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MEDICAL BIOTECHNOLOGY

Modern Nanocarriers as a Factor in Increasing the Bioavailability and Pharmacological Activity of Flavonoids

Ya. F. Zverev[a], * and A. Ya. Rykunova[b]

[a] *Altai State Medical University, Barnaul, 656038 Russia*

[b] *Barnaul Law Institute, Ministry of Internal Affairs of Russia, Barnaul, 656038 Russia*

**e-mail: zveryasha@mail.ru*

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Abstract—This review is devoted to modern systems of nanocarriers that ensure the targeted delivery of flavonoids to various organs and systems. Flavonoids have wide range of effects on the human body due to their antioxidant, anti-inflammatory, antitumor, antimicrobial, antiplatelet and other types of activity. However, the low bioavailability of flavonoids significantly limits their practical application. To overcome this disadvantage, serious efforts have been made in recent years to develop nanoscale carriers for flavonoids. This is particularly important in view of the known antitumor effect of these compounds, which allows them to target tumor cells without affecting surrounding healthy tissues. Nanocarriers provide increased penetration of biologicals into specific organs in combination with controlled and prolonged release, which markedly improves their effectiveness. This review summarizes data on the use of phytosomes, lipid-based nanoparticles, as well as polymeric and inorganic nanoparticles; their advantages and drawbacks are analyzed; the prospect of their use is discussed that opens new possibilities for the clinical application of flavonoids.

Keywords: flavonoids, nanoparticles, flavonoid nanobiomaterials, drug delivery systems

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INTRODUCTION

Flavonoids are becoming more interesting as evidence accumulates about the beneficial effect of foods containing these compounds on human health. It is well known that flavonoids have antioxidant, anti-inflammaroty, anticarcinogenic, neuroprotective, antidiabetic, antimicrobial, and antitrombotic activity, and their application facilitates the course of various diseases [1–5]. This is of special importance due to the high availability and relative low cost of dietary flavonoids. However, it should be noted that flavonoid aglycons or polyphenol-rich extracts have mostly been studied in vitro, which raises two main concerns. First, in vivo, target organs in the body never come into direct contact with flavonoid aglycones, but only with their metabolites or conjugated forms. Second, the aglycone concentrations used in in vitro experiments are practically never achieved in the body [6, 7]. Moreover, with rare exceptions, native flavonoids (aglycones) cannot be detected in the blood [6–9], hence, there is no direct correlation between in vitro and in vivo experiments, and out-of-body reslts should be treated with caution.

The above problem, which often negates the therapeutic effectiveness of flavonoids, is mainly due to the low bioavailability of these compounds, i.e., only a small portion of the administered drug can reach the systemic circulation and target organs. The bioavailability of dietary polyphenols, like most other plant compounds, depends on numerous physicochemical and pharmacokinetic factors, including the chemical structure of representatives of a particular subclass of flavonoids, their polarity, molecular mass, plant matrix, sensitivity to pH and gastrointestinal enzymes, and degree of absorption in the small and large intestines. After absorption, lipophilic aglycones undergo metabolic transformation in the small intestine, liver, and colon. Conjugated products entering the systemic circulation after methylation, sulfation and glucuronization of flavonoids are devoid of the pronounced biological activity characteristic of aglycones in vitro [10, 11]. As an example, the blood serum of healthy people, who received 240 mg of flavonolignane silybin, con-

Abbreviations: AgNP, argentum-based nanoparticle; AuNP, aurum-based nanoparticle; EGCG, epigallocatechin-3-gallate; HEB, hematoencephalic barrier; GIT, gastrointestinal tract; MSN, silica-based nanoparticle; NLC, nanostructured lipid carrier; PAMAM, polyamidoamine; NS, nanosphere; PAMAM, polyamidoamine; PCL, polycaprolactone; PCR, polymerase chain reaction; PEG, polyethylene glycol; PLA, polylactic acid; PLGA, plyglycolic acid; PNP, polymer nanoparticle; PVP, polyvinylpirrolidone; RES, reticuloendothelial system; ROS, reative oxygen species; SLN, solid lipid nanoparticle.

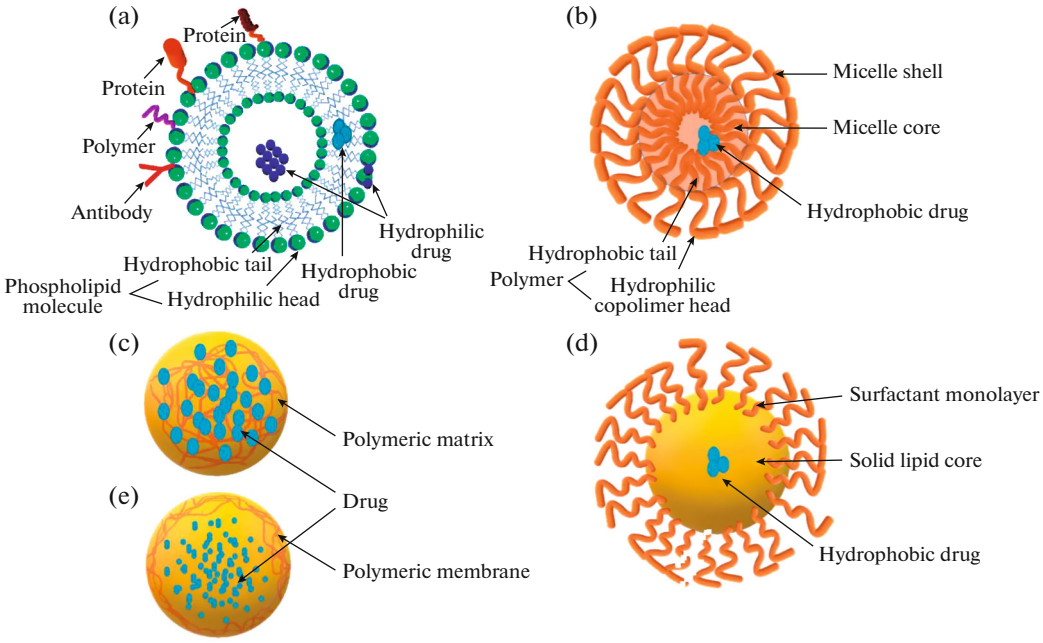

Fig. 1. A schematic representation of nanoscale drug delivery systems: liposome (a), polymer micelle (b), nanosphere (NS) (c), nanocapsule (NLC) (d), and solid lipid nanoparticle (SLN) (e). Modified from [21].

tained only 0.18–0.62 μg/mL of this compound, and in bile it ranged 11–14 μg/mL [12].

