyhydroxyalkanoates; PEG, polyethylene glycol; PEGDMA, poly (ethylene glycol) dimethacrylate; pecn-H, pectin hydrazide; PMMA, poly (methyl methacrylate); PPS-PEG, poly (propylene sulfide)-polyethylene glycol; PTA, poly(N-acryloylglycylglycine) amine; PTT, photothermal therapy; PVA, polyvinyl alcohol; PVC, polyvinylpyridinium chloride; RBCM, red blood cell membrane; ROS, reactive oxygen species; rPPNc, regenerated nanofibrillated cellulose; RT, radiotherapy; SA, sodium alginate; SF, silk fibroin; SFMA, silk fibroin methacrylate; SLN, solid lipid nanoparticle; TEM, tumor endothelial marker; TME, tumor microenvironment; TNBC, triple-negative breast cancer; ULK1, Unc-51-like autophagy-activated kinase 1; VEGF, vascular endothelial growth factor; ZIF, zeolitic imidazolate framework; ZnO-NPs, zinc oxide nanoparticles.

Availability of Data and Materials

No new data were generated or analyzed in this review. All cited literature and datasets are publicly available in the references listed.

Author Contributions

YNH, DW, HML, LDZ, and WFL contributed to the design of this work. YNH, JYY, and YXL contributed to data collection. YNH, JYY, YXL, DW, YTR, ZHF, and YXY contributed to manuscript preparation and editing. LDZ and WFL revised critically for important intellectual content. HML, LDZ, and WFL contributed to funding acquisition and conceptualization. All authors read and approved the final manuscript. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgments

Not applicable.

Funding

This work was supported by the National Natural Science Foundation of China (32000977), the Natural Science Foundation of Shandong Province (ZR2020QH188/ZR2024QH602/ZR2021QC084), the Youth Innovation Team of Higher Education of Shandong Province (2022KJ262), and the Science and Technology Development Project of Weifang (2022ZJ1058).

Conflict of Interest

The authors declare no conflict of interest.

References

[1] Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, *et al.* Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: A Cancer Journal for Clinicians. 2024; 74: 229–263. https://doi.org/10.3322/caac.21834.

[2] Liu YQ, Wang XL, He DH, Cheng YX. Protection against chemotherapy- and radiotherapy-induced side effects: A review based on the mechanisms and therapeutic opportunities of phytochemicals. Phytomedicine: International Journal of Phytotherapy and Phytopharmacology. 2021; 80: 153402. https://doi.org/10.1016/j.phymed.2020.153402.

[3] Wang S, Fu JL, Hao HF, Jiao YN, Li PP, Han SY. Metabolic reprogramming by traditional Chinese medicine and its role in effec-

tive cancer therapy. Pharmacological Research. 2021; 170: 105728. https://doi.org/10.1016/j.phrs.2021.105728.

[4] Wang K, Chen Q, Shao Y, Yin S, Liu C, Liu Y, *et al.* Anticancer activities of TCM and their active components against tumor metastasis. Biomedicine & Pharmacotherapy = Biomédecine & Pharmacothérapie. 2021; 133: 111044. https://doi.org/10.1016/j.biopha.2020.111044.

[5] Liu Y, Liu X, Zhang N, Yin M, Dong J, Zeng Q, *et al.* Berberine diminishes cancer cell PD-L1 expression and facilitates antitumor immunity via inhibiting the deubiquitination activity of CSN5. Acta Pharmaceutica Sinica. B. 2020; 10: 2299–2312. https://doi.org/10.1016/j.apsb.2020.06.014.

[6] Silva B, Biluca FC, Gonzaga LV, Fett R, Dalmarco EM, Caon T, *et al.* In vitro anti-inflammatory properties of honey flavonoids: A review. Food Research International. 2021; 141: 110086. https://doi.org/10.1016/j.foodres.2020.110086.

[7] Wei L, Yang M, Huang L, Lin Li J. Antibacterial and antioxidant flavonoid derivatives from the fruits of Metaplexis japonica. Food Chemistry. 2019; 289: 308–312. https://doi.org/10.1016/j.foodchem.2019.03.070.

[8] Wang Y, Liu XJ, Chen JB, Cao JP, Li X, Sun CD. Citrus flavonoids and their antioxidant evaluation. Critical Reviews in Food Science and Nutrition. 2022; 62: 3833–3854. https://doi.org/10.1080/10408398.2020.1870035.

[9] Gansukh E, Nile A, Kim DH, Oh JW, Nile SH. New insights into antiviral and cytotoxic potential of quercetin and its derivatives - A biochemical perspective. Food Chemistry. 2021; 334: 127508. https://doi.org/10.1016/j.foodchem.2020.127508.

[10] Khan H, Belwal T, Efferth T, Farooqi AA, Sanches-Silva A, Vacca RA, *et al.* Targeting epigenetics in cancer: therapeutic potential of flavonoids. Critical Reviews in Food Science and Nutrition. 2021; 61: 1616–1639. https://doi.org/10.1080/10408398.2020.1763910.

[11] Wen L, Zhou T, Jiang Y, Chang SK, Yang B. Prenylated flavonoids in foods and their applications on cancer prevention. Critical Reviews in Food Science and Nutrition. 2022; 62: 5067–5080. https://doi.org/10.1080/10408398.2021.1881437.

[12] Ali Reza ASM, Nasrin MS, Hossen MA, Rahman MA, Jantan I, Haque MA, *et al*. Mechanistic insight into immunomodulatory effects of food-functioned plant secondary metabolites. Critical Reviews in Food Science and Nutrition. 2023; 63: 5546–5576. https://doi.org/10.1080/10408398.2021.2021138.

[13] Rengasamy KRR, Khan H, Gowrishankar S, Lagoa RJL, Mahomoodally FM, Khan Z, *et al*. The role of flavonoids in autoimmune diseases: Therapeutic updates. Pharmacology & Therapeutics. 2019; 194: 107–131. https://doi.org/10.1016/j.pharmthera.2018.09.009.

[14] Atta A, Salem MM, El-Said KS, Mohamed TM. Mechanistic role of quercetin as inhibitor for adenosine deaminase enzyme in rheumatoid arthritis: systematic review. Cellular & Molecular Biology Letters. 2024; 29: 14. https://doi.org/10.1186/s11658-024-00531-7.

[15] Yuan D, Guo Y, Pu F, Yang C, Xiao X, Du H, *et al*. Opportunities and challenges in enhancing the bioavailability and bioactivity of dietary flavonoids: A novel delivery system perspective. Food Chemistry. 2024; 430: 137115. https://doi.org/10.1016/j.foodchem.2023.137115.

[16] Aiello P, Consalvi S, Poce G, Raguzzini A, Toti E, Palmery M, *et al*. Dietary flavonoids: Nano delivery and nanoparticles for cancer therapy. Seminars in Cancer Biology. 2021; 69: 150–165. https://doi.org/10.1016/j.semcancer.2019.08.029.

[17] Dewanjee S, Chakraborty P, Bhattacharya H, Singh SK, Dua K, Dey A, *et al*. Recent advances in flavonoid-based nanocarriers as an emerging drug delivery approach for cancer chemotherapy. Drug Discovery Today. 2023; 28: 103409. https://doi.org/10.1016/j.drudis.2022.103409.

[18] Teng H, Zheng Y, Cao H, Huang Q, Xiao J, Chen L. Enhancement of bioavailability and bioactivity of diet-derived flavonoids by application of nanotechnology: a review. Critical Reviews in Food Science and Nutrition. 2023; 63: 378–393. https://doi.org/10.1080/10408398.2021.1947772.

[19] Tang N, Ding Z, Zhang S, Luo D, Liu X, Bao X, *et al*. Nanoassemblies Derived from Natural Flavonoid Compounds as New Antioxidant Oral Preparations for Targeted Inflammatory Bowel Disease Therapy. Advanced Functional Materials. 2023; 33: 2305133. https://doi.org/10.1002/adfm.202305133.

