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Controlled drug delivery systems for improved efficacy and bioavailability of flavonoids

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ABSTRACT

Purpose: In past decades, experiments have been done to find the properties of plant polyphenols and their protective role in various diseases. In the present study, a brief review has been done on flavonoids' protective role in different diseases and controlled drug delivery systems that can be feasible for improving flavonoids' bioavailability as well as their efficacy in the biological system.

Design/methodology/approach: Keywords searched in PubMed, and Google Scholar are "Flavones and cardiovascular diseases, flavones and neurodegenerative diseases, isoflavones and neurodegenerative diseases, Flavonoids and ageing, Flavonoids and diseases, total flavonoid content in vegetables, total flavonoid content in fruits, controlled drug delivery system and flavonoids" and the significant recent articles are selected for writing this review.

Findings: Flavonoids are active components present in plant products that have been found to exert several health benefits, especially in retarding the deleterious effects of CVD, cancer, ageing, diabetes, and neurodegenerative diseases. The different clinical studies have also supported the above notions, and in this commentary, we have highlighted some important findings in the field of flavonoid research. Even though it has various bioactive efficacy, most flavonoids have less bioavailability, requiring controlled drug delivery methods that can also improve flavonoids' bioavailability and stability. pH-, electro-, infrared radiation-, redox-responsive methods of controlled drug release systems are some of the valuable techniques for improving the rate of drug release and bioavailability at the targeted site.

Research limitations/implications: Research is warranted in this field for improving and developing various materials that can be utilized in the formation of scaffolds/polymers that improves drug loading and controlled drug release properties at the targeted site.

Originality/value: This review will help the readers to design new strategies in flavonoid research with the help of controlled drug release methods for increased bioavailability and rate of drug release/ controlled drug release.

Keywords: Flavonoids, Controlled drug delivery systems, pH-responsive, Electro-responsive, NIR-responsive

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1. Introduction

Flavonoids are polyphenolic compounds that widely occur in nature as glycosides and are found in fruits, vegetables, plants such as aerial parts of *Limonium sinense*, leaves, stem bark, roots of *Annonaceae* family species, roots of *Lonchocarpus latifolius* species. Grapes, green tea, cabbage, apples, berries, cherries, soybeans, citrus fruits, and onions are some known fruits and vegetables that contain a substantial amount of flavonoids [1-3]. The backbone structure of various types of flavonoids is shown in Figure 1. Flavonoids are antioxidants that can degrade free radicals generated by various reactions *in vitro* and *in vivo*. Flavonoids also exert effects like immune regulators and anti-inflammatory effects**,** showing anti-carcinogenic effects by regulating the cell cycle, cell signal transduction pathways and inhibiting angiogenesis [4]. Due to their antioxidant properties, flavonoids also mimic α-tocopherol, an endogenous membrane antioxidant, and can activate GSH without α-tocopherol to scavenge the free radicals [5]. Flavonoids act as immune modulators by acting on p38 mitogen-activated protein kinases (p38 MAPK), nuclear factor kappa B (NF-kB), signal transducer and activator of transcription 1(STAT1) signalling, interleukin 4 (IL-4), interleukin 10 (IL-10), interferon-α (INF-α), etc. and play a major role in the remedy of various disease [6]. Epigallocatechin gallate (EGCG) is a known flavonoid present in green tea. EGCG-treated human monocytes were found to release a higher amount of IL-1-like factor and can also initiate monocyte differentiation to dendritic cells [7]. Life span studies in some worms and flies suggest that flavonoids could extend their lifespan [8]. Some studies also suggested that polyphenolic compounds protect from oxidative stress-induced DNA damage and age-related diseases such as cardiovascular diseases, diabetes, neurodegenerative diseases, and cancer [9-11].

There are various nanoformulation techniques available for different types of molecules to overcome some limitations, such as hydrophilicity, hydrophobicity, bioavailability, stability, or several types of biological conditions, like, acidic or basic pH, or different types of drug administration routes, such as oral, nasal, intravenous routes.