Similar problems arise when it is necessary to overcome the skin barrier with topical application of flavonoids [13–15]. In this regard, increase in the bioavailability of flavonoids becomes a fundamentally important factor in enhancing their biological action. This problem is most relevant in oncological practice, where flavonoids, due to their anticarcinogenic activity, are becoming more widespread [16–19]. This led to the idea of using artificial carriers to increase the efficiency of flavonoid penetration to target organs. This method of delivery, on the one hand, increases the penetration and targeted action of higher drug concentrations on specific organs, and on the other hand, reduces its effect on intact cells and tissues.

This review covers publications (until September 1, 2021) of PubMed (including MEDLINE) and Scopus. Domestic publications were taken from various open sources, in particular, from the eLIBRARY database. The search was focused on systems for nanodelivery of flavonoids using the following keywords: *flavonoids*, *flavonoid nanoparticles*, *flavonoid nanobiomaterials*, *flavonoid nanoparticles and cancer*, *flavonoid nanoparticles and inflammation*. A series of polyphenols (kurkumin, resveratrol, and some others) was excluded from the search. A total of 174 reports over the past 10 years in Russian and English were analyzed, including in vivo and in vitro results.

THE MAIN WAYS OF TARGETED DELIVERY OF FLAVONOIDS

The development of means for targeted drug delivery is a relevant area in medical science and practice that has intensely been developed in recent decades. All delivery systems must meet quite stringent requirements: they should increase the treatment effectiveness, while reducing undesirable effects, be highly biocompatible, chemically inert and not form toxic compounds as a result of metabolic processes in the body.

At present, many drug carriers have been developed of various origins and chemical structures with molecular sizes ranging from one to hundreds of nm [20]. To deliver flavonoids, second generation carriers, combined into the group of so-called colloidal carriers, with a size of below 1 μm, are mainly used [17]. Nanosystems for delivery of plant polyphenols are as follows:

(1), phytosomes;

(2), lipid-based nanoparticles: liposomes, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), nano- and microemulsions;

(3), polymeric nanoparticles (PNPs): based on polylactic and polyglycolic acids (PLA/PLGA), chitosan-based, polymeric mycelles, dendrimers, cyclodextrins, and hydrogels;

(4), inorganic nanoparticles: gold-based (AuNPs), silver-based (AgNPs), and silica-based (MSNs).

These carriers will be discussed in terms of targeted delivery of flavonoids. Fig. 1 shows schematic representations of the main nanocarriers.

PHYTOSOMES

A phytosome is a complex consisting of a plant extract bound electrostatically to at least one phospholipid molecule, whose role of is usually played by phosphatidylcholine [22]. The amphiphilic properties of this molecule ensure its solubility both in water and in a lipid medium. In addition, phosphatidylcholin is an important component of cell membranes; therefore, its complex in the phytosome composition has higher biocompatibility and lower toxicity than phosphatidylcholin in the extract of the same plant. Sometimes, lecithin based on phospholipids is used as a component of this complex [22–24].

Clinical trials showed [25] that silybin (the main component of the flavolignan silymarin) in complex with phosphatidylcholin provided a significantly higher biocompatibility of the flavonoid and its elevated plasma concentration than silybin alone. The use of another complex drug, Realsil®, which contains vitamin E along with silybin (47 mg) and phosphatidylcholine, led to the presence of the flavonoid in the blood of 12 healthy donors at a concentration of 213 ng/mL and 117 ng/mL for granulated and encapsulated phytosomes, respectively. At the same time, when silybin alone in granular form was administered (58 mg and 80 mg), its blood concentration was only 18 ng/mL and 5 ng/mL, respectively [12, 26]. For the biological activity of phytosomes containing silybin, it was reported that their hepatoprotective effect exceeded that of the flavonoid alone [22, 27]. This effect of the silybin–phospholipid complex was confirmed in animal experiments [28, 29].

The development of phyto-phospholipid complexes in the form of phytosomes for both experimental and clinical practice was also extended to other flavonoids. As an example, the beneficial influence of a complex of the flavonol quercetin with a phospholipid on ovariectomized rats was manifested in a positive metabolic effect, which was stronger than that of free quercetin [30]. As was shown on a rat model, the biocompatibility of phytosomes including the phospholipid complex of the *Gingko biloba* extract containing flavonoids quercetin, kaempferol and isorhamnetin, was much higer than that of the pure extract of this plant [31]. The blood plasma of volunteers who were injected with phytosomes with the quercetin–lecithin complex contained the maximum flavonoid concentration that significantly exceeded that after the introduction of quercetin alone, and did not cause side effects [32]. A prospective randomized controlled study of quercetin-containing phytosomes included 152 outpatients with initial PCR-confirmed COVID-19 symptoms. The addition of the flavonoid at a dose of 1000 mg per day to standard therapy was accompanied by a significant decrease in the frequency and duration of hospitalizations in 50% of patients, a marked reduction in the number of patients requiring non-invasive oxygen therapy and patients with a fatal outcome [33]. In experiments on rats, this quercetin-lipid complex enhanced the flavonoid biocompatibility and exhibited a hepatoprotective effect in toxic liver damage [34].

A hepatoprotective effect on rats was also observed for phytosomes containing a phospholipid complex with the flavone luteolin [35]. The biocompatibility of the isoflavone puerarin after the intravenous injection of a phospholipid complex containing this isoflavone was higher than that of free puerarin in an equivalent dose; the predominant accumulation of this isoflavone as component of the complex in the heart, lungs and brain was also shown [36]. Phytosomes with the flavone naringenin turned out to be highly effective when inhaled in rats with acute lung injury [37]. Nanophytosomes loaded with green tea extract, 75% of which was represented by epigallocatechin-3-gallate (EGCG), induced a pronounced anti-inflammatory effect in rats, which was much stronger than that of free EGCG [38].

Undoubtedly, phytosomes containing flavonoids will play an important role in the treatment of oncological diseases. These drug delivery agents, like the majority of other carriers, are characterized by a prolonged tumor targeting action without toxic effects on surrounding healthy cells and tissues. The silibinin–phospholipid complex had a 2–2.5 times greater effect on breast cancer SKBR3cells than free silibinin [39]. It was proven that the growth of a model malignant tumor (lung cancer) was significantly inhibited by phytosomes consisting of a mixture of grape seeds and soybean phospholipid [40]. Clinical trials showed that phytosomes with a catechin-containing green tea extract and lecithin used for 4 weeks before surgery for early-stage breast cancer reduced the cancer cell proliferation in 12 patients and ensured high drug bioavailability [41].

The practice of local treatment with phytosomes loaded with flavonoids has also been reported [23]. It turned out that phyto-phospholipid complexes can easily pass from the hydrophilic to the lipophilic environment of the cell membrane and then penetrate into the cell. This means that inclusion into phytosomes improves the transdermal transport of phytocompounds. These data stimulated the development of creams based on phytosomes containing a complex of phospholipid and quercetin for the treatment of skin diseases and the prevention of skin aging [23, 42, 43]. A matrix patch based on a rutin-phospholipid complex (rutin is a quercetin glycoside), exhibited an anti-inflammaroty effect comparable to that of diclofenac in a rat paw edema model [44].