[20] Sun G, Wu Y, Li J, Yang M, Xu H, Li Y, *et al*. Quercetin liposomes conjugated with hyaluronidase: An efficient drug delivery system to block pancreatic cancer. Journal of Controlled Release: Official Journal of the Controlled Release Society. 2025; 382: 113642. https://doi.org/10.1016/j.jconrel.2025.113642.

[21] Askar MA, El Shawi OE, Abou Zaid OAR, Mansour NA, Hanafy AM. Breast cancer suppression by curcumin- naringenin-magnetic-nano-particles: In vitro and in vivo studies. Tumour biology : the journal of the International Society for Oncodevelopmental Biology and Medicine. Tumor Biology: The Journal of the International Society for Oncodevelopmental Biology and Medicine. 2021; 43: 225–247. https://doi.org/10.3233/TUB-211506.

[22] Li Y, Wang Y, Ding Y, Fan X, Ye L, Pan Q, *et al.* A Double Network Composite Hydrogel with Self-Regulating Cu(2+)/Luteolin Release and Mechanical Modulation for Enhanced Wound Healing. ACS Nano. 2024; 18: 17251–17266. https://doi.org/10.1021/acsnano.4c04816.

[23] Li W, Meng X, Peng K, Han Y, Liu H, Zhao W, *et al*. Boosting Microglial Lipid Metabolism via TREM2 Signaling by Biomimetic Nanoparticles to Attenuate the Sevoflurane-Induced Developmental Neurotoxicity. Advanced Science. 2024; 11: e2305989. https://doi.org/10.1002/advs.202305989.

[24] Zhang B, Wang C, Guo M, Zhu F, Yu Z, Zhang W, *et al.* Circadian Rhythm-Dependent Therapy by Composite Targeted Polyphenol Nanoparticles for Myocardial Ischemia-Reperfusion Injury. ACS Nano. 2024; 18: 28154–28169. https://doi.org/10.1021/acsnano.4c07690.

[25] Liao Y, Xie X, Zhang C, Zhong H, Shan L, Yu P, *et al.* Quercetin exerts anti-tumor immune mechanism by regulating IL-6/JAK2/STAT3 signaling pathway to deplete Treg cells. Toxicon: Official Journal of the International Society on Toxinology. 2024; 243: 107747. https://doi.org/10.1016/j.toxicon.2024.107747.

[26] Fan Z, Xia G, Zhu F, Yang N, Ma A, Shi Y, *et al*. Ruthenium-quercetin coordinated nanotherapeutics with macrophage polarization regulation to rapidly promote bacterial-infected wound healing. Materials Today. Bio. 2025; 33: 101983. https://doi.org/10.1016/j.mtbio.2025.101983.

[27] He D, Chen S, Wang X, Wen X, Gong C, Liu L, *et al*. Icaritin Represses Autophagy to Promote Colorectal Cancer Cell Apoptosis and Sensitized Low-Temperature Photothermal Therapy via Targeting HSP90-TXNDC9 Interactions. Advanced Science. 2025; 12: e2412953. https://doi.org/10.1002/advs.202412953.

[28] Wang Y, Zhang H, Xu Z, Zhu W, Chang S, Wei J, *et al*. Icariin-loaded GelMa hydrogel encapsulated potassium sodium niobate biomimetic piezoelectric scaffold regulates macrophage polarization to accelerate bone defect repair. Materials Today. Bio. 2025; 35: 102476. https://doi.org/10.1016/j.mtbio.2025.102476.

[29] Zeng Y, Xiong Y, Yang T, Wang Y, Zeng J, Zhou S, *et al*. Icariin and its metabolites as potential protective phytochemicals against cardiovascular disease: From effects to molecular mechanisms. Biomedicine & Pharmacotherapy = Biomédecine & Pharmacothérapie. 2022; 147: 112642. https://doi.org/10.1016/j.biopha.2022.112642.

[30] Gu J, Zhang P, Li H, Wang Y, Huang Y, Fan L, *et al*. Cerium-Luteolin Nanocomplexes in Managing Inflammation-Related Diseases by Antioxidant and Immunoregulation. ACS Nano. 2024; 18: 6229–6242. https://doi.org/10.1021/acsnano.3c09528.

[31] Yang S, Wang L, Pan X, Liang Y, Zhang Y, Li J, *et al*. 5-Methoxyflavone-induced AMPKα activation inhibits NF-κB and

P38 MAPK signaling to attenuate influenza A virus-mediated inflammation and lung injury in vitro and in vivo. Cellular & Molecular Biology Letters. 2022; 27: 82. https://doi.org/10.1186/s11658-022-00381-1.

[32] Morsy HM, Zaky MY, Yassin NYS, Khalifa AYZ. Nanoparticle-based flavonoid therapeutics: Pioneering biomedical applications in antioxidants, cancer treatment, cardiovascular health, neuroprotection, and cosmeceuticals. International Journal of Pharmaceutics. 2025; 670: 125135. https://doi.org/10.1016/j.ijpharm.2024.125135.

[33] Parvin N, Aslam M, Joo SW, Mandal TK. Nano-Phytomedicine: Harnessing Plant-Derived Phytochemicals in Nanocarriers for Targeted Human Health Applications. Molecules : A Journal of Synthetic Chemistry and Natural Product Chemistry. 2025; 30: 3177. https://doi.org/10.3390/molecules30153177.

[34] Pang X, Zhang X, Jiang Y, Su Q, Li Q, Li Z. Autophagy: Mechanisms and Therapeutic Potential of Flavonoids in Cancer. Biomolecules. 2021; 11: 135. https://doi.org/10.3390/biom11020135.

[35] Duan N, Hu X, Zhou R, Li Y, Wu W, Liu N. A Review on Dietary Flavonoids as Modulators of the Tumor Microenvironment. Molecular Nutrition & Food Research. 2023; 67: e2200435. https://doi.org/10.1002/mnfr.202200435.

[36] Sun Q, Liu Q, Zhou X, Wang X, Li H, Zhang W, *et al.* Flavonoids regulate tumor-associated macrophages - From structure-activity relationship to clinical potential (Review). Pharmacological Research. 2022; 184: 106419. https://doi.org/10.1016/j.phrs.2022.106419.

[37] Singh S, Raza W, Parveen S, Meena A, Luqman S. Flavonoid display ability to target microRNAs in cancer pathogenesis. Biochemical Pharmacology. 2021; 189: 114409. https://doi.org/10.1016/j.bcp.2021.114409.

[38] Tiwari P, Mishra KP. Flavonoids sensitize tumor cells to radiation: molecular mechanisms and relevance to cancer radiotherapy. International Journal of Radiation Biology. 2020; 96: 360–369. https://doi.org/10.1080/09553002.2020.1694193.

[39] Zhai K, Mazurakova A, Koklesova L, Kubatka P, Büsselberg D. Flavonoids Synergistically Enhance the Anti-Glioblastoma Effects of Chemotherapeutic Drugs. Biomolecules. 2021; 11: 1841. https://doi.org/10.3390/biom11121841.

[40] Mohi-Ud-Din R, Mir RH, Sabreen S, Jan R, Pottoo FH, Singh IP. Recent Insights into Therapeutic Potential of Plant-Derived Flavonoids against Cancer. Anti-Cancer Agents in Medicinal Chemistry. 2022; 22: 3343–3369. https://doi.org/10.2174/1871520622666220421094055.

[41] Proença C, Freitas M, Ribeiro D, Rufino AT, Fernandes E, Ferreira de Oliveira JMP. The role of flavonoids in the regulation of epithelial-mesenchymal transition in cancer: A review on targeting signaling pathways and metastasis. Medicinal Research Reviews. 2023; 43: 1878–1945. https://doi.org/10.1002/med.21966.