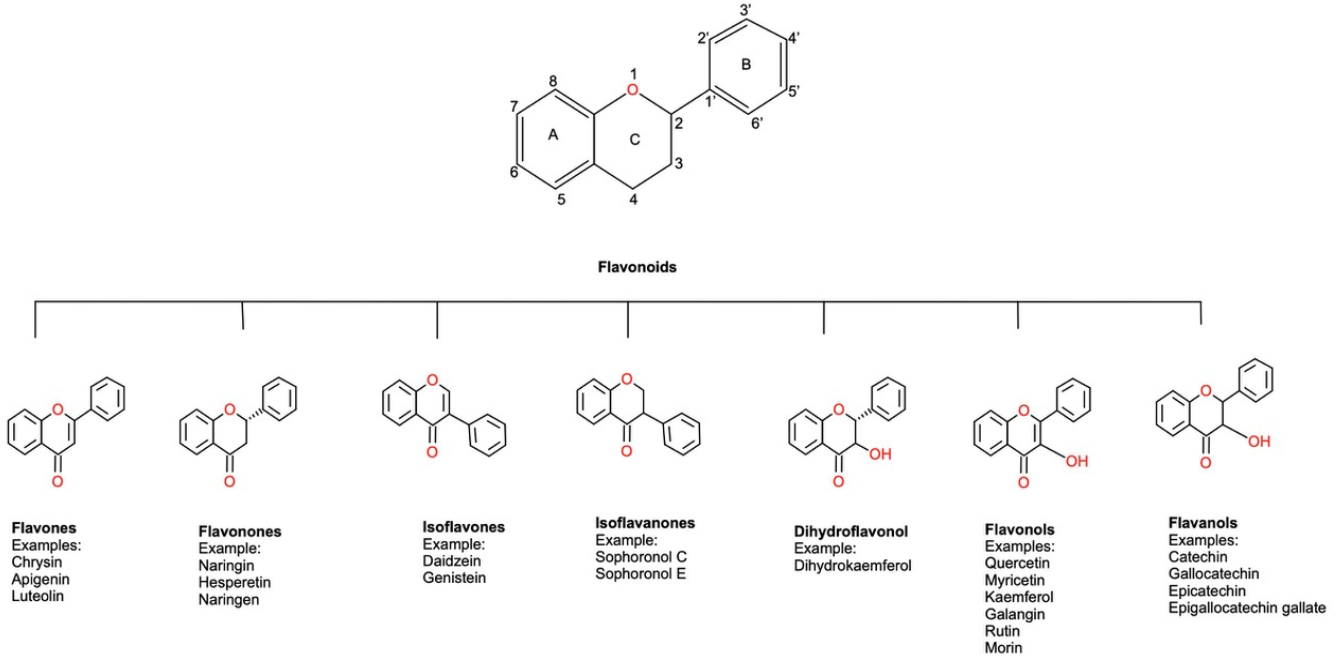

Fig. 1. The backbone structures of different flavonoids

Numerous traditional nanoformulations are developed to enhance the bioavailability of the drug, such as micelles, liposomes, polymeric nanoparticles, gold nanoparticles, and solid lipid nanoparticles. Liposomes are spherical-shaped vesicles synthesized from cholesterol and phospholipids, and liposomes consist of a hydrophilic head and hydrophobic tail representing the phospholipid membrane. Liposomes can be used to carry drugs to selective sites as a drug delivery system. Agraharam et al. reported liposomal nanoparticles loaded with myricetin. The results showed that myricetin-loaded liposomal nanoparticles showed increased antioxidant activity than myricetin alone [2]. Solid lipid nanoparticles (SLNs) consist of fatty acids or mono-, di, triglycerides with highly lipophilic property that facilitates SLNs' efficient drug delivery and blood-brain barrier crossing property to deliver the therapeutic drugs to the brain. SLNs characteristics include high bioavailability, capable of the central nervous system (CNS) targeting, good tolerance, and biodegradable without forming toxicity [12].

Polymers are important in encapsulating drug molecules/lead molecules for efficient drug delivery. Chitosan has more advantages than the other type of polymers for stabilizing food nano nanoparticles that have antimicrobial activity, cost, and excess availability, structure, and charge. Numerous data exist on nanoformulations using chitosan to deliver miscellaneous molecules or drugs [13]. Ullah et al. reported chitosan and starch copolymerized nano hydrogels for the controlled drug delivery of hydrophobic drugs. This is multi-responsive to various factors such as pH, temperature, ionic strength, and urea [14,15]. Graphene-based polymeric nano-composites also have a pivotal role in nanotechnology for drug delivery [16]. Mucoadhesive nanoparticles show a prominent role in stomach-specific oral drug delivery of molecules such as drugs, proteins, and peptides for optimal bioavailability by bonding and releasing the drugs near the site of absorption of GI tract mucosal layers [17]. There are also advancements in developing membrane-encapsulated drugs by isolating the membranes from the various types of cells obtained from the host. This can further facilitate developing the nano-formulated personalised medicines [18].