LIPID-BASED NANOPARTICLES

Liposomes

Liposomes have been used since the 1970s [45]. These are artificial spontaneously forming amphi-

philic spherical vesicles with a diameter of 20 to 50 nm, containing one or more lipid bilayers with a space inside them that is usually filled with water and compounds dissolved in it [16]. An important characteristic of liposomes is their amphiphilicity, which allows them to encapsulate water- and fat-soluble substances, as well as amphiphilic compounds, and to release these compounds under certain conditions. Another feature of liposomes is that their membrane can be adsorbed on the cell membrane, then fuse with it and be absorbed by the cell *via* endocytosis, followed by *uncapping* of the liposomes and the release of the drugs contained in them [16, 17, 21, 24, 46, 47].

The drawback of liposomes is the high cost of production and low stability in the bloodstream due to their lysis by cells of reticuloendothelial system (RES). To increase their resistance and circulation time, liposome particles are stabilized by coating with polyethylene glycol (PEG) and/or other polymers. This procedure reduces the recognition of liposomes by macrophages and thereby protects them from RES degradation and prolongs their vascular circulation. It was shown in a mouse model that PEGylation of liposomes loaded with quercetin increased their half life from less than 30 min to 5 h [48]. In addition, PEGylated liposomes are biocompatible with blood cells: they remain in suspension, do not adhere to erythrocytes and leucocytes, do not fix opsonins on their surface and do not induce hemolysis. As well, PEG increases the osmotic pressure around liposomes, which prevents their contact with macrophages. As a result, PEGylated liposomes circulate in the blood for a long time and accumulate in target tissues in amounts higher than standard liposomes [29, 24, 46–48]. In addition, chitosan and its salts are often incorporated into liposomes to increase their bioavailability and effectiveness. Chitosan, encapsulated in liposomes, provides a longer release of the drug and allows regulating its entry into the bloodstream due to the adhesion of this polysaccharide to the mucosa of the gastrointestinal tract [20, 49–51].

Use of liposomes in anticarcinogenic therapy is most promising. Liposomes loaded with the flavone luteolin and coated with tocoferyl polyethylene glycol succinate (TPGS) showed an increased cytotoxicity and accumulation in human lung carcinoma cells (A549) transplanted into mice; at the same time, they did not adversely affect the surrounding healthy tissues [52]. Lecitin-based liposomes with luteolin inhibited the growth of CT26 cancer cells more actively that the free flavonoid in a model of murine colorectal carcinoma [53]. Similar activity was also detected in catechins. These flavonoids encapsulated into chitosan-containing liposomes demonstrated an elevated oral bioavailability due to enhanced penetration into the intestinal epithelium [54]. Chitosan-coated liposomes loaded with EGCG provided a higher content of this catechin inside the cell compared with free EGCG, and demonstrated an antiproliferative effect on MCF-7 breast cancer cells [55]. The isoflavone puerarin, encapsulated in PEG-coated liposomes, specifically penetrated in vivo and in vitro into liver HpeG2 cells and accumulated in the liver and spleen of mice due to its prolonged circulation in the body and reduced rate of excretion. This allowed researchers to use the puerarin liposomal form for the therapy of alcoholic liver diseases [56].

The use of liposomes loaded with quercetin is of great interest. It was shown that this compound as part of the liposomal drug Lipoflavon exhibits pronounced cardioprotective, antioxidant, angioprotective, and anti-inflammatory activity [47]. A significant antioxidant effect of quercetin was also observed in EUDRAGIT®, a liposomal drug of polymeric composition [57]. The polymer coating of liposomes provided quercetin stability in fluids, mimicking the gastrointestinal environment, and the optimal protection of human intestinal cells from oxidative stress owing to the reduced production of reactive oxygen species (ROS).

A series of publications have recently appeared on the anticarcinogenic activity of liposomes loaded with quercetin alone and in certain combinations. Nanoliposomes with quercetin demonstrated strong antitumor effect against HeLa cervical cancer cells. These liposomes were also more effective in inhibiting the growth of U14 cervical cancer cells in BALB/c mice than free quercetin [58]. PEGylted liposomes with quercetin inhibited in vitro proliferation of A2780s and A2780cp cells, induced apoptosis and of cell cycle arrest, and reduced the density of microvessels in cancer cells. These liposomes also suppressed the in vivo growth of both cisplatin-sensitive and cisplatin-resistant mouse models of ovarian cancer. We note that the effectiveness of flavonoid-containing liposomes was much higher than that of free quercetin and unloaded control liposomes [59].

A similar effect of PEGylated nanoliposomes with quercetin was also observed against glyoma cancer cells both in vitro and in vivo [60]. The combined loading of liposomes with quercetin and the natural phytoalexin resveratrol caused a pronounced antioxidant effect due to reactive oxygen scavenging by fibroblasts. Local application of these liposomes in model skin lesions led to a significant reduction in edema and leucocyte infiltration. The obtained data allowed Spanish researchers to propose these liposomes as agents for treating inflammations and oxidative stress associated with precancerous and cancerous skin lesions [61]. Finally, polymeric liposomes DSPE-PEG2000 designed for penetration the hematoencephalic barrier (HEB) and loaded with quercetin together with the antitumor preparation temosolamid were effectively absorbed by U87 glyoma cells. At the same time, the separate assimilation of either of these drugs was minimal. In addition to a high concentration in blood plasma, liposomes significantly accumu-

lated in brain tissues in vivo, which gave grounds to consider them as effective carriers for increased drug delivery to brain tumors [48].

Solid Lipid Nanoparticles

In 1991, a revolutionary method was developed to overcome the disadvantages of emulsions, liposomes, and polymeric micro- and nanoparticles: solid lipid nanoparticles (SLNs) were created. The drug delivery system based on SLNs consists of inclusion of the drug into a core formed by natural and synthetic lipids and free from organic solvents. Together with SLNs, nanostructured lipid carriers also belong to the discussed type of such delivery systems.

SLNs are spherical nanoparticles ranging in size from 40 to 1000 nm, obtained by dispersing molten solid lipid in water in the presence of a surfactant, acting as a stabilizer. The introduction of an SLN into a pharmaceutical composition results in the formation of a high-lipophilic matrix, in which the drug is dissolved or dispersed [16]. The dispersed phase of SLNs is a lipid matrix that retains a solid state at ambient body temperature. As lipid components, highly pure mono-, di-, and triglycerides, as well as complex glyceride mixtures, fatty acids, fatty alcohol, sterenes, and waxes are used. All of them ensure the stability of the surfactant and range from 0.5 to 5% by weight of the pharmaceutical composition. SLNs have a number of important advantages, as they provide controlled release and targeted delivery of the drug. In addition, they are resistant to sterilization, are biodegradable, can protect labile compounds from chemical degradation, and have a high safety profile. The nanocarriers developed in this way are therapeutically effective upon various routes of administration [63].