[42] Mazurakova A, Koklesova L, Csizmár SH, Samec M, Brockmueller A, Šudomová M, *et al.* Significance of flavonoids targeting PI3K/Akt/HIF-1α signaling pathway in therapy-resistant cancer cells - A potential contribution to the predictive, preventive, and personalized medicine. Journal of Advanced Research. 2024; 55: 103–118. https://doi.org/10.1016/j.jare.2023.02.015.

[43] Wang Y, Huang M, Zhou X, Li H, Ma X, Sun C. Potential of natural flavonoids to target breast cancer angiogenesis (review). British Journal of Pharmacology. 2025; 182: 2235–2258. https://doi.org/10.1111/bph.16275.

[44] Qiao C, Hu S, Wang D, Cao K, Wang Z, Wang X, *et al*. Effectiveness and safety of Shenqi Fuzheng injection combined with platinum-based chemotherapy for treatment of advanced non-small cell lung cancer: a systematic review and meta-analysis. Frontiers in Oncology. 2023; 13: 1198768. https://doi.org/10.3389/fonc.2023.1198768.

[45] Zhang H, Chen T, Shan L. ShenQi FuZheng injection as an adjunctive treatment to chemotherapy in breast cancer patients: a meta-analysis. Pharmaceutical Biology. 2019; 57: 612–624. https://doi.org/10.1080/13880209.2019.1660383.

[46] Meng FX, Yang X, Li ML. Shenqi Fuzheng Injection () Combined with Chemotherapy for Acute Leukemia: A Meta-Analysis. Chinese Journal of Integrative Medicine. 2022; 28: 81–87. https://doi.org/10.1007/s11655-020-3264-7.

[47] Jin J, Ren S, Shi Q, Jiang H, Rong F, Cen W, *et al*. Shengbai oral solution for chemotherapy-induced neutropenia and symptom management in non-small cell lung cancer: A multicenter, randomized, open-label trial. Phytomedicine: International Journal of Phytotherapy and Phytopharmacology. 2025; 148: 157502. https://doi.org/10.1016/j.phymed.2025.157502.

[48] Wu S, Wu R, Ma S, Zhu Y, Zhao J, Zhang M, *et al*. System pharmacology reveals the mechanism of action of Shengbai Oral Liquid alleviates chemotherapy-induced leukopenia by interfering the pro-platelet basic protein: Integrated network study of multi-omics. Journal of Ethnopharmacology. 2025; 353: 120351. https://doi.org/10.1016/j.jep.2025.120351.

[49] Song J, Zhang Z, Hu Y, Li Z, Wan Y, Liu J, *et al*. An aqueous extract of Prunella vulgaris L. inhibits the growth of papillary thyroid carcinoma by inducing autophagy in vivo and in vitro. Phytotherapy Research: PTR. 2021; 35: 2691–2702. https://doi.org/10.1002/ptr.7015.

[50] Liu Y, Hao Y, Chen J, Chen M, Tian J, Lv X, *et al*. An Injectable Puerarin Depot Can Potentiate Chimeric Antigen Receptor Natural Killer Cell Immunotherapy Against Targeted Solid Tumors by Reversing Tumor Immunosuppression. Small. 2024; 20: e2307521. https://doi.org/10.1002/smll.202307521.

[51] Yuqing Y, Yuhuan C, Chunxiao LI, Xiao L, Panpan W, Jing G, *et al*. Effectiveness and safety of Pingxiao capsule as adjuvant therapy in treatment of breast cancer: a systematic review and Meta-analysis. Journal of Traditional Chinese Medicine = Chung I Tsa Chih Ying Wen pan/sponsored by All-China Association of Traditional Chinese Medicine, Academy of Traditional Chinese Medicine. 2023; 43: 851–859. https://doi.org/10.19852/j.cnki.jtcm.20230713.001.

[52] Xie D, Wu C, Wang D, Nisma Lena BA, Liu N, Ye G, *et al*. Wei-fu-chun tablet halted gastric intestinal metaplasia and dysplasia associated with inflammation by regulating the NF-κB pathway. Journal of Ethnopharmacology. 2024; 318: 117020. https://doi.org/10.1016/j.jep.2023.117020.

[53] Shang J, Yang J, Deng Q, Zhou M. Nano-scale drug delivery systems for luteolin: advancements and applications. Journal of Materials Chemistry. B. 2023; 11: 11198–11216. https://doi.org/10.1039/d3tb01753b.

[54] Hassani S, Maghsoudi H, Fattahi F, Malekinejad F, Hajmalek N, Sheikhnia F, *et al*. Flavonoids nanostructures promising therapeutic efficiencies in colorectal cancer. International Journal of Biological Macromolecules. 2023; 241: 124508. https://doi.org/10.1016/j.ijbiomac.2023.124508.

[55] Peng Y, Liu H, Liang X, Cao L, Teng M, Chen H, *et al*. Self-assembling chemodrug fiber-hydrogel for transarterial chemoembolization and radiotherapy-enhanced antitumor immunity. Journal of Controlled Release: Official Journal of the Controlled Release Society. 2025; 380: 1–16. https://doi.org/10.1016/j.jconrel.2025.01.088.

[56] Mi X, Hu M, Dong M, Yang Z, Zhan X, Chang X, *et al*. Folic Acid Decorated Zeolitic Imidazolate Framework (ZIF-8) Loaded with Baicalin as a Nano-Drug Delivery System for Breast Cancer Therapy. International Journal of Nanomedicine. 2021; 16: 8337–8352. https://doi.org/10.2147/IJN.S340764.

[57] Fu QT, Zhong XQ, Chen MY, Gu JY, Zhao J, Yu DH, *et al*. Luteolin-Loaded Nanoparticles for the Treatment of Melanoma. International Journal of Nanomedicine. 2023; 18: 2053–2068. https://doi.org/10.2147/IJN.S400329.

[58] Mu M, Chen B, Li H, Fan R, Yang Y, Zhou L, *et al*. Augmented the sensitivity of photothermal-ferroptosis therapy in triple-negative

breast cancer through mitochondria-targeted nanoreactor. Journal of Controlled Release: Official Journal of the Controlled Release Society. 2024; 375: 733–744. https://doi.org/10.1016/j.jconrel.2024.09.042.

[59] Ran Y, Hu J, Chen Y, Rao Z, Zhao J, Xu Z, *et al*. Morusin-Cu(II)-indocyanine green nanoassembly ignites mitochondrial dysfunction for chemo-photothermal tumor therapy. Journal of Colloid and Interface Science. 2024; 662: 760–773. https://doi.org/10.1016/j.jcis.2024.02.121.

[60] Chen Y, Li H, Liu N, Feng D, Wu W, Gu K, *et al*. Multi-mechanism antitumor/antibacterial effects of Cu-EGCG self-assembling nanocomposite in tumor nanotherapy and drug-resistant bacterial wound infections. Journal of Colloid and Interface Science. 2024; 671: 751–769. https://doi.org/10.1016/j.jcis.2024.05.080.

[61] Li XR, Qi L, Zhang XW, Wei C, Yu B, Pei TL. Quercetin and Nano-Derivatives: Potential and Challenges in Cancer Therapy. International Journal of Nanomedicine. 2025; 20: 6701–6720. https://doi.org/10.2147/IJN.S509877.

[62] Yang H, Yang T, Heng C, Zhou Y, Jiang Z, Qian X, *et al*. Quercetin improves nonalcoholic fatty liver by ameliorating inflammation, oxidative stress, and lipid metabolism in db/db mice. Phytotherapy Research: PTR. 2019; 33: 3140–3152. https://doi.org/10.1002/ptr.6486.

