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*Review*
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# Encapsulation Systems for Delivery of Flavonoids: A Review

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**Abstract:** Encapsulation of bioactive compounds s been considered a promising tool for preserving these compounds. Several studies on dietary sources and health benefits of flavonoids, their chemical and stability properties, and encapsulation methods used for delivery of flavonoids were reviewed. Flavonoids comprise the main group of polyphenols widely found in fruits and vegetables responsible for numerous biological activities. They have a flavan nucleus with 15 carbon atoms organized in three rings and are categorized into six subgroups. The main dietary sources of flavonoids are fruits, vegetables, cereals, tea, and some herbs such as *Viola odorata* Linn. These compounds can prevent diseases such as cardiovascular, cancers, neurodegenerative, diabetes, and inflammatory bowel disease. Despite these beneficial biological activities, flavonoids are not stable against environmental conditions, have low water solubility and low bioavailability after oral administration, which restricts their application. Accordingly, encapsulation has been utilized in order to improve the stability and solubility of flavonoids. Various approaches such as spray drying, molecular complexes, liposomes, nanoparticles, emulsification, and multilamellar vesicles have been applied in the entrapment of flavonoids. Encapsulation can improve the stability of flavonoids as well as solubility, controlled release, and bioavailability.

**Keywords:** flavonoid; encapsulation, stability; *Viola odorata* L.; health benefits.

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## 1. Introduction

In recent years, the role of diet-derived polyphenolic compounds in preventing diseases has been realized [1] that has motivated the consumption of plant-based foods and the development of functional food products enriched with polyphenols. They include a wide variety of diverse structures, which belong to two main classes: non-flavonoids (especially phenolic acids, stilbenes, and lignans) and flavonoids which are characterized by the basic $C_6$-$C_3$-$C_6$ skeleton [2]. Flavonoids are a group of polyphenolic compounds derived from benzo-pyrone and broadly distributed in fruits and vegetables [3]. They are synthesized as secondary metabolites in plants through the shikimic pathway by acetic acid/ /phenylalanine [4]. Besides

their functionality as natural pigments, it has been reported that they possess antioxidant [5, 6], anticancer [7], anti-inflammatory [8, 9], antimicrobial and antiviral [10, 11] characteristics. Despite these health-promoting activities, flavonoids have poor stability against environmental conditions (heat, light and oxidation, pH, etc.), low water solubility, and low bioavailability after oral administration, which restrict their applications and health benefits [3, 12, 13]. In this regard, attempts have been conducted to encapsulate flavonoids to preserve their stability and pharmacological activities and masking unpleasant flavor at high concentrations [14].

Encapsulation is a process for entrapment of active ingredients (solid, liquid, or gas) in a wall material to fabricate capsules with a micrometer to millimeter size [15-17]. To prepare capsules with desired properties, the selection of encapsulating agents and method of encapsulation are of great importance. Encapsulating materials must be noticed as "generally recognized as safe" GRAS, inexpensive without reactivity with the core material [18]. Furthermore, functionality, capsule level, target release, and stability should be considered in the coating agent's designation [19]. The main materials used for encapsulation are based on carbohydrates, proteins, and lipids. Microencapsulation techniques are subdivided into three groups; physical methods (spray drying, lyophilization, supercritical fluid precipitation, and solvent evaporation); physicochemical methods (coacervation, liposomes, and ionic gelation), and chemical methods (interfacial polymerization and molecular inclusion complexation) [15, 16, 20]. Therefore, using suitable wall material and encapsulation methods leads to capsules' production with favorable physicochemical properties and acceptable release in the gastrointestinal tract. Overall, in the present review, information on chemistry and dietary sources of flavonoids, their stability, and various encapsulation and delivery systems used for flavonoids are covered to give a better perspective for potential applications in food and future researches.

## 2. Flavonoids in *Viola odorata* L. and Health Benefits

Flavonoids are the most common phenolic compounds present in all plant parts such as *Viola odorata* L. and an integral part of human and animal diets. Till now, more than 9000 flavonoids have been reported that and their daily intake is in the range of 20-500 mg, principally from dietary sources including tea, red wine, apples, berries, onions, and tomatoes [4]. The presence of flavonoids in vegetables and fruits depends on the type of crop, climate, plant species, type of processing, and storage [21]. The highest level of flavonoids in the human diet consisted of soy isoflavones (genistein, daidzein, biochanin A), flavonols (quercetin, myricetin, kaempferol), and flavones (luteolin and apigenin) [22]. Figure 1 shows flavonoids subgroups, and Table 1 summarizes sources of flavonoids and their level in some foods. More information on the flavonoid content of various foods is supplied by [23].