Along with the described advantages, SLNs are characterized by a number of drawbacks. The latter include limited options of drug loading due to the high density of the solid lipid core, storage problems associated with the possible gelation of the dispersed phase, and high water content (70–90%), which reduces their stability [63, 64]. Nevertheless, the advantages of SLNs are so great that they outweigh the drawbacks, which makes it possible to consider SLNs as ideal drug carriers superior to other known delivery systems [65].

The greatest number of studies on flavonoids encapsulated into SLNs are associated with quercetin. In 2009, one of the first such works was published [66]. It was shown that the bioavailability of SLNs loaded with quercetin is much higher than that of the suspension of this flavonoid when administered orally to rats. In in vitro experiment with an artificial intestinal liquid, the bioavailability of SLNs with quercetin was 35 compared to 7% for a free flavonol solution [67]. It was found that SLNs with quercetin are suitable not only for enteral use. As an example, quercetin as part of SLNs administered by inhalation was predominantly distributed over tracheobronchial and lung areas with a more profound penetration into the lung tissues [68, 69]. Recently, it was shown [70] that SLNs loaded with quercetin readily cross the HEB and enter the brain. In in vitro experiments, nanoparticles with lipid carriers penetrated HEB 1.5 times more intensively within 4 h of incubation than nanoparticles without lipid carriers and they did not have a toxic effect on the hCMEC/D3 line cells.

Taking the multifaceted pharmacological activity of quercetin and, above all, its antioxidant activity, into consideration researchers suggest that this flavonoid in the composition of SLNs may be effective in the treatment of Alzheimer's disease. This assumption is consistent with the data obtained using the quercetin glycoside, rutin. This SLN-encapsulated flavonoid manifested pronounced antioxidant activity against the U373 human hemoblastoma cell culture, which exceeded that of free rutin [71]. Recently, these researchers formulated the idea that intranasal administration of SLN-encapsulated rutin may be helpful in neurodegenerative diseases caused by oxidative stress [71].

The antioxidant activity of quercetin-loaded SLNs was also confirmed by another research group [72]. Information has emerged on the anticarcinogenic effect of SLN-encapsulated quercetin [73]. In MCF-7 human breast cancer cells treated with these SLNs the proliferative activity and viability were reduced; the cytotoxic effect of these SLNs was much higher than of free quercetin. Interestingly, this effect was not observed in the noncarcinogenic MCF-10A cell line. The SLN-encapsulated flavonoid constantly released from the complex during 48 h. Researchers [73] associated the found cytotoxicity with enhanced ROS formation and a decrease in the activity of antioxidant enzymes in tumor cells under the action of quercetin, which caused their apoptosis. In addition, attempts are being made for local application of carriers in a complex with quercetin. It was reported that this flavonoid has a greater effect due to longer retention in all human skin layers compared to a control drug with the same particle size [74, 75].

It should be noted that encapsulation into SLNs also increases the bioavailability of other flavonoids. Similar compositions with EGCG are regarded as promising. This catechin is extremely unstable, in particular at pH changes, which leads to losses in its pharmacological activity. The introduction of EGCG into the SLN matrix restricted the release of catechin in artificially reproduced gastric and intestinal fluids and also led to stabilization of the composition during long-term storage [76]. The low toxicity and high bioavailability of EGCG as part of SLNs in comparison with free catechin was confirmed in in vivo experiments on rats [77]. Using rabbit cornea and sclera, it was shown that EGCG encapsulation into SLNs provides a prolonged release of the flavonoid in both

anterior and posterior eye segments without irritating effect. This composition is considered a promising drug for the treatment of eye diseases associated with oxidative stress and inflammation [78]. The anticarcinomic activity of EGCG predetermined the study of this compound as an agent for encapsulation into SLNs. The in vitro antiproliferative activity of EGCG-containing SLNs against five cell lines was found, with the highest effect on human breast cancer MCF-7 cells [79]. Another study showed [80] that the cytotxicity of the EGCG-SLN complex exceeded that of free EGCG towards human breast cancer MDA-MB-231 cells by 8.1 times and was 3.8 times higher towards human prostate cancer DU-145 cells [80].

Promising results were obtained in encapsulation of the flavone naringenin into SLNs. A pharmacokinetic study showed that upon intratracheal instillation to rats this compound loaded into SLNs was 2.53 times more bioavailable than the same drug used as a suspension [81, 82]. Using the flavone miricetin, it was shown that its biodegradation was 300 times lower and its half life was 4500 times longer compared to free miricetin dissolved in saline [83]. Enteral administration of SLNs containing puerarin increased the oral bioaccesibility of the flavone, as well as its accumulation in the heart and brain [84, 85]. The application of PEGylated SLNs with puerarin provided a prolonged release of this compound, its elevated concentrations in the heart and blood plasma, and a reduced size of myocardial infarction in rats [86].

Nanostructured Lipid Carriers

NLCs have been developed as next-generation lipid carriers devoid of a number of disadvantages inherent in the previous SLNs. The main difference consisted in the structure of the formed matrix, which now contained not only solid, but also a mixture of solid and liquid lipids (oils). The advantage of NLCs is that the presence of liquid lipids causes incompleteness of the lipid matrix crystalline lattice, which provides more space for transported drug molecules and thereby significantly increases the drug load of the nanoparticle [63]. In additions, this structure of the lipid matrix prevents drug losses during long-term storage and reduces its tendency to gelation [63, 64, 70, 87–89].

Both in vitro and in vivo experiments showed that NLCs loaded with quercetin provide a constant release of the flavonoid and its accumulation in the lungs, liver, and kidneys, which is important for its anticarcinogenic activity [72, 90, 91]. It has been shown that the quercetin release from NLCs exceeded that from SLNs [74]. The local application of quercetin as part of NLCs stimulated the flavonoid penetration into the skin layers, its retention by the epidermis and dermis, and provided its anti-oxidant and anti-inflammatory effects [13].

High bioavailability of the NLC-encapsulated flavones naringenin, baicalein, flavonolignan silymarin, EGCG cathechin and genistein isofalvone was demonstrated in experiments in vivo and in vitro. As an example, the level of baicalein in the blood plasma when used as part of NLCs was much higher than as an aqueous solution, and its accumulation in the cerebral cortex and brainstem was 7.5 and 4.7 times larger, respectively. This allows considering this targeted delivery system promising for the therapy of diseases of the central nervous system [92]. The oral absorption and bioavailability of NLC-encapsulated silymarin in dogs exceeded those of silymarin granules by more than 3 times [93]. The encapsulation of EGCG into NLCs limited the release of catechin under the conditions of the artificial gastric and intestinal environment and ensured high stability of the drug during long-term storage [94]. Loading with genistein of NLCs modified with chitosan hydrochloride enhanced the bioflavone absorption by human lens epithelial cells and its antiproliferative effect [95]. Finally, co-encapsulation of naringenin and oxaliplatin, an anticancer agent, into NLCs largely enhanced apoptosis in HT-29 human colorectal cancer cells compared to the anti-blastoma drug alone; a significant reduction of the activity of anti-apoptosis factors and an increase in the expression of mRNA of the BID pro-apoptosic factor were observed [96].