[63] Novais EJ, Tran VA, Johnston SN, Darris KR, Roupas AJ, Sessions GA, *et al.* Long-term treatment with senolytic drugs Dasatinib and Quercetin ameliorates age-dependent intervertebral disc degeneration in mice. Nature Communications. 2021; 12: 5213. https://doi.org/10.1038/s41467-021-25453-2.

[64] Zu G, Sun K, Li L, Zu X, Han T, Huang H. Mechanism of quercetin therapeutic targets for Alzheimer disease and type 2 diabetes mellitus. Scientific Reports. 2021; 11: 22959. https://doi.org/10.1038/s41598-021-02248-5.

[65] Khursheed R, Singh SK, Wadhwa S, Gulati M, Awasthi A. Enhancing the potential preclinical and clinical benefits of quercetin through novel drug delivery systems. Drug Discovery Today. 2020; 25: 209–222. https://doi.org/10.1016/j.drudis.2019.11.001.

[66] Joshi H, Gupta DS, Kaur G, Singh T, Ramniwas S, Sak K, *et al*. Nanoformulations of quercetin for controlled delivery: a review of preclinical anticancer studies. Naunyn-Schmiedeberg's Archives of Pharmacology. 2023; 396: 3443–3458. https://doi.org/10.1007/s00210-023-02625-z.

[67] Ghanbari-Movahed M, Mondal A, Farzaei MH, Bishayee A. Quercetin- and rutin-based nano-formulations for cancer treatment: A systematic review of improved efficacy and molecular mechanisms. Phytomedicine: International Journal of Phytotherapy and Phytopharmacology. 2022; 97: 153909. https://doi.org/10.1016/j.phymed.2021.153909.

[68] Li L, Zhang M, Liu T, Li J, Sun S, Chen J, *et al*. Quercetin-ferrum nanoparticles enhance photothermal therapy by modulating the tumor immunosuppressive microenvironment. Acta Biomaterialia. 2022; 154: 454–466. https://doi.org/10.1016/j.actbio.2022.10.008.

[69] Qiao Y, Cao Y, Yu K, Zong L, Pu X. Preparation and antitumor evaluation of quercetin nanosuspensions with synergistic efficacy and regulating immunity. International Journal of Pharmaceutics. 2020; 589: 119830. https://doi.org/10.1016/j.ijpharm.2020.119830.

[70] Chen G, Song W, Wang X, Mao G, Hu W, Dou R, *et al*. Quercetin combined with shTERT induces apoptosis in ovarian cancer via the P53/Bax pathway, and RGD-MSN/QR/shTERT nanoparticles enhance the therapeutic efficacy. Journal of Nanobiotechnology.. 2025; 23: 536. https://doi.org/10.1186/s12951-025-03546-0.

[71] Wang W, Yu J, Lin Y, Li M, Pan Y, He Y, *et al*. NIR absorptive croconic acid/quercetin/CaO(2) nanoplatform for tumor calcium overload therapy combined mild photothermal therapy. Biomaterials Advances. 2023; 149: 213418. https://doi.org/10.1016/j.bioadv.2023.213418.

[72] Asl AM, Kalaee M, Abdouss M, Homami SS. Novel targeted delivery of quercetin for human hepatocellular carcinoma using starch/polyvinyl alcohol nanocarriers based hydrogel containing Fe(2)O(3) nanoparticles. International Journal of Biological Macromolecules. 2024; 257: 128626. https://doi.org/10.1016/j.ijbiomac.2023.128626.

[73] Sun Y, Bai Y, Liu S, Cui S, Xu P. Thermosensitive Micelles Gel to Deliver Quercetin Locally for Enhanced Antibreast Cancer Efficacy: An In Vitro Evaluation. IET Nanobiotechnology/IET. 2023; 2023: 7971492. https://doi.org/10.1049/2023/7971492.

[74] Lin M, Liu X, Li J, Zou H, Wang J, Yan Z, *et al*. Hybrid NIR-responsive liposome/hydrogel platform mediating chemo-photothermal therapy of retinoblastoma enhanced by quercetin as an adjuvant. Theranostics. 2025; 15: 3995–4015. https://doi.org/10.7150/thno.108471.

[75] Jia M, Lu R, Li P, Liao X, Tan Y, Zhang S. Inflammation-reducing thermosensitive hydrogel with photothermal conversion for skin cancer therapy. Journal of Controlled Release: Official Journal of the Controlled Release Society. 2025; 378: 377–389. https://doi.org/10.1016/j.jconrel.2024.12.027.

[76] Li Y, Zhao P, Li J, Han Y, Gao Z, Cai X, *et al*. A 5-Fluorouracil-Constituted DNA Hydrogel Embedded with Quercetin Remodels Tumor Microenvironment for Robust Chemoimmunotherapy. Advanced Healthcare Materials. 2026: e03744. https://doi.org/10.1002/adhm.202503744.

[77] Abbaszadeh S, Rashidipour M, Khosravi P, Shahryarhesami S, Ashrafi B, Kaviani M, *et al*. Biocompatibility, Cytotoxicity, Antimicrobial and Epigenetic Effects of Novel Chitosan-Based Quercetin Nanohydrogel in Human Cancer Cells. International Journal of Nanomedicine. 2020; 15: 5963–5975. https://doi.org/10.2147/IJN.S263013.

[78] Zou J, Jiang C, Hu Q, Jia X, Wang S, Wan S, *et al*. Tumor microenvironment-responsive engineered hybrid nanomedicine for photodynamic-immunotherapy via multi-pronged amplification of reactive oxygen species. Nature Communications. 2025; 16: 424. https://doi.org/10.1038/s41467-024-55658-0.

[79] Mi Y, Zhong L, Lu S, Hu P, Pan Y, Ma X, *et al*. Quercetin promotes cutaneous wound healing in mice through Wnt/β-catenin signaling pathway. Journal of Ethnopharmacology. 2022; 290: 115066. https://doi.org/10.1016/j.jep.2022.115066.

[80] Xu Q, Su W, Huang C, Zhong H, Huo L, Cai J, *et al.* Multifunctional Polysaccharide Self-Healing Wound Dressing: NIR-Responsive Carboxymethyl Chitosan / Quercetin Hydrogel. Advanced Healthcare Materials. 2025; 14: e2403267. https://doi.org/10.1002/adhm.202403267.

[81] Liu X, Ju Y, Yang P, Shen N, Shao Y, Yang A, *et al*. Enhanced hydrogel loading of quercetin-loaded hollow mesoporous cerium dioxide nanoparticles for skin flap survival. Materials Today. Bio. 2024; 30: 101432. https://doi.org/10.1016/j.mtbio.2024.101432.

[82] Liu Y, Yang X, Wu K, Feng J, Zhang X, Li A, *et al*. Skin-Inspired and Self-Regulated Hydrophobic Hydrogel for Diabetic Wound Therapy. Advanced Materials. 2025; 37: e2414989. https://doi.org/10.1002/adma.202414989.

[83] Wang Z, Cheng X, Meng F, Guo H, Liu Z, Wang H, *et al*. Wheat gliadin hydrolysates based nano-micelles for hydrophobic naringin: Structure characterization, interaction, and in vivo digestion. Food Chemistry: X. 2024; 21: 101136. https://doi.org/10.1016/j.fochx.2024.101136.

[84] Shilpa VS, Shams R, Dash KK, Pandey VK, Dar AH, Ayaz Mukarram S, *et al*. Phytochemical Properties, Extraction, and Pharmacological Benefits of Naringin: A Review. Molecules: A Journal of Synthetic Chemistry and Natural Product Chemistry. 2023; 28: 5623. https://doi.org/10.3390/molecules28155623.