Tefas et al. reported the optimization of quercetin-loaded liposomes through a D-optimal experimental design. They found the DPPC, DPPC: CHOL molar ratio, and quercetin optimum values as 89.99 mM, 5.31, and 3.32 mM, respectively. The experimental values indicated that under predicted optimum values of materials used, the nanoparticle size was around 211.90 nm, and the encapsulation efficiency was around 61.25% [19]. Jangde et al. synthesized quercetin-loaded liposomal nanoparticles by following a thin film hydration method for wound healing purposes. They found that the particle size and entrapment efficiency were around 146.8, and 86.5%, respectively. The drug release profile of quercetin-loaded liposomes showed prolonged release during 24 h, with up to 75.09% drug being released [20]. Solid lipid nanoparticles loaded with total flavonoid extract extracted from *Dracocephalum moldavica L.* were reported, and the average nanoparticle size was 104.83 nm with a zeta potential value of -28.7. The pharmacodynamics study revealed that total flavonoid extract-loaded solid lipid nanoparticles showed myocardial protection than alone treatment of total flavonoid extract in myocardial ischemia-reperfusion injured rats [21]. Liu et al. formulated quercetin-loaded nanoparticles by solid lipid nanoparticles and nanoemulsion, and the particle size was around 150-345 nm. Quercetin delivery from SLNs was confirmed by ex vivo porcine eyes and confocal microscopy, which indicated that quercetin-loaded SLNs could protect cornea and retinal ganglion cells [22].

Metal nanoparticles such as gold, iron, and zinc also play a pivotal role in delivering drugs, therapies, and biomedical imaging [23-27]. Nanotechnology is a blooming field of biomedical science with enormous applications in drug delivery, imaging, theranostics, and biosensors [28,29]. This review paper briefly deals with the protective effects of different types of dietary polyphenols, such as flavonoids, flavonols, flavones against various diseases, and controlled drug delivery systems for delivering flavonoids at the targeted site that could help to improve bioavailability, stability, and efficacy of the drug.

2. Effects of flavonoids intake on cardiovascular diseases

Cardiovascular diseases rank first as the leading cause of death globally [30]. In atherosclerosis, the arteries become hard and narrow, making it difficult for the blood to pass and eventually leading to bold clot formation, causing cardiovascular disease (CVD) and heart attacks. Previous reports exist that the intake of citrus fruits alleviates the levels of plasma triglycerides in CVD patients, and the intake of glucosyl hesperidin (500 mg/day for 6/24 weeks) decreased triglycerides in people with hyperlipidemia and hyperglyceridemia. Moreover, intake of naringin (400 mg/day for 56 days) could reduce around 17% of low-density lipoprotein cholesterol (LDL-C) and apoB levels in plasma [31]. Treatment with naringenin and naringin to the rabbit under a high cholesterol diet showed reduced aortic fatty streaks. Rabbits fed with cholesterol and 500 mg/kg naringin decreased vascular fatty streak arrangement and macrophage infiltration in vascular walls [32]. In a randomized, double-blind study by Sánchez Macarro and colleagues for the efficiency of an 8-week daily regimen of flavones and flavanones such as grapefruit, bitter orange

immature fruits, and olive leaf extracts on the reduction of cardiovascular risk in humans was done. A total of 51 subjects were finalized. The study resulted in improved endothelial function, reduced blood pressure and lipid metabolism-related parameters, and improved antioxidant and inflammatory status by consuming flavones and flavanones [33]. An eight-week daily regimen with supplementation of 2 capsules a day (500 mg each) that contained grapefruit, bitter orange immature fruits, and olive leaf extracts. These extracts contained naringin, narirutin, rhoifolin, poncirin, apigenin, *Citrus paradisi* Macfad, *Citrus aurantium* L., neohesperidin, neodiosmin, luteolin, *Olea europaea* L., olive secoiridois, oleuropein family, hydroxytyrosol and the tablets were consumed in the morning and evening for the reduction of cardiovascular risk. The results showed changes in flow-mediated dilation (FMD), blood pressure and lipid profile, antioxidant and anti-inflammatory status, and there was a 63-65% increase in GSH/GSSH ratio, a 30-32% reduction in the protein carbonyl level and reduction in ox-LDL was observed [33]. 40 Obese/ overweight adult individuals who were at high risk of CVD received grape seed extract (300 mg/day, 12 weeks) that resulted in improved LDL-C, high-density lipoprotein cholesterol (HDL-C), visceral adiposity index (VAI), atherogenic index of plasma (AIP) [34]. An effect of high dose consumption of flavonoids within less time (black tea flavonols, 400 mg for 120 min) and lower dose for a more extended period (apple flavonols, 270 mg/day, four weeks; epicatechin, 25 mg/day, two weeks) has no protective effect on endothelial function, cardiometabolic risk factors [35-37].