Nano- and Microemulsions

Emulsions are colloidal systems consisting of two immiscible liquids, one of which is dispersed in the other in the form of small drops; surfactants adsorbed on the surface of new-formed droplets stabilize the system. A nanoemulsion is thermodynamically unstable and contains droplets with a diameter of less than 100 nm; a microemulsion is a stable system with a droplet size of less than 200 nm. Nano- and microemulstion are usually divided into far-forward and reverse groups. In members of the first group, water, the most polar liquid, often plays the role of a dispersion medium, while in the second, it is a dispersed phase. Consequently, far-forward and reverse nano- and microemulsions are called *oil-in-water* (o/w) and *water-in-oil* (w/o) emulsions, respectively. The organic phase is often represented by vegetable oils (olive, soy, corn, and others) and/or fish fat. As surfactant stabilizers, long-chained triglycerides and phospholipids (soy lecithin), proteins (caseinate) or Tweens (Tween 60 and Tween 80) are used. The chemical characteristics of the system give reason to consider it ideal for drugs with different solubilities. Hydrophilic compounds are loaded into the aqueous phase and hydrophobic ones enter the oil phase of the system [24].

Such systems are quite convenient and effective for targeted delivery of flavonoids. When a quercetin-containing nanoemulsion is introduced into an artifi-

cial gastric environment, the bioavailability of this flavonoid increases to 60%, which is much larger than in either SLN-encapsulted drug (35%) or free flavonoid. Quercetin oral administration to mice as part of a nanoemulsion showed its markedly higher cytotoxicity against the subcutaneous melanoma line B16-F10 than that of the free flavonoid [97]. A nanoemulsion based on soy protein and encapsulated green tea catechins greately improved the stability, bioavailability and intestinal penetrability of EGCG; the bioavailability of the catechin exceeded that of the free drug by 2.78 times [98].

The intranasal administration to mice of a mucoadhesive chitosan nanoemulsion loaded with kaempferol, substantially increased the nasal mucosa permeability, while maintaining the high antioxidant activity of the drug, as well as membrane safety. A stronger inhibition of the viability of C6 glyoma cells due to apoptosis induction was also observed in kaempferol-loaded NLCs compared to free kaempferol [99].

The self-emulsifying naringen nanoemulsion improved the pharmacokinetics of this flavone, increasing its dissolution and providing its rapid and complete release [100]. Naringenin and hesperetin introduced into emulsion and targeted to vascular cell adhesion molecules (VCAM-1) expressed on epithelial cells were characterized by good stability and constant release of flavonoids, as well as lack of cytotoxicity towards human epithelial cells [101]. Using an inflammation model in mice, the researchers also showed that the intravenous injection of a naringenin-containing emulsion caused a selective accumulation of this flavone in the heart and lungs of animals with a simultaneous decrease in the mRNA level of some inflammation mediators, which testified to the anti-inflammatory potential of naringenin [102].

The local application of an o/w emulsion containing the flavone luteolin showed its pronounced antioxidant effect, as well as the ability to stimulate hair growth upon reaching the hair follicles; this effect was comparable to that of minoxidil, a well-known hair growth stimulator [103].

For the microemulsion, it turned out that, unlike the free compound, quercetin in its composition actively penetrated through pig skin and remained stable for 12 months [104]. Similar pharmacokinetics was characteristic of a microemulsion with hesperitin and hesperidin applied to rat and guinea pig skin, where they exhibited whitening and anti-inflammatory activity [15, 105].

POLYMERIC NANOPARTICLES

PNPs are colloidal particles of spherical or irregular shape ranging in size from 1 nm to 1000 nm that are obtained from biocompatible and biodegradable polymers of natural or synthetic origin. As alternative to liposomes, PNPs have a number of advantages, such as enhanced stability, uniform particle distribution, higher drug load, higher biocompatibility and biodegradability, and a simplified manufacturing process [20, 47].

Nanoparticles Based on Polylactic and Polyglycolic Acids

To prepare such nanoparticles, the following polyesters are more often used as polymers: polylactic acid (PLA); copolymers of lactic and glycolic acids (PLGA), polycaprolactone (PCL), polyvinylpirrolidone (PVP), and others. Nanoparticles are loaded with drugs either by absorption or conjugation with side acidic groups, while the polymer terminal groups bind to vector molecules [20, 47, 48]. To optimize the drug pharmacokinetics, these nanoparticles are often modified with other polymers, such as PEG or chitosan. In particlar, PEG, in coating the nanoparticle surface, significantly improves their hydrophilicity and stability, and also ensures their rapid penetration through the mucous layer upon oral application. Chitosan stongly stimulates the nanoparticle penetration and improves their target characteristics by interacting with negatively charged polymers, thereby facilitating the targeted drug delivery to specific organs and tissues.

Currently, PNPs based on chitosan, cyclodextrines, hydrogels and dendrimers are used for delivery of flavonids [16, 24]. Using nanoparticles PLA, PLA/PLGA, and their combinations, it became possible to increase the water solubility and stability of flavonoids. The kinetics of drug release from such preparations is initially fast and then slows down, which facilitates the regulation of the process. In addition, PLA/PLGA nanoparticles themselves are able to enhance the functional activity of flavonoids, including anti-inflammatory, antioxidant and anticarcinogenic actions [24]. This is well illustrated by attempts to increase the EGCG antitumor activity. This catechin ensapsulated into PLA/PEG particles enhanced apoptosis by more than 10 times and inhibited angiogenesis in both in vivo and in vitro experiments compared to free EGCG. This effect was due to increased bioavailability and directed action of the encapsulated drug on tumor cells [106]. For the prevention and treatment of prostate cancer, targeted PLGA/PEG PNPs with encapsulated EGCG were developed. It was shown that they specifically bound to tumor cells and strongly inhibited the specific membrane antigen of prostate cancer, while being characterized by limited systemic toxicity [107].

It was shown in vitro that PLA/PLGA nanoparticles loaded with quercetin exhibited pronounced antiproliferative activity. This made it possible to consider this flavonoid as a potential drug for antitumor therapy [3]. For example, quercetin-loaded PLGA nanoparticles protected rat liver mitochondrial membrane from cancer induced by diethylnitrosamine

[108]. Oral administration to rats with model breast cancer of nanoparticles containing quercetin and the antiestrogen preparation tamoxifen showed that the bioavailability of these drugs was 3–5 times higher than of either of ingredients taken alone. In addition, these nanoparticles penetrated cells more efficiently and manifested high cytotoxicity against MCF-7 breast cancer cells [109].