[85] Chen J, Qin X, Chen M, Chen T, Chen Z, He B. Biological activities, Molecular mechanisms, and Clinical application of Naringin in Metabolic syndrome. Pharmacological Research. 2024; 202:

107124. https://doi.org/10.1016/j.phrs.2024.107124.

[86] Dadwal V, Gupta M. Recent developments in citrus bioflavonoid encapsulation to reinforce controlled antioxidant delivery and generate therapeutic uses: Review. Critical Reviews in Food Science and Nutrition. 2023; 63: 1187–1207. https://doi.org/10.1080/10408398.2021.1961676.

[87] Wang W, Liu Q, Liang X, Kang Q, Wang Z. Protective role of naringin loaded solid nanoparticles against aflatoxin B1 induced hepatocellular carcinoma. Chemico-biological Interactions. 2022; 351: 109711. https://doi.org/10.1016/j.cbi.2021.109711.

[88] Yang Y, Tao B, Gong Y, Chen R, Yang W, Lin C, *et al*. Functionalization of Ti substrate with pH-responsive naringin-ZnO nanoparticles for the reconstruction of large bony after osteosarcoma resection. Journal of Biomedical Materials Research. Part A. 2020; 108: 2190–2205. https://doi.org/10.1002/jbm.a.36977.

[89] Mohamed EE, Ahmed OM, Zoheir KMA, El-Shahawy AAG, Tamur S, Shams A, *et al.* Naringin-Dextrin Nanocomposite Abates Diethylnitrosamine/Acetylaminofluorene-Induced Lung Carcinogenesis by Modulating Oxidative Stress, Inflammation, Apoptosis, and Cell Proliferation. Cancers. 2023; 15: 5102. https://doi.org/10.3390/cancers15205102.

[90] Ge X, Jiang F, Wang M, Chen M, Li Y, Phipps J, *et al*. Naringin@Metal-Organic Framework as a Multifunctional Bioplatform. ACS Applied Materials & Interfaces. 2023; 15: 677–683. https://doi.org/10.1021/acsami.2c19904.

[91] Elnawasany S, Haggag YA, Shalaby SM, Soliman NA, El Saadany AA, Ibrahim MAA, *et al.* Anti-cancer effect of nano-encapsulated boswellic acids, curcumin and naringenin against HepG-2 cell line. BMC Complementary Medicine and Therapies. 2023; 23: 270. https://doi.org/10.1186/s12906-023-04096-4.

[92] Secerli J, Adatepe Ş, Altuntas S, Topal GR, Erdem O, Bacanlı M. In vitro toxicity of naringin and berberine alone, and encapsulated within PMMA nanoparticles. Toxicology in Vitro: An International Journal Published in Association with BIBRA. 2023; 89: 105580. https://doi.org/10.1016/j.tiv.2023.105580.

[93] Hanna DMF, Youshia J, Fahmy SF, George MY. Nose to brain delivery of naringin-loaded chitosan nanoparticles for potential use in oxaliplatin-induced chemobrain in rats: impact on oxidative stress, cGAS/STING and HMGB1/RAGE/TLR2/MYD88 inflammatory axes. Expert Opinion on Drug Delivery. 2023; 20: 1859–1873. https://doi.org/10.1080/17425247.2023.2228685.

[94] Dai H, Zhang H, Ma L, Zhou H, Yu Y, Guo T, *et al.* Green pH/magnetic sensitive hydrogels based on pineapple peel cellulose and polyvinyl alcohol: synthesis, characterization and naringin prolonged release. Carbohydrate Polymers. 2019; 209: 51–61. https://doi.org/10.1016/j.carbpol.2019.01.014.

[95] George D, Maheswari PU, Begum KMMS. Cysteine conjugated chitosan based green nanohybrid hydrogel embedded with zinc oxide nanoparticles towards enhanced therapeutic potential of naringenin. Reactive and Functional Polymers. 2020; 148: 104480. https://doi.org/10.1016/j.reactfunctpolym.2020.104480.

[96] Said-Elbahr R, Nasr M, Alhnan MA, Taha I, Sammour O. Simultaneous pulmonary administration of celecoxib and naringin using a nebulization-friendly nanoemulsion: A device-targeted delivery for treatment of lung cancer. Expert Opinion on Drug Delivery. 2022; 19: 611–622. https://doi.org/10.1080/17425247.2022.2076833.

[97] Zhu J, Huang Y, Zhang J, Feng Y, Shen L. Formulation, Preparation and Evaluation of Nanostructured Lipid Carrier Containing Naringin and Coix Seed Oil for Anti-Tumor Application Based on "Unification of Medicines and Excipients". Drug Design, Development and Therapy. 2020; 14: 1481–1491. https://doi.org/10.2147/DDDT.S236997.

[98] Yen JH, Chio WT, Chuang CJ, Yang HL, Huang ST. Improved Wound Healing by Naringin Associated with MMP and the VEGF Pathway. Molecules: A Journal of Synthetic Chemistry and Natural Product Chemistry. 2022; 27: 1695. https://doi.org/10.3390/molecules27051695.

[99] Pérez-Garibay MS, Lara-Rodríguez GÁ, Bucio E. Functionalization of Polyvinylpyrrolidone Films by Grafting Maleic Acid from PVP Gels for Loading Studies of Naringin and Silver Nanoparticles as Potential Wound Dressings. Gels. 2025; 11: 147. https://doi.org/10.3390/gels11020147.

[100] Wei Z, Robertson M, Qian J, Qiang Z, Ren J. In Situ Self-Assembled Naringin/ZIF-8 Nanoparticle-Embedded Bacterial Cellulose Sponges for Infected Diabetic Wound Healing. ACS Applied Materials & Interfaces. 2025; 17: 6103–6115. https://doi.org/10.1021/acsami.4c20399.

[101] Chen H, Tan L, Li L, Zheng Y, Li M, He S, *et al*. Multifunctional layered microneedle patches enable transdermal angiogenesis and immunomodulation for scarless healing of thermal burn injuries. Materials Today. Bio. 2024; 29: 101359. https://doi.org/10.1016/j.mtbio.2024.101359.

[102] Yang H, Xu H, Lv D, Li S, Rong Y, Wang Z, *et al*. The naringin/carboxymethyl chitosan/sodium hyaluronate/silk fibroin scaffold facilitates the healing of diabetic wounds by restoring the ROS-related dysfunction of vascularization and macrophage polarization. International Journal of Biological Macromolecules. 2024; 260: 129348. https://doi.org/10.1016/j.ijbiomac.2024.129348.

[103] Yi Y, Adrjan B, Li J, Hu B, Roszak S. NMR studies of daidzein and puerarin: active anti-oxidants in traditional Chinese medicine. Journal of Molecular Modeling. 2019; 25: 202. https://doi.org/10.1007/s00894-019-4090-8.

[104] Liu X, Huang R, Wan J. Puerarin: a potential natural neuroprotective agent for neurological disorders. Biomedicine & Pharmacotherapy = Biomédecine & Pharmacothérapie. 2023; 162: 114581. https://doi.org/10.1016/j.biopha.2023.114581.

[105] Wang D, Bu T, Li Y, He Y, Yang F, Zou L. Pharmacological Activity, Pharmacokinetics, and Clinical Research Progress of Puerarin. Antioxidants. 2022; 11, 2121. https://doi.org/10.3390/antiox11112121.

[106] Xu H, Hu M, Liu M, An S, Guan K, Wang M, *et al*. Nano-puerarin regulates tumor microenvironment and facilitates chemo- and immunotherapy in murine triple negative breast cancer model. Biomaterials. 2020; 235: 119769. https://doi.org/10.1016/j.biomaterials.2020.119769.

[107] Deng XQ, Zhang HB, Wang GF, Xu D, Zhang WY, Wang QS, *et al*. Colon-specific microspheres loaded with puerarin reduce tumorigenesis and metastasis in colitis-associated colorectal cancer. International Journal of Pharmaceutics. 2019; 570: 118644. https://doi.org/10.1016/j.ijpharm.2019.118644.