3. Effects of flavonoids intake on neurodegenerative diseases

In a study on Parkinson's disorder (PD) patients, Fan et al. reported that supplementation of blackcurrant capsules (35% anthocyanins) that consisted of Cyclic Glycine-Proline (cGP), a neuropeptide for 28 days resulted in enhancement of CSF cGP concentration in a dose-dependent manner. The mean percentage of cGP concentration was increased by 74.36% after supplementation, which could help to improve IGF-1 function in PD brains [38]. In a study on 51 multiple cases of sclerosis (MS) patients, supplementation of EGCG for a 4-month duration resulted in no difference between the control and intervention groups. The same 48 weeks of EGCG treatment on MS atrophy patients showed no difference, and a higher dose (1200 mg/ day) caused hepatotoxic effects [39,40]. Cosmos caudatus capsule that contains quercetin, catechin, epicatechin, and proanthocyanidins (250 mg of CC powder and 250 mg of maltodex/ 12 weeks) were supplemented to older adults with mild cognitive impairment aged between 60-75 years. It was found that CC supplementation ameliorated global cognitive function and improved tension and mood disturbance, decreased malondialdehyde levels and increased serum glutathione (GSH) levels [41].

4. Intake of flavonoids for healthy ageing

Ageing is associated with postprandial muscle vascular and metabolic dysfunction. An effect of acute 33 g of high cocoa flavanol chips that contained 450 -500 mg of cocoa flavanols supplementation on older adults aged >65 resulted in increased microvascular blood volume (MBV) [42]. Fifty-one subjects aged over 60 years who consumed polyphenol-rich food found that dietary polyphenols have initiated disturbance in the gut microbiota composition. This led to intestinal permeability, increased bioavailability, and different microbial metabolites that might contribute to the biological activity of the polyphenols in older adults [43]. In a total of 118 subjects with peripheral artery disease, a 6-month chronic supplementation of cocoa beverage that contained 15 g of cocoa (75 mg of epicatechin) improved walking performance, mitochondrial cytochrome c oxidase activity, and increased capillary density in treatment groups [44].

5. Other protective effects of flavonoids

Flavonoids are plant polyphenols that have been shown to exert many beneficial effects, and their effects are enhanced with nanoformulations [45]. Insomnia is a common sleep disorder defined as difficulties in sleeping [46]. Food anthocyanins by consumption of 250 mL of Queen Garnet plum juice in a 4-day period alleviated vascular and inflammatory responses to a high fat and high energy diet in obese adults when tested on 16 subjects aged >55 years. This improved various CVD biomarkers overnight, and beneficial effects were observed in macrovascular and microvascular function and inflammatory biomarkers [47]. Mild cognitive impairment (MCI) is an early stage of memory loss where inflammatory markers are also involved. In a study on 31 elderly subjects who consumed 250 mL of fruit juice consumption daily for eight weeks with a high dose of anthocyanins content (201 mg/ day), a decrease in the concentrations of serum tumour necrosis factor-alpha (TNF- α) was observed compared to control and the group with low anthocyanin supplementation [48]. 38 Parkinson's disease (PD) patients were supplemented with soy isoflavone 100 mg/day for eight weeks and the results showed that fasting serum glucose and pentosidine reduced significantly in the isoflavone group at the end of the 8th week compared to the control group who did not consume soy flavone [49]. These reports indicate the

importance of the intake of flavonoids through our food sources. Table 1 contains the number of flavonoids present in the different types of fruits and vegetables.