Quetcetin/PLA/PEG nanoparticles demonstrated a pronounced anticarcinogenic potential against the breast cancer cell line MDA-MB-231 due to the induction of apoptosis [110]. PLGA nanoparticles with rutin, a quercetin glycoside, had an antitumor effect provided by their ability to reduce the infiltration of inflammatory cells and the activity of proinflammatory cytokines [111]. Similar anticarcinogenic and anti-inflammatory activity was also found when using the PCL/PEG and PLA/PEG polymeric carriers loaded with the flavone luteolin [112, 113]. Combinations of luteolin with PLA/PEG exhibited high anticarcinogenic effect in vitro on lung cancer cells (H292 line) and squamous cell carcinoma of head and neck (Tu212 line), as well as in vivo, on the SCCHN tumor xenograft in mice [114].

We note that the above listed PNPs with encapsulated flavonoids are already widespread as antitumor agents. As an example, nanoparticles with the flavone apigenin reached cancer cells and actively released their contents, suppressing the development of tumor cells in vitro, and inhibiting the progress of induced hepatocarcinoma in rats in vivo [115]. Apigenin-containing PLGA particles exhibited a stronger anticarcinogenic effect than the free flavone when applied topically to mice with skin tumors induced by ultraviolet irradiation and benzpyrene [116].

PVP-based nanoparticles loaded with naringenin strongly improved the bioavailability and gradual release of the flavonoid, which has a short half life and rapidly passes into a crystalline form that can weakly penetrate through the membrane. Apparently, this is the reason that PNPs with encapsulated naringenin demonstrated the ability to easily overcome the membrane barrier and gradually release the drug into cell culture (89% within 12 h) in in vitro experiments without a toxic effect on neighboring tissues [82]. It has recently been shown that the antitumor activity of the flavone chrysin greatly increases as a result of its incorporation into PLGA-based particles. Co-introduction of chrysin and the antiblastoma preparation doxorubicin into these nanocarriers resulted in the pH-dependent release of both drugs with inhibition of the viability of human lung epithelium cancer cells A549. The combined cytotoxic effect exceeded that of each preparation alone, used either free or encapsulated into nanoparticles [117].

Chitosan-Based Nanoparticles

In recent years, PNPs developed on the basis of chitosan have attracted increasing interest. Chitosan is a semisynthetic polysaccharide obtained by deacetylation of chitin, which is widespread in nature. Chitosan is characterized by such useful properties as good biocompatibility, biodegradability, high penetrability, nontoxicity and lack of immunogenicity. This compound also has pronounced adhesive properties and is able to reversibly open tight intercellular junctions stimulating the paracellular penetration of drugs. In addition, chitosan readily interacts with negatively charged polymers imparting target properties to nanoparticles [24].

EGCG, encapsulated into the nanodelivery system containing fucose-conjugated chitosan, as well and the PEG-conjugated chitosan-gelatin complex, effectively inhibited the growth of the MKN-Luc gastric cancer cells in vitro, inducing apoptosis and reducing the espression of vascular endothelial growth factor (VEGF). These particles significantly suppressed the tumor development and the inflammatory response in the stomach and intestines in a model of gastric cancer in mice in vivo [118]. Similarly, EGCG incorporated into chitosan-based nanoparticles considerably enhanced apoptosis in human melanoma cells [49]. The enteral administration of chitosan-loaded particles containing EGCG was much more effective in surrpession the prostate cancer cell growth compared to the free catechin [119]. It has recently been shown that nanoparticles with chitosan dextran sulfate and naringenin introduced into their composition had a noticeable cytostatic effect on the MCF-7 breast cancer cell line [82]. Thus, there are already a number of works demonstrating that nanoparticles based on chitosan and other ingredients enhance the bioavailability and therapeutic (primarily, anticarcinogenic) efficacy of drugs [120].

Polymeric Micelles

Polymeric micelles composed of amphiphilic molecules are a new type of self-assembling colloidal carriers and are currently attracting much attention as promising targeted drug delivery systems. Micelles are built from a hydrophobic core with incorporated drugs and a hydrophilic shell. The latter protects the core, prevents its interaction with blood components and the micelle destruction by RES, and increases the circulation time of the nanosystem. Micelle-forming structures include hydrophobic and hydrophilic polymers [21, 23]. Polymeric micelles are most convenient for targeted delivery of anticarcinogenic drugs due to their small size (<100 nm), which allows them to selectively affect the tumor, migrating from the vacular wall to cancer cells. Polymeric micelles, being sensitive to microenvironmental factors (primarily, to low pH

in the tumor), are rapidly destroyed with targeted release of incorporated drugs [21, 23, 121, 122].

Mixed polymeric micelles loaded with the flavone apigenin showed cytotoxicity towards the HepG2 and MCF-7 tumor cell lines [123]. Luteilin-loaded nanomicelles based on PLGA/PCL exhibited cytotoxicity against breast carcinoma and colorectal carcinoma C-26 cells [112]. Similar results were also obtained by other researchers [124]. Morin incorporated into mixed polymeric micelles, 3.6 times more effectively penetrated into Caco-2 cells in comparison with the free flavone, owing to its higher bioavailability partially due to enhanced paracellular transport [125].

When using naringenin in the composition of polymeric micelles of various amphiphilic structures, its solubility, bioavailability, biodegradability and penetrability into intestinal epithelium cells increased significantly both in vivo and in vitro compared to the free flavone [82]. Nanomicelles containing quercetin retained a stable effect on Caco-2 cells in model gastric and intestinal juices, regardless of pH. At the same time, the anticarcinogenic activity of quercetin as part of micelles against A549 cells of model lung cancer in mice was considerably higher than that the free preparation [126]. Recently, it has been shown that polymeric nanomicelles based on PCL/PEG loaded with luteolin inhibit much more strongely than the free drug the growth of glyoblastome cells (GL261) both in vitro and in vivo after intravenous injection. The authors attribute this effect to enhanced apoptosis of tumor cells [127].

Dendrimers

These are polydispersed 3-dimentional tree-like branched radially symmetric polymers with a hollow core containing some flavonoid. The branches can be modified or complexed with other compounds [20, 24, 47, 128]. Dendrimers of polyamidoamine (PAMAM) are most often used. Drugs (proanthocyanidins) are released from hybrid silicon and PAMAM nanoparticles within 6 days; the drug cytotxicity against neuroblastoma cells reached 87.9% after 134 h without toxic effect on healthy cells [129]. Efficient loading and the formation of stable complexes was observed when using PAMAM generations 3 and 4 (PAMAM-G3 and PAMAM-G4, respectively) in complex with the isoflavone genistein [130].