[108] Yi T, Huang J, Chen X, Xiong H, Kang Y, Wu J. Synthesis, characterization, and formulation of poly-puerarin as a biodegradable and biosafe drug delivery platform for anti-cancer therapy. Biomaterials Science. 2019; 7: 2152–2164. https://doi.org/10.1039/c9bm00111e.

[109] Zhao Y, Liu K, Li J, Liao J, Ma L. Engineering of hybrid anticancer drug-loaded polymeric nanoparticles delivery system for the treatment and care of lung cancer therapy. Drug Delivery. 2021; 28: 1539–1547. https://doi.org/10.1080/10717544.2021.1934187.

[110] Wang S, Chen B, Ouyang L, Wang D, Tan J, Qiao Y, *et al*. A Novel Stimuli-Responsive Injectable Antibacterial Hydrogel to Achieve Synergetic Photothermal/Gene-Targeted Therapy towards Uveal Melanoma. Advanced Science. 2021; 8: e2004721. https://doi.org/10.1002/advs.202004721.

[111] Li S, Yang P, Ding X, Zhang H, Ding Y, Tan Q. Puerarin improves diabetic wound healing via regulation of macrophage M2 polarization phenotype. Burns & Trauma. 2022; 10: tkac046. https://doi.org/10.1093/burnst/tkac046.

[112] Zeng X, Chen B, Wang L, Sun Y, Jin Z, Liu X, *et al*. Chitosan@Puerarin hydrogel for accelerated wound healing in diabetic subjects by miR-29ab1 mediated inflammatory axis suppression. Bioactive Materials. 2022; 19: 653–665. https://doi.org/10.1016/j.bioactmat.2022.04.032.

[113] Ou Q, Zhang S, Fu C, Yu L, Xin P, Gu Z, *et al*. More natural more better: triple natural anti-oxidant puerarin/ferulic acid/polydopamine incorporated hydrogel for wound healing. Journal of Nanobiotechnology. 2021; 19: 237. https://doi.org/10.1186/s12951-021-00973-7.

[114] Wan R, Lin Z, Xu M, Luo W, Jia H, Hu Z, *et al*. An injectable hyaluronic acid-silanol hydrogel containing arginine and puerarin for immune modulation and enhanced diabetic wound healing. Bioactive Materials. 2025; 54: 850–870. https://doi.org/10.1016/j.bioactmat.2025.08.040.

[115] Yang D, Zhao W, Zhang S, Liu Y, Teng J, Ma Y, *et al*. Dual Self-Assembly of Puerarin and Silk Fibroin into Supramolecular Nanofibrillar Hydrogel for Infected Wound Treatment. Advanced Healthcare Materials. 2024; 13: e2400071. https://doi.org/10.1002/adhm.202400071.

[116] Yang H, Lv D, Qu S, Xu H, Li S, Wang Z, *et al*. A ROS-Responsive Lipid Nanoparticles Release Multifunctional Hydrogel Based on Microenvironment Regulation Promotes Infected Diabetic Wound Healing. Advanced Science. 2024; 11: e2403219. https://doi.org/10.1002/advs.202403219.

[117] Chen B, Zhang H, Qiu J, Wang S, Ouyang L, Qiao Y, *et al*. Mechanical Force Induced Self-Assembly of Chinese Herbal Hydrogel with Synergistic Effects of Antibacterial Activity and Immune Regulation for Wound Healing. Small. 2022; 18: e2201766. https://doi.org/10.1002/smll.202201766.

[118] Jin F, Cao M, Zhang H, Qin S, Tian B, Zhang J. Preparation of zein-rutin supramolecular nanoparticles using pH-ultrasound-shifting: binding mechanism, functional properties, and in vitro release kinetics. Food Chemistry. 2025; 483: 144087. https://doi.org/10.1016/j.foodchem.2025.144087.

[119] Liu Y, Wang Q, Liu C, Yang H, Jia L, Zhao L, *et al*. Improved antioxidant activity of rutin via lipase-mediated esterification with oleic acid. Journal of the Science of Food and Agriculture. 2023; 103: 3489–3500. https://doi.org/10.1002/jsfa.12486.

[120] Muvhulawa N, Dludla PV, Ziqubu K, Mthembu SXH, Mthiyane F, Nkambule BB, *et al*. Rutin ameliorates inflammation and improves metabolic function: A comprehensive analysis of scientific literature. Pharmacological Research. 2022; 178: 106163. https://doi.org/10.1016/j.phrs.2022.106163.

[121] Sun XY, Li LJ, Dong QX, Zhu J, Huang YR, Hou SJ, *et al*. Rutin prevents tau pathology and neuroinflammation in a mouse model of Alzheimer's disease. Journal of Neuroinflammation. 2021; 18: 131. https://doi.org/10.1186/s12974-021-02182-3.

[122] Foudah AI, Alqarni MH, Alam A, Devi S, Salkini MA, Alam P. Rutin Improves Anxiety and Reserpine-Induced Depression in Rats. Molecules: A Journal of Synthetic Chemistry and Natural Product Chemistry. 2022; 27: 7313. https://doi.org/10.3390/molecules27217313.

[123] Nouri Z, Fakhri S, Nouri K, Wallace CE, Farzaei MH, Bishayee A. Targeting Multiple Signaling Pathways in Cancer: The Rutin Therapeutic Approach. Cancers. 2020; 12: 2276. https://doi.org/10.3390/cancers12082276.

[124] Farha AK, Gan RY, Li HB, Wu DT, Atanasov AG, Gul K, *et al*. The anticancer potential of the dietary polyphenol rutin: Current status, challenges, and perspectives. Critical Reviews in Food Science and Nutrition. 2022; 62: 832–859. https://doi.org/10.1080/10408398.2020.1829541.

[125] Ning N, Nan Y, Chen G, Huang S, Lu D, Yang Y, *et al*. Anti-Tumor Effects and Toxicity Reduction Mechanisms of Prunella vulgaris: A Comprehensive Review. Molecules: A Journal of Synthetic Chemistry and Natural Product Chemistry. 2024; 29: 1843. https://doi.org/10.3390/molecules29081843.

[126] Pandian SRK, Pavadai P, Vellaisamy S, Ravishankar V, Palanisamy P, Sundar LM, *et al*. Formulation and evaluation of rutin-loaded solid lipid nanoparticles for the treatment of brain tumor. Naunyn-Schmiedeberg's Archives of Pharmacology. 2021; 394: 735–749. https://doi.org/10.1007/s00210-020-02015-9.

[127] Wu P, Wang X, Yin M, Zhu W, Chen Z, Zhang Y, *et al*. ULK1 Mediated Autophagy-Promoting Effects of Rutin-Loaded Chitosan Nanoparticles Contribute to the Activation of NF-κB Signaling Besides Inhibiting EMT in Hep3B Hepatoma Cells. International Journal of Nanomedicine. 2024; 19: 4465–4493. https://doi.org/10.2147/IJN.S443117.

[128] Fu S, Cai Z, Gu H, Lui S, Ai H, Song B, *et al*. Rutin-coated ultrasmall manganese oxide nanoparticles for targeted magnetic resonance imaging and photothermal therapy of malignant tumors. Journal of Colloid and Interface Science. 2024; 670: 499–508. https://doi.org/10.1016/j.jcis.2024.05.067.

[129] Paudel KR, Wadhwa R, Tew XN, Lau NJX, Madheswaran T, Panneerselvam J, *et al*. Rutin loaded liquid crystalline nanoparticles inhibit non-small cell lung cancer proliferation and migration in vitro. Life Sciences. 2021; 276: 119436. https://doi.org/10.1016/j.lfs.2021.119436.