Table 1.
Flavonoids content in fruits and vegetables [50,51]

S/ No.	Name of the fruit/ vegetable	Total content of flavonoids, mg/kg
1.	Onion leaves	2720.5
2.	Semambu leaves/ neem leaves	2041
3.	Bird chilli	1663
4.	Black tea	1491
5.	Papaya shoots	1264
6.	Guava	1128.5
7.	Turmeric	92.5
8.	Green chilli	83.5
9.	Saybean sprout	78.5
10.	Snake gourd	73.9
11.	Limau purat leaves	72
12.	White radish	65
13.	mint	48.5
14.	Red spinach	29.5
15.	Broccoli	197
16.	Lemon grass	178
17.	Drumstick leaves	232.5
18.	pumpkin	371
19.	brinjal	219.5
20.	Cashew shoots	450.5
21.	garlic	957
22.	Bell pepper	892
23.	cabbage	147.5
24.	Bell pepper	892
25.	cauliflower	219
26.	Lady's fingers	260

6. Controlled drug delivery systems

The types of controlled drug delivery systems and materials used are shown in Table 2 and described in the following subsections.

6.1. pH- / Redox- responsive drug delivery systems

The interstitial pH of the normal tissues is in the range of 7.3 to 7.4. Still, under some conditions, this value fluctuates, such as, in the pancreas, colon, and ventricle epithelia, due to the secretion of intense acid and base and in skeletal muscle during physical activities. Other than these, various non-cancerous disease conditions such as inflammatory states, ischemia, and systematic respiratory or metabolic disturbances are also associated with acidosis. The tumour microenvironment's characteristics provide an acidic condition ranging from 5.6 to 7 [52]. These differential pH conditions at different biological environments provide a way to develop pH-dependent drug-releasing material/ polymers to release loaded drugs at specific pH conditions.

Kundu et al. reported the delivery of curcumin via phenylboronic acid-functionalized ZnO nanoparticles that are pH responsive and used them for breast cancer therapy. The group first synthesized ZnO and ZnO-NH_2 nanoparticles, and then the nanoparticles were tagged with 3-carboxybenzeneboronic acid (PBA). Further, the formulated nanoparticles were added to the curcumin solution for loading. The TEM analysis of curcumin-loaded ZnO-PBA NPs showed a size of around 30-40 nm. The average hydrodynamic diameter was measured for ZnO NPs (166.3 nm), ZnO-PBA (284.96), and curcumin-loaded ZnO-PBA (413.63 nm). The pH response was tested, and it was found that approximately 56% of the loaded curcumin was released from the nanoparticle at pH. 5.0. *In vitro* cytotoxic studies on MCF-7(breast cancer cells) indicated that rather than ZnO NP's, curcumin the curcumin-loaded ZnO-PBA nanoparticle exhibited higher cytotoxic effect, indicating improved efficacy of the polyphenol-loaded nanoparticles [53].

At pH 3.5, gellan gum is a polyanionic polysaccharide, which gives a dense polyelectrolyte composite with polycationic materials. de Oliveira *et al*. also reported chitosan/ gellan gum hydrogel beads incorporated with the β-cyclodextrin/curcumin complex for effective curcumin delivery. The encapsulation efficiency (EE) was 83.24-85.94% [54]. Dey *et al.* reported that they had prepared quercetin-loaded gellan gum hydrogels using calcium chloride as a crosslinking agent with intestinal stability and pH-sensitive release of the loaded drug. The size of the formulated hydrogel beads was 560-844 nm, and the entrapment efficiency was 58.56-93.71 % [55].

Tan et al. reported ROS-responsive nanoparticles loaded with luteolin for treating ulcerative colitis. The nanoparticle was fabricated for ROS cleavage with a D-α-tocopherol polyethylene glycol succinate-b-poly(β-thioester) copolymer (TPGS-PBTE). The TPGS-PBTE showed a size change in response to ROS and released the drug. *In vitro* drug release kinetics showed 88.6% luteolin released in the presence of H_2O_2. *In vivo* study was executed on the dextran sulfate sodium-induced acute colitis murine model. Luteolin-loaded TPGS-PBTE NPs were found to elicit lower loss in body weight, reduced colonic tissue damage by alleviating ROS, and attenuated colon length shortening and pro-inflammatory cytokines [56].