Emerging evidence from studies has demonstrated the protective effects of food sources rich in flavonoids against different diseases. Altogether, flavonoids represent a broad spectrum of pharmacological properties, including antioxidative, antiallergic, anti-inflammatory, antidiabetic, hepato- and gastro-protective, antiviral, antibacterial, and anticancer activities [29]. Flavonoids are capable of scavenging free radicals and active oxygen species due to their conjugated ring structures and hydroxyl groups. It has been reported that increasing the number of hydroxyl groups and a decrease in glycosylation increased the antioxidant activity of flavonoids [22]. Various flavonoid classes such as flavonol, flavone, and flavanone or isoflavone are potent inhibitors of cycloxygenase-2 (COX-2) and inflammation [30]. Flavonoids exhibit antidiabetic activity by translating glucose transporter type 4 (GLUT4)

vesicles to the cell membrane, increasing the number of pancreatic β cells and insulin secretion, reducing insulin resistance and oxidative stress [31, 32].

Antibacterial activity of flavonoids arises from inactivation of microbial adhesins, inhibition of enzymes and cytoplasmic membrane function, alteration of the membrane permeability, and weakening of the pathogenicity [33, 34]. It has been reported that there is a relation between the structure and inactivation of enzymes associated with the life cycle of the viruses [33].

Flavonoids are effective in different stages of carcinogenesis, including initiation, promotion, and progression. The mechanisms of action consist of inactivation of carcinogens, cell proliferation inhibition, enhancement of DNA repair processes, and reduction of oxidative stress at the initiation stage.

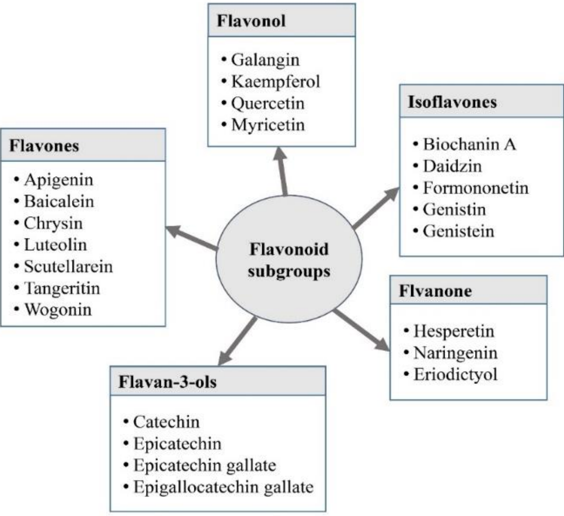


**Figure 1.** Different subgroups of flavonoids.

**Table 1**. Sources of flavonoids present in food.

| Food sample | Type of flavonoid | Concentration (mg/100 g or 100 mL sample) | Reference |
|---|---|---|---|
| Grapefruit juice<br>Lemon juice<br>Orange juice | Naringenin | 43.5<br>0.38<br>2.13 | [24] |
| Grapes<br>Red sorghum<br>Green olive | Luteolin | <0.1–2.6<br><0.2–18.2<br>0.2–1.2 | [25] |
| Lettuce<br>Chinese cabbage | Apigenin | <0.7-2.7<br><0.1-4.5 | [25] |
| Basil<br>Bay | Quercetin | 41-86.5<br>71-250 | [26] |
| Buckwheat leaves | Rutin | 3417 | [27] |
| Raw cocoa beans | Epicatechin | 270 - 1235 | [28] |
| Oregano<br>Peppermint | Eriodictyol | 85.33<br>30.92 | [23] |
| Carob kibbles | Myricetin | 11.67 | [23] |
| Raw capers<br>Raw chives<br>Fresh tarragon | kaempferol | 259.19<br>17.11<br>11 | [23] |

In the progression phase, flavonoids may induce apoptosis, inhibit angiogenesis, exhibit antioxidant activity, and induce cytotoxic or cytostatic action against cancer cells [35]. More findings and related studies regarding the exact mechanisms of action and biological activities of flavonoids can be found in the authors' review articles [30, 33, 36-39]. Some biological activities of flavonoids are summarized in Table 2.