[130] Radwan RR, Ali HE. Radiation-synthesis of chitosan/poly (acrylic acid) nanogel for improving the antitumor potential of rutin in hepatocellular carcinoma. Drug Delivery and Translational Research. 2021; 11: 261–278. https://doi.org/10.1007/s13346-020-00792-7.

[131] Münster L, Capáková Z, Fišera M, Kuřitka I, Vícha J. Biocompatible dialdehyde cellulose/poly(vinyl alcohol) hydrogels with tunable properties. Carbohydrate Polymers. 2019; 218: 333–342. https://doi.org/10.1016/j.carbpol.2019.04.091.

[132] Li W, Gong H, Yan S, Fu Y, Huang J, Mei Y, *et al*. Effective Delivery of Rutin Through Astragalus Polysaccharides Micelles for Downregulating PD-L1 by Inhibiting Matrix Metalloproteinases. ACS Applied Materials & Interfaces. 2025; 17: 56422–56438. https://doi.org/10.1021/acsami.5c11872.

[133] Stoyanova N, Spasova M, Manolova N, Rashkov I, Georgieva A, Toshkova R. Quercetin- and Rutin-Containing Electrospun Cellulose Acetate and Polyethylene Glycol Fibers with Antioxidant and Anticancer Properties. Polymers. 2022; 14: 5380. https://doi.org/10.3390/polym14245380.

[134] Yue S, Zhang P, Qin M, Zhu L, Qiao Y, Li Q, *et al*. An Enzyme-Like Activity Nanoprobe Based on Fe(III)–Rutin Hydrate Biomineral for MR Imaging and Therapy of Triple Negative Breast Cancer. Advanced Functional Materials. 2022; 32: 2202848. https://doi.org/10.1002/adfm.202202848.

[135] Zhang W, Wang X, Wang P, Li Q, Zhang Y, Meng X, *et al*. Glucose transporter protein 1-targeted polymetallic coordination nanopolymer remodeled cisplatin-resistant microenvironment for enhanced chemotherapy of lung cancer. Journal of Colloid and Interface Science. 2025; 700: 138424. https://doi.org/10.1016/j.jcis.2025.138424.

[136] Lu M, Ding J, Zhang Y, Gu X, Liu J, Wang Q, *et al*. Fe-coordinated carbon dots with single atom nanozyme catalytic activity for synergistic catalytic/chemo-therapy in breast cancer. International Journal of Biological Macromolecules. 2024; 283: 137776. https://doi.org/10.1016/j.ijbiomac.2024.137776.

[137] Pan RY, Ma J, Kong XX, Wang XF, Li SS, Qi XL, *et al*. Sodium rutin ameliorates Alzheimer's disease-like pathology by enhancing microglial amyloid-β clearance. Science Advances. 2019; 5: eaau6328. https://doi.org/10.1126/sciadv.aau6328.

[138] Ouyang Q, Liu K, Zhu Q, Deng H, Le Y, Ouyang W, *et al*. Brain-Penetration and Neuron-Targeting DNA Nanoflowers Co-Delivering miR-124 and Rutin for Synergistic Therapy of Alzheimer's Disease. Small. 2022; 18: e2107534. https://doi.org/10.1002/smll.202107534.

[139] Zhang L, Hou S, Movahedi F, Li Z, Li L, Hu J, *et al*. Amyloid-β/Tau burden and neuroinflammation dual-targeted nanomedicines synergistically restore memory and recognition of Alzheimer's disease mice. Nano Today. 2023; 49: 101788. https://doi.org/10.1016/j.nantod.2023.101788.

[140] Chau Y, Li FS, Levsh O, Weng JK. Exploration of icariin ana-

log structure space reveals key features driving potent inhibition of human phosphodiesterase-5. PLoS One. 2019; 14: e0222803. https://doi.org/10.1371/journal.pone.0222803.

[141] He C, Wang Z, Shi J. Pharmacological effects of icariin. Advances in Pharmacology. 2020; 87: 179–203. https://doi.org/10.1016/bs.apha.2019.10.004.

[142] Zheng X, Li D, Li J, Wang B, Zhang L, Yuan X, *et al*. Optimization of the process for purifying icariin from Herba Epimedii by macroporous resin and the regulatory role of icariin in the tumor immune microenvironment. Biomedicine & Pharmacotherapy = Biomédecine & pharmacothérapie. 2019; 118: 109275. https://doi.org/10.1016/j.biopha.2019.109275.

[143] Song L, Chen X, Mi L, Liu C, Zhu S, Yang T, *et al*. Icariin-induced inhibition of SIRT6/NF-κB triggers redox mediated apoptosis and enhances anti-tumor immunity in triple-negative breast cancer. Cancer Science. 2020; 111: 4242–4256. https://doi.org/10.1111/cas.14648.

[144] Zhao M, Xu P, Shi W, Wang J, Wang T, Li P. Icariin exerts anti-tumor activity by inducing autophagy via AMPK/mTOR/ULK1 pathway in triple-negative breast cancer. Cancer Cell International. 2024; 24: 74. https://doi.org/10.1186/s12935-024-03266-9.

[145] Ji Y, Zhang Z, Hou W, Wu M, Wu H, Hu N, *et al*. Enhanced antitumor effect of icariin nanoparticles coated with iRGD functionalized erythrocyte membrane. European Journal of Pharmacology. 2022; 931: 175225. https://doi.org/10.1016/j.ejphar.2022.175225.

[146] Gao X, Wang W, Gao M. Preparation of Novel ICT-CMC-CD59sp Drug-Loaded Microspheres and Targeting Anti-Tumor Effect on Oral Squamous Cell Carcinoma. Frontiers in Bioengineering and Biotechnology. 2022; 10: 878456. https://doi.org/10.3389/fbioe.2022.878456.

[147] Liu J, Lin S, Dang J, Wang S, Cheng W, Ran Z, *et al*. Anticancer and bone-enhanced nano-hydroxyapatite/gelatin/polylactic acid fibrous membrane with dual drug delivery and sequential release for osteosarcoma. International Journal of Biological Macromolecules. 2023; 240: 124406. https://doi.org/10.1016/j.ijbiomac.2023.124406.

[148] Xiong B, Shao X, Fang G, Dong M, Han H, Li Q. Porous PLGA microspheres for the inhalation delivery of icariin and miR-23b in the treatment of metastatic lung cancer. Asian Journal of Pharmaceutical Sciences. 2025; 20: 101008. https://doi.org/10.1016/j.ajps.2024.101008.

[149] Liu M, Wang B, Guo C, Hou X, Cheng Z, Chen D. Novel multifunctional triple folic acid, biotin and CD44 targeting pH-sensitive nano-actiniaes for breast cancer combinational therapy. Drug Delivery. 2019; 26: 1002–1016. https://doi.org/10.1080/10717544.2019.1669734.

[150] Poon CC, Au-Yeung C, Wong KY, Chan Z, Zhou LP, Li G, *et al*. Icariin promotes cell adhesion for osteogenesis in bone marrow stromal cells via binding to integrin $\alpha5\beta1$. Phytomedicine: International Journal of Phytotherapy and Phytopharmacology. 2024; 133: 155887. https://doi.org/10.1016/j.phymed.2024.155887.

[151] Bai L, Liu Y, Zhang X, Chen P, Hang R, Xiao Y, *et al*. Osteoporosis remission via an anti-inflammaging effect by icariin activated autophagy. Biomaterials. 2023; 297: 122125. https://doi.org/10.1016/j.biomaterials.2023.122125.

[152] Li X, Sun Z, Shang X, Chen L, Shi X, Xu W, *et al*. Sequential delivery of IL-10 and icariin using nanoparticle/hydrogel hybrid system for prompting bone defect repair. Materials Today. Bio. 2024; 29: 101374. https://doi.org/10.1016/j.mtbio.2024.101374.