Cyclodextrins

Cyclodextrins are natural cyclic oligosaccharides resulting from cellulose degradation. They form hollow pyramidal structures in the form of a truncated cone linked to glucose residues *via* glycosidic bonds. Internal hydrophobic cavities in cyclodextrins are used for drug encapsulation [24, 27]. Recent studies have shown that the loading of cyclodextrins with flavonoids resulted in improving their solubility, stability, and bioavailability [131]. For the pharmacological activity of this type complex containing baicalein, genistein, hesperidin, galangin and rutin, antioxidant, antiproliferative, anti-inflammatory and antiangiogenic activities of these compounds were observed [131–135].

Hydrogels

Hydrogels are 3-dimensional porous shape-retaining chemically or physically cross-linked water soluble polymers. They are characterized by mechanical resistance, swelling, and water-retaining capacity. Their introduction into hydrogels ensures the maximal delivery of drugs to the target organ, which is most important for treatment tumors and the local application for the healing of damaged skin [16, 24]. Gel prepared from carbopol and the flavone naringenin had a pronounced anti-inflammatory and antioxidant effect on ultraviolet-damaged skin in mice. A reduction in inflammatory edema, as well as production of inflammatory cytokines, lipid hydroperoxides, and superoxyde anion was observed. The gel maintained the expression level of mRNA of cellular antioxidants and the Nrf2 transcription factor [136].

A quercetin-containing hydrogel was used in clinical trials to cure lower extremity skin wounds in diabetic patients, who had previously been unsuccessfully treated with mechanical compression. This approach led to complete wound healing in 9 out of 58 patients and health improvment in the rest [137]. Similar results were obtained in model diabetes mellitus in rats and mice using hydrogels with quercetin and an extract containing a mixture of flavonoids [138, 139].

INORGANIC NANOPARTICLES

This group of cariers is represented by nanostructures based on a number of metals (gold, silver, platinum and titanium), as well as silicon dioxide. These particles often have a silicon core and an outer shell of metal atoms. These nanocarriers effectively penetrate various biological barriers and are sometimes capable of changing the activity of drug molecules delivered by them due to a synergistic effect.

Gold-Based Nanoparticles (AuNPs)

Gold is the most common among other metal carriers owing to a number of advantages of this metal. AuNPs range in size from 1 to 100 nm and vary in shape; they are negatively charged, easily interact with biological molecules, freely penetrate target organs, and are considered nontoxic [24]. However, one should be cautious about possible long-term toxicity of AuNPs, since, as a result of prolonged use, they can accumulate in the liver and kidney tissues and may have a negative effect [29, 140].

Nevertheless, numerous studies have been carried out in recent years on the effectiveness of AuNP conjugates with drugs. Various preparations bind to AuNPs *via* covalent and noncovalent bonds. It was shown that PEGylated AuNPs are highly efficient in delivering hydrophobic drugs. Such systems are obviously likely to be promising for anti-tumor therapy [47, 141]. As an example, quercetin conjugated with AuNPs slowed down the growth of induced breast cancer in rats more rapidly than the free flavonole, and inhibited the viability of breast cancer cells, their angiogenesis, and metastasis in vitro [142]. Later, in the same laboratory, it was shown that the effect of AuNPs-conjugated quercetin was due to apoptosis activation [143]. It was found [144] that the addition of PLGA to quercetin-containing AuNPs led to effective suppression of liver cancer cells and their migration and colony formation and also enhanced apoptosis by stimulating the degradation activity of caspase-9 and caspase-3, and inducing cytochrome C release.

A similar effect of quercetin-loaded AuNPs and PLGA was observed on neuroglyoma and cervical cancer cells [145, 146]. In addition, quercetin conjugated with AuNPs suppressed the lipopolysaccharide-induced inflammation of microglyal cells and inhibited the synthesis and release of E2 prostaglandin and nitric oxide controlled by cyclooxygenase 2, as well as the production of mRNA of pro-inflammatory cytokins [147]. EGCG conjugated with AuNPs inhibited the growth of cancer cells of the PC3 and MDA-MB-231 lines much more strongely compared to the free catechin and control citrate-gold nanoparticles [24]. EGCG-loaded AuNPs also suppressed MBT-2 tumor cell growth in a mouse bladder cancer model, stimulating the caspase cascade through the Bcl family proteins in the mitochondrial apoptosis pathway. In addition, unlike free EGCG orally administered to mice, the above composition was introduced directly into the tumor area and activated cellular immune signaling [148, 149].

An analogous effect was observed for AuNPs/EGCG particles towards PC-3 prostate tumor cells and B16F10 melanoma cells [150, 151]. A group of Indian researchers [152] showed that EGCG conjugated with AuNPs has a selective cytotoxic effect on B16F10 cells and breast cancer MCF-7 cells, but not on normal murine hepatocytes. AuNPs/EGCG activated apoptosis due to accelerated RES formation and depletion of the antioxidant protection mechanism in hepatocytes. Finally, the nanocomposite consisting of fucosylated carboxymethyl chitosan and AuNPs/EGCG inhibited division of gastric tumor cells much more effectively than the same catechin in the free state. Based on the obtained results, the authors concluded that nanocarriers loaded with green tea polyphenols in general, and EGCG in particular, may form the basis for the development of an optimized drug delivery system with high bioavailability and therapeutic efficacy combined with minimal toxicity [152].

Anticarcinogenic effects were observed not only in quercetin and EGCG. Not long ago, it was shown that the flavonole kaempferol conjugated with AuNPs specifically destroys the nuclei of A549 lung cancer cells [153]. The flavonoid hesperitin, a well-known hepatoprotector, conjugated with PEGylated AuNPs exhibited a stronger anti-tumor effect against an experimental liver tumors in rats than free hesperitin for 16 weeks [154].

Silver-Based Nanoparticles (AgNPs)

AgNPs themselves have anti-inflammatory, antibacterial, anticarcinogenic, and other pharmacological activities [155, 156]. The flavonole myricetin conjugated with AgNPs demonstrated a pronounced antimicrobial action and antioxidant properties [157]. Similar characteristics were described for the flavone apigenin as part of AgLPs. In experiments on mice, a high anticarcinogenic activity of apigenin-loaded AgNPs was observed due to enhanced apoptosis together with an antibacterial effect, which exceeded that of sodium citrate conjugated with the same AgNPs [158].

Compared to AuNPs, AgNPs conjugated with luteolin tetraphosphate exhibited a higher antimicrobial and antifungal effect [159]. It was also observed that both nanocarriers in complex with quercetin manifested antimicrobial properties by inducing oxidative stress in cells of gram-positive and gram-negative bacteria [160].

Silica-Based Nanoparticles

Silicon dioxide (silica) in the form of colloidal mesoporous nanoparticels (MSNs) is used as a nanocrrier for targeted drug delivery. Nanostructured silicas have a number of advantages: they are nontoxic, biocompatible, biodegradable in the body, and have a large specific surface area, which facilitates dosing of the drugs encapsulated in matrix mesopores [29, 161, 162]. As a rule, silica is used for the transport of flavonoids *via* the formation of hybrid nanoparticles, more often, with the use of polymeric molecules, which results in organo-inorganic nanocarriers [163].