Table 2.
Type of controlled drug delivery systems and materials used

S/No.	Type of controller for the drug delivery	Name of the flavonoid	Name of the nanoformulation/ material used	References
1.	pH- / Redox- responsive	Curcumin	ZnO-3-carboxybenzeneboronic acid (PBS) (ZnO-PBA NPs)	[53]
2.	pH- / Redox- responsive	Curcumin	Chitosan/ gellan gum hydrogel beads	[54]
3.	pH- / Redox- responsive	Quercetin	gellan gum hydrogels	[55]
4.	pH- / Redox- responsive	luteolin	D-α-tocopherol polyethylene glycol succinate-b-poly(β-thioester) copolymer (TPGS-PBTE) NPs	[56]
5.	Photothermal- responsive	Quercetin	Prussian blue (PB) and zeolite imidazolate framework 8 (ZIF-8) ZIF-8/PB NPs	[57]
6.	NIR responsive	Quercetin	Gold nanocages (AuNPs)	[58]
7.	Electro-responsive	Quercetin	Graphene Oxide (GO), poly-lactic acid (PLA). GO/PLA NPs	[59]
8.	Thermo-responsive	Quercetin	mesoporous silica nanoparticle (MSN)	[60]
9.	Thermo-responsive	Curcumin	Poly (N-isopropylacrylamide-co-N,N-dimethylacrylamide)-b-poly(D,L-lactide) (PN-co-DM-bPA) and Polyvinyl alcohol (PVA)	[61]
10.	Sustained drug release	Myricetin	Liposomes	[2]

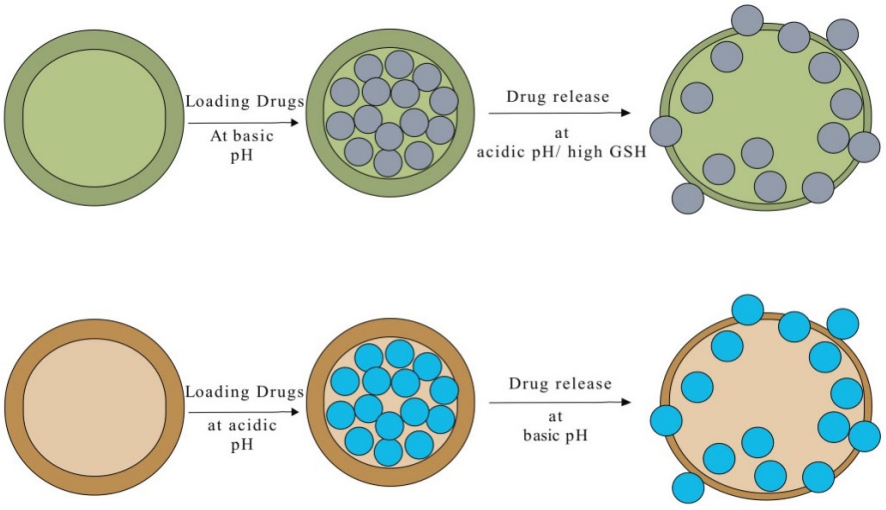

Fig. 2. Schematic representation of pH-responsive drug delivery

Sharmiladevi *et al*. developed Carbon decorated ferrite nanodots (CDs@MNFs) that sized D_h was 142 nm, and the zeta-potential was found to be -53.6 mV indicating strong stability, which can be used for magnetic resonance imaging (MRI). Doxorubicin was loaded into Carbon decorated ferrite nanodots through the electrostatic interactions. The loading efficiency was found to be 51.2%. The drug release was 88.91%, 58.87% at pH 6.2 and 7.4, respectively, indicating the acidic pH-responsive drug release property of the doxorubicin-loaded Carbon decorated ferrite nanodots (CDs@MNFs-DOX) [62]. Figure 2 represents the pH-responsive drug delivery.

6.2. Near-Infrared radiation / Photothermal-responsive drug delivery

Near-Infrared radiation (NIR) induced local mild hyperthermia has a negligible effect on normal tissue and