[153] Zeng J, Sun P, Zhao Y, Fang X, Wu Z, Qi X. Bone mesenchymal stem cell-derived exosomes involved co-delivery and synergism effect with icariin via mussel-inspired multifunctional hydrogel for cartilage protection. Asian Journal of Pharmaceutical Sciences. 2023; 18: 100799. https://doi.org/10.1016/j.ajps.2023.100799.

[154] Hu X, Yang S, Zhao W, Zhang Z, Qiao L, Wu H, *et al*. Novel multi-functional microsphere scaffold with shape memory function for bone regeneration. Biomaterials Advances. 2024; 163: 213958. https://doi.org/10.1016/j.bioadv.2024.213958.

[155] Wu Y, Zhu Y, Chen J, Song L, Wang C, Wu Y, *et al*. Boosting mRNA-Engineered Monocytes via Prodrug-Like Microspheres for Bone Microenvironment Multi-Phase Remodeling. Advanced Healthcare Materials. 2025; 14: e2403212. https://doi.org/10.1002/adhm.202403212.

[156] Chen J, Cong X. Surface-engineered nanoparticles in cancer immune response and immunotherapy: Current status and future prospects. Biomedicine & Pharmacotherapy = Biomédecine & Pharmacothérapie. 2023; 157: 113998. https://doi.org/10.1016/j.biopha.2022.113998.

[157] Gowd V, Ahmad A, Tarique M, Suhail M, Zughaibi TA, Tabrez S, *et al*. Advancement of cancer immunotherapy using nanoparticles-based nanomedicine. Seminars in Cancer Biology. 2022; 86: 624–644. https://doi.org/10.1016/j.semcancer.2022.03.026.

[158] Osborn LJ, Claesen J, Brown JM. Microbial Flavonoid Metabolism: A Cardiometabolic Disease Perspective. Annual Review of Nutrition. 2021; 41: 433–454. https://doi.org/10.1146/annurev-nutr-120420-030424.

[159] Wang D, Chen J, Pu L, Yu L, Xiong F, Sun L, *et al*. Galangin: A food-derived flavonoid with therapeutic potential against a wide spectrum of diseases. Phytotherapy Research: PTR. 2023; 37: 5700–5723. https://doi.org/10.1002/ptr.8013.

[160] Zhu M, Sun Y, Su Y, Guan W, Wang Y, Han J, *et al*. Luteolin: A promising multifunctional natural flavonoid for human diseases. Phytotherapy Research: PTR. 2024; 38: 3417–3443. https://doi.org/10.1002/ptr.8217.

[161] Liu F, Xiang Q, Luo Y, Luo Y, Luo W, Xie Q, *et al*. A hybrid nanopharmaceutical for specific-amplifying oxidative stress to initiate a cascade of catalytic therapy for pancreatic cancer. Journal of Nanobiotechnology. 2023; 21: 165. https://doi.org/10.1186/s12951-023-01932-0.

[162] Khan H, Ullah H, Martorell M, Valdes SE, Belwal T, Tejada S, *et al*. Flavonoids nanoparticles in cancer: Treatment, prevention and clinical prospects. Seminars in Cancer Biology. 2021; 69: 200–211. https://doi.org/10.1016/j.semcancer.2019.07.023.

[163] Peng S, Wang Y, Sun Z, Zhao L, Huang Y, Fu X, *et al*. Nanoparticles loaded with pharmacologically active plant-derived natural products: Biomedical applications and toxicity. Colloids and Surfaces. B, Biointerfaces. 2023; 225: 113214. https://doi.org/10.1016/j.colsurfb.2023.113214.

[164] Alhalmi A, Amin S, Ralli T, Ali KS, Kohli K. Therapeutic role of naringin in cancer: molecular pathways, synergy with other agents, and nanocarrier innovations. Naunyn-Schmiedeberg's Archives of Pharmacology. 2025; 398: 3595–3615. https://doi.org/10.1007/s00210-024-03672-w.

[165] Zhang L. Pharmacokinetics and drug delivery systems for puerarin, a bioactive flavone from traditional Chinese medicine. Drug Delivery. 2019; 26: 860–869. https://doi.org/10.1080/10717544.2019.1660732.

[166] Zheng H, Chen Y, Luo W, Han S, Sun M, Lin M, *et al*. Integration of active ingredients from traditional Chinese medicine with nano-delivery systems for tumor immunotherapy. Journal of Nanobiotechnology. 2025; 23: 357. https://doi.org/10.1186/s12951-025-03378-y.

[167] Fang H, Xu J, Zhu J, Ma H, Feng Z, Du J, *et al*. A Multifunctional Microneedle Patch Combined with Quercetin Nanoparticles for Local Drug Release Therapy and Wound Healing after Skin Tumor Surgery. ACS Applied Materials & Interfaces. 2025; 17: 50261–50278. https://doi.org/10.1021/acsami.5c10174.

[168] Cristani M, Citarella A, Carnamucio F, Micale N. Nano-Formulations of Natural Antioxidants for the Treatment of Liver Cancer. Biomolecules. 2024; 14: 1031. https://doi.org/10.3390/biom14081031.

[169] Dobrzynska M, Napierala M, Florek E. Flavonoid Nanoparticles:

A Promising Approach for Cancer Therapy. Biomolecules. 2020; 10: 1268. https://doi.org/10.3390/biom10091268.

[170] Rebouças LM, Sousa ACC, Sampaio CG, Silva LMR, Costa PMS, Pessoa C, *et al*. Microcapsules based on alginate and guar gum for co-delivery of hydrophobic antitumor bioactives. Carbohydrate Polymers. 2023; 301: 120310. https://doi.org/10.1016/j.carbpol.2022.120310.

[171] Rashedi J, Ghorbani Haghjo A, Mesgari Abbasi M, Dastranj Tabrizi A, Yaqoubi S, Sanajou D, *et al*. Anti-tumor Effect of Quercetin Loaded Chitosan Nanoparticles on Induced Colon Cancer in Wistar Rats. Advanced Pharmaceutical Bulletin. 2019; 9: 409–415. https://doi.org/10.15171/apb.2019.048.

[172] Wang L, He S, Liu R, Xue Y, Quan Y, Shi R, *et al*. A pH/ROS dual-responsive system for effective chemoimmunotherapy against melanoma via remodeling tumor immune microenvironment. Acta Pharmaceutica Sinica. B. 2024; 14: 2263-2280. https://doi.org/10.1016/j.apsb.2023.12.001.

[173] Jin QR, Zhou TJ, Yao YT, Yu HQ, Che HB, Zhang MM, *et al*. Icaritin-incorporated dual-sensitizing hydrogel for osteosarcoma doxorubicin treatment and bone regeneration. Chinese Chemical Letters. 2025; 37: 111539. https://doi.org/10.1016/j.cclet.2025.111539.

[174] Xia J, Xu M, Hu H, Zhang Q, Yu D, Cai M, *et al*. 5,7,4'-Trimethoxyflavone triggers cancer cell PD-L1 ubiquitin-proteasome degradation and facilitates antitumor immunity by targeting HRD1. MedComm. 2024; 5: e611. https://doi.org/10.1002/mco2.611.

[175] Gao S, Lv R, Hao N, Wang H, Lv Y, Li Y, *et al*. Fabrication of pH/photothermal-responsive ZIF-8 nanocarriers loaded with baicalein for effective drug delivery and synergistic chem-photothermal effects. Colloids and Surfaces A: Physicochemical and Engineering Aspects. 2023; 668: 131401. https://doi.org/10.1016/j.colsurfa.2023.131401.

Editor's note: The Scientific Editors responsible for this paper were Yang Liu and Kelong Fan.

Received: 25th August 2025; **Accepted**: 18th March 2026; **Published**: 29th May 2026