Quercetin-loaded MSNs functionalized with amino groups were shown to release flavonole in pH- and glutathione-dependent mode [164]. In other experiments with quercetin, it was found that encapsulation into MSNs conjugated with folic acid led to the increase in flavonole bioavailability and more efficient uptake by cells, which induced cell apoptosis and the resulting anticarcinogenic effect of the drug [165]. In experiments on local application of quercetin-loaded MSNs functionalized with aminopropyl, an increased penetration of the flavonoid was observed into skin layers accompanied by inhibition of prolifer-

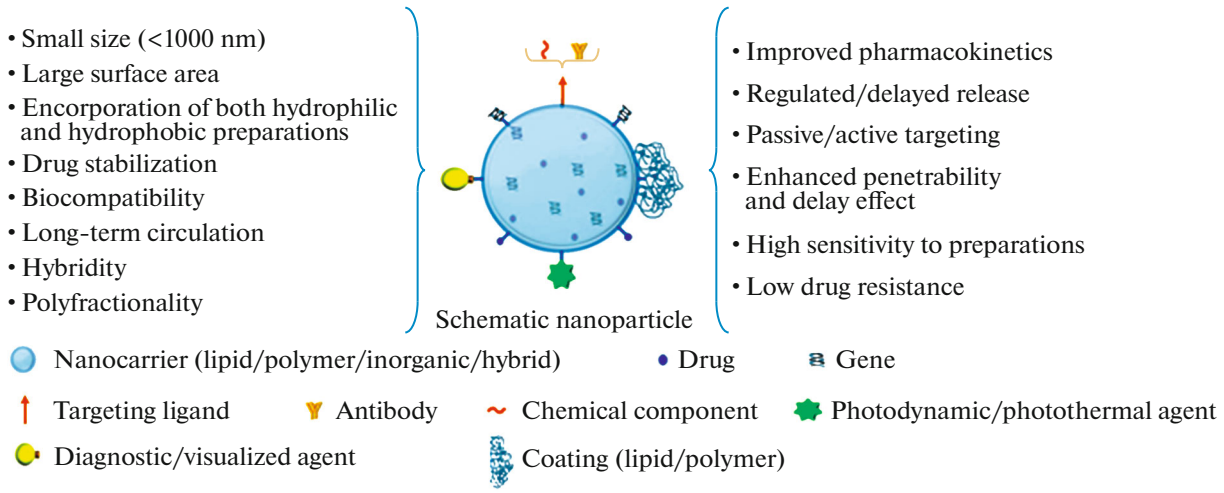

Fig. 2. A schematic representation of a universal nanocarrier and its characteristics (modified from [174]).

ation of human melanoma JR8 cells [166]. It is important to emphasize that, as shown in a series of experimental studies, quercetin encapsulated into MSNs had anticarcinogenic activity and enhanced the effects of other therapeutic manipulations, in particular, radiation therapy [167], as well as that of other antiblastoma drugs. For example, the combined loading of MSNs with quercetin and paclitaxel solved the problem of multidrug resistance to the latter when used against breast cancer MCF-7 cells [168].

Table 1. The sizes of flavonoid-loaded nanoparticles studied in experiments on animal models [19, 21, 89]

Flavonoid class	Flavonoid	Formulation	Average size, nm
Flavonols	Quercetin	PNPs (PLGA)	270.0
		PNPs (PLA-PEG)	155.3
		PNPs (PCL-PEG)	34.8
		PNPs with chitosan	468.0
		AuNPs	5.2
		AuNPs (PLA)	106.7
Flavones	Luteolin	PNPs (PLA-PEG)	115.0
	Apigenin	PNPs (PLGA)	101.3
	Apigenin (+ 5-fluorouracil)	Liposomes	105.0
Flavan-3-ols (catechins)	EGCG	PNPs (PLA-PEG)	285.0
		PNPs with chitosan	203.5
		PNPs with chitosan-PEG	395.0
		SLN	114.5
		AuNPs	50.0
		AuNPs	64.7
Flavanones	Naringenin	Liposomes with EUDRAGIT E100	430.0
		PNPs (PLA-EUDRAGIT)	90.0
Isoflavones	Genistein	PNPs (PCL)	181.8
		PNPs (PLGA)	225.7
	Genistein (+ plumbagin)	Liposomes (PEG 2000)	100.0

A similar effect was observed with the combined action of quercetin and doxorubicin on human colorectal cancer cells [169, 170]. We note that the use of this targeted delivery method also increased the effectiveness of other flavonoids. Myricetin loaded into MSNs together with folic acid was released and absorbed by A549 lung cancer cells and NCI-H1299 non-small cell lung carcinoma cells. Myricetin accumulation was observed in the tumor area accompanied by a significant decrease in the viability of cancer cells due to apoptosis [171].

A carcinogenic effect was also found in catechin EGCG and isoflavone genistein [172, 173]. The latter, encapsulated into PEGylated MSNs, had antioxidant and antiproliferative effects on HT29 colorectal cancer cells. Interestingly, this isoflavone as part of composite nanoparticles induced cell death by simultaneous activation of two processes, apoptosis and autophagy, while free genistein only induced weak apoptosis [173]. These results allowed the authors to assume that in the nearest future genistein encapsulated into nanocarriers can be used as an alternative drug for colorectal cancer treatment.

CONCLUSIONS

To conclude this review, let us discuss the scheme combining the main characteristics of nanoparticles used as reservoirs for drug loading, including flavonoids (Fig. 2).

In addition, let us summarize the data on the composition and size of nanoparticles used for targeted delivery of flavonoids (Table 1).

We emphasize once again that flavonoids have a number of useful properties, forming the basis of the so-called *Mediterranean diet*. However, low bioaccessibility and stability largely restrict their clinical application. Nanosize carriers for drug targeted delivery are designed to overcome these disadvantages by putting under control the targeted release and activity of flavonoids. In this regard, there is no doubt that the further intorduction of nanotechnologies into pharmacology and pharmaceutical technology opens up new prospects in strategies for the treatment of various diseases.

The prospects for the application of nanocarriers for targeted delivery of drugs with low bioavailability, including flavonoids, are beyond doubt. Unfortunately, to date, the promising flavonoid delivery systems, described in this review, have mostly been reproduced in vitro and, to a lesser extent, in animal models. We are convinced that clinical trials to be conducted in the nearest future will greatly contribute to improving the effectiveness and safety of new treatment methods for a number of human diseases, as well as the further development of pharmacology and drug technology in general.

COMPLIANCE WITH ETHICAL STANDARDS

The authors declare that they have no conflicts of interest.

This article does not contain any studies involving animals performed by any of the authors.

This article does not contain any studies involving human participants performed by any of the authors outside the scope of people's normal professional activities.

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