can deeply penetrate target tissues, which can be used as a therapeutic technique. Suppose NIR/ Photothermal-responsive nanoformulation-contained target site is exposed to the NIR. In that case, the nanoformulation starts to release the loaded drugs at the target site due to NIR/PT-induced temperature. Zhang *et al*. demonstrated gold nanocages (AuNCs) that are loaded with quercetin, doxorubicin as a drug, and tetradecanol (TD) as gatekeepers due to their melting point (39°C). The drug-loaded gold nanoparticles were coated with biotin for passage through the biotin receptors into the cell. The average D_h of AuNCs was 93.1 ± 1.2 nm, and the drug-loaded AuNPs (AuNPs-DQ) was 121.6 ± 2.4 nm. The results showed that zeta potential values for AuNPs-DQ were -18.3 ± 2.1. The loaded drug was 7.1 wt% for doxorubicin and 1.2% for quercetin, and it was found that AuNPs-DQ released drugs faster under NIR irradiation at 808 nm at 2.5 W/cm^2 / 40°C compared to body temperature [58]. Liu *et al*. reported the synthesis of Prussian blue (PB) and zeolite imidazolate framework 8 (ZIF-8) to formulate photothermal responsive nanocages. PB was used as photothermal responsive material due to its photo-absorbing property with strong light absorption in the 500-1000 nm band. US FDA approves PB, and PB nanoparticles can reverse radiation-induced damage. ZIF-8 has high thermal stability, can self-assemble around bio entities, and form a protective crystalline coating. This engineered shell acts as a smart gatekeeper to facilitate the loading and delivery of the loaded drugs. The prepared size of ZIF-8/PB NPs is 107 nm, and ZIF-8/PB-Q NPs is 143 nm, and the quercetin encapsulation efficiency was 61.3%, exhibiting high stability [57]. The schematic representation of NIR/PT responsive drug delivery is shown in Figure 3.

6.3. X-Ray irradiation responsive drug delivery

ROS is known to be generated in many types of cancer cells, which can act as endogenous stimuli to trigger drug release from ROS-responsive drug delivery materials. Zhang *et al*. reported diselenide-based nanocarriers that can cause X-ray-mediated, reactive oxygen species (ROS) dependent drug release. Diselenide-based nanocarriers can be easily prepared, biodegradable, and biocompatible, and also diselenides are responsive to ROS. Doxorubicin-loaded diselenide nanoparticle (Se-DOX-NPs) was prepared based on the amphiphilic triblock copolymer method with multiple diselenide groups. They found that the Se-NPs were insensitive at 2, 5, or 10 Gy of X-ray, but, in the presence of ROS, 2 Gy X-ray triggered the disassembly of the Se-NPs and released the drug. The authors reported that ROS stabilize the radiation-induced broken Se-Se linkages and facilitates the dissociation of Se-NPs that lead to the release of the entrapped drug. The preparation method includes synthesising selenium polymer (Se- Polymer) that can self-assemble into spherical micellar nanoparticles (Se-NPs) in an aqueous solution. Adding therapeutic drugs or flavonoids to the formulated Se- polymer could lead to the deformation of flavonoid-loaded x-ray-responsive Se- NPs. This technique can impart an impact on designing any formulation of flavonoid loaded X-ray responsive Se-NPs, that could be more efficient in the treatment of various diseases such as site-specific cancers [63].

6.4. Electro-responsive drug delivery systems

This method used electric stimulation to increase the drug release rate at the targeted site. Using compounds that

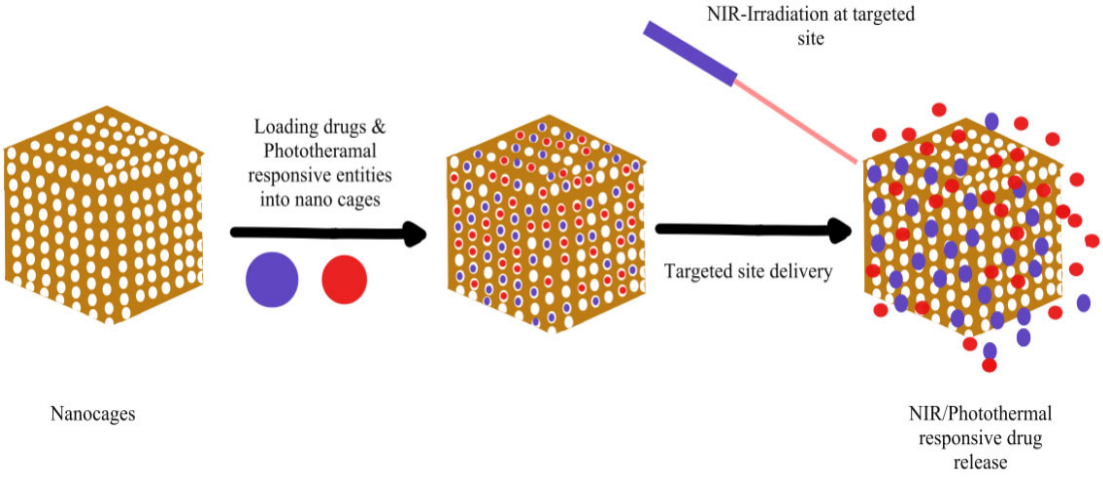

Fig. 3. Schematic representation of NIR responsive drug delivery

have the properties to be stimulated by electricity plays a pivotal role in developing polymer matrices/scaffolds. Using compounds such as Graphene Oxide (GO) that have electricity-triggering properties is one of the versatile methods for developing electro-responsive controlled drug delivery scaffolds. Croitoru et al. followed the electro-spinning method to prepare the electrically triggered drug-loaded scaffolds for wound healing purposes. They found that adding GO increased the hydrophilicity and permeability of the membranes by 8%. Quercetin (Q) was loaded in the nano scaffold composed of poly-lactic acid (PLA) and GO at the ratio 10% and 1%, respectively, with a size of 1.19 ± 163 µm. Electric stimulation (10/50 Hz) was applied to the scaffolds to increase the drug release rate within 1-2 min, whereas the same drug release rate was hundreds of min in other methods. PLA possesses drug compatibility and drug release kinetics by providing a hydrophobic barrier against water, and the use of GO improved the mechanical and physical properties of the polymer matrix. The increased recovery rate was observed for the bacteria *S. aureus*, *E. coli*, and *C. albicans*. These scaffolds showed >80% cell viability when L929 fibroblast cells were cultured on them. Moreover, quercetin-loaded scaffolds also stimulated the production of IL-6, indicating the potential wound healing property and the biocompatibility of PLA/GO/Q scaffold [59].

6.5. Thermoresponsive drug delivery system

Ugazio et al. formulated a thermoresponsive mesoporous silica nanoparticle (MSN) loaded with the flavonoid quercetin for the skin. The group functionalized two types of matrices, such as N-isopropylacrylamide (NIPAM) and 3-(methacryloxypropyl)trimethoxysilane (MPS), which represented as Copoly-MSN with a pore size of 3.5 nm and 5.0 nm. Then they added nanoparticles (bare/functionalized) to the quercetin. The reported nanoparticle size was 100-150 nm for the MSN nanoparticles. The quercetin-loaded MSN(Q/MSN) with pore size 3.5 nm showed optimum loading efficiency of quercetin (49.5%) than other functionalized and higher pore-sized nanoparticles, but the radical scavenging assay indicated that Q/MSN showed 72% of radical scavenging activity than free quercetin (3-40%), Q/copoly-MSN [60]. Ju et al. encapsulated curcumin (Cur) in thermo-sensitive PVA (Polyvinyl alcohol). The group first encapsulated curcumin in amphiphilic poly (N-isopropylacrylamide-co-N, N-dimethylacrylamide)-b-poly(D,L-lactide) (PN-co-DM-bPA) to form Cur-loaded micelles (CurM). Then the CurM was assembled with PVA by electrospinning method, and they formed PVA/CurM nanofibrous membranes (PCM). The drug loading efficiency was found to be around 58.5% with a micelle size of 292.8 nm, and the PCM nanofiber's average diameter was 251 nm. The temperature-responsive drug release experiments revealed 63.47% release of curcumin after 96h at temperatures higher than the 41°C. They found that the antibacterial activity of PCM was 95.16% and 93.59% on E.coli and S. aureus, respectively [61].

7. Conclusions

Flavonoids are plant polyphenols that have bioactive properties, and enormous *in vitro* and *in vivo* experiments have suggested their antioxidant properties and effectiveness in alleviating various disease conditions, thereby ameliorating the healthy condition. Due to the lower bioavailability, flavonoids cannot get absorbed as per requirement. The use of nanotechnology in improving drugs' bioavailability plays a vital role in treating many diseases. Still, the controlled drug delivery system is an in-depth branch of nanotechnology to improve drugs' bioavailability by utilizing various biological conditions such as pH, redox conditions, and oxidative stress to facilitate efficient drug delivery. This review has discussed the different roles of flavonoids in different diseased conditions. Later we discussed some of the types of targeted drug delivery systems. Future research is warranted to develop various controlled drug delivery systems with increased efficiency.

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Additional information

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