**Table 2**. Some biological activities of flavonoids

| Biological activity | Study model and evaluation method | Concentration of flavonoids | Results | Reference |
|---|---|---|---|---|
| Antioxidant | DPPH, ABTS scavenging activity, and ferric reducing assay | 25-1000 µM | Quercetin 7-rhamnoside from *Hypericum japonicum* showed antioxidant activity. | [40] |
| Anti-inflammatory | Release of β-glucuronidase in rat polymorphonuclear leukocytes induced by platelet activating-factor | 10 µM | Four flavonoid alkaloids showed anti-inflammatory activities, with IC50 values against the release of β-glucuronidase from polymorphonuclear leukocytes of rats being in the range 5.16-5.85 µM. | [41] |
| | murine macrophage RAW 264.7 cells stimulated by LPS and acute lung injury induced by LPS in mice were adopted as in vitro and in vivo models | 12.5-100 µg/mL | Production of NO, PGE2, TNF-α, IL-6, MCP-1 and reactive oxygen species (ROS) was significantly reduced by flavonoids extracted from *Artemisia scoparia* Waldst. et kit. Moreover, alveolar hemorrhage and neutrophil infiltration, as well as pulmonary histopathologic changes, were substantially suppressed in lung tissues. | [42] |
| Antidiabetic | Biochemical and histopathological studies carried out in type 2 diabetic Wistar albino rats | 30 and 60 mg/kg | Daily oral administration of flavonoid-rich extract of Synsepalum dulcificum leaf for 21 days improved biochemical markers and pathological changes in diabetic rats. | [43] |
| | α-glycosidase inhibiting activity was evaluated in vitro, and antidiabetic activity was tested in alloxan-induced mice for 14 days | 10, 50, and 100 mg/kg body weight | Ethyl acetate extract of Binahong Leaves showed α-glycosidase inhibition of 81.23 µg/mL. The compound 8-Glucopyranosylapigenin isolated from Binahong Leaves had enzyme inhibiting activity with $IC_{50}$ value of 20.23 µg/mL and decreased blood glucose. | [44] |
| Anticancer | Cellular proliferation and migration were investigated in human neuroblastoma (SH-SY5Y) cells incubated with isoliquiritigenin | 20-100 µM | The results showed that the flavonoid had anti-proliferative and cytotoxic activity on SH-SY5Y cells via the ATP loss, induction of cell cycle arrest, and cell death largely through a necroptotic without apoptotic activity | [45] |
| Anticancer | Effect of xanthohumol on gastric cancer cells proliferation, apoptosis and metastasis was investigated | 1-100 µM | Xanthohumol reduced viability of gastric cancer cells. Also, it prevented proliferation, apoptosis, and metastasis in AGC cells. | [46] |
| Antimicrobial | Disc diffusion and broth dilution assays were used to investigate the antimicrobial activity of flavonoids from *Trianthema decandra* | Not mentioned | Diameter of the inhibition zone for microorganisms was in the range of 20-23 mm, and minimal inhibitory concentration was in the range of 39.05-312.5 µg/mL. | [47] |
| Antiviral | Human rhabdomyosarcoma cells infected with human enterovirus A71 (HEVA71) | 0.005-100 µM | Flavonoids showed antiviral activity at the level of 50 µM and prevented replication of HEVA71. | [48] |
| Cardioprotective | Cardiotoxicity was evaluated in rats by using serum biomarkers, lipid profile, tissue antioxidants, and histopathological examinations | 100 mg/kg | Pretreatment of rats with flavonoids alleviated the levels of pathological biochemical markers and increased the levels of endogenous protective antioxidant proteins in rats | [49] |

## 3. Chemical Properties and Stability of *Viola odorata* L. flavonoids

, The chemical structure of flavonoids consists of a fifteen-carbon skeleton involving two benzene rings (A and B) linked via a heterocyclic pyrane ring (C) (Figure 2) [33]. They are classified into different groups, including flavanol (e.g., epicatechin, catechin, epicatechin gallate), flavanone (e.g., naringenin, naringin, hesperetin), flavonol (e.g., kaempferol, quercetin, fisetin), flavone (e.g., luteolin, apigenin, chrysin), isoflavone (e.g., daidzein, genistein, daidzin) and anthocyanins [39]. These classes differ in degree of oxidation and substituents of the C ring, whereas the difference within a class is related to the substitution of the A and B rings [50].

Flavonoids are based on 2-phenylchromans (flavonols, flavones, flavanones, flavan-3-ols, anthocyanidins, and condensed tannins) and 3-phenylchromans (iso-flavonoids) [37, 51].

They can be present as aglycones, glycosides, and methylated derivatives [33]. Flavonoids exhibit various biological activities such as antioxidant and radical scavenging activity, which is originated from a double bond situated between carbons two and three, a hydroxyl group in carbon three, poly-hydroxylation of the aromatic rings A and B, and a carbonyl group located in the carbon four [52]. Flavonoids are crystalline substances with different molecular weights and melting points depending on their structure. Catechins, leucoanthocyanidins, flavanes, isoflavanes, flavanones, flavanonoles are colorless, whereas flavones, flavonoles, chalcones, and aurones are yellow. Flavonoids in glycoside form are soluble in diluted alcohols and hot water and in aglycon form, are soluble in apolar organic solvents, and insoluble in water [37, 53].

Preparation and food processing can decrease the level of flavonoids depending on the method used [22]. The effect of food processing and formulation on flavonoid behavior has been reviewed [54]. It has been pointed out that different thermal processes degrade flavonoids depending on the time duration and temperature of the process and flavonoid structure, food matrix, and presence of oxygen [55-57]. On the other hand, more innovative processes such as microwave, infra-red, high-pressure processing have slightly degraded flavonoids [58, 59]. Moreover, mechanical processes such as peeling, trimming, chopping, slicing, crushing and pressing can decrease the level of flavonoids [60, 61]. Flavonoids are also damaged by common domestic processes, including boiling, frying, baking, steam-cooking, and microwaving [62-64]. Studies regarding the effect of light on flavonoids revealed that these compounds might either increase depending on the type of food (fresh or processed). In fresh fruit and vegetables, light induces stress signals and increases flavonoid synthesis [65-67]. The light wavelength, pH, concentration, and structure of flavonoids affect flavonoids' degradation by light [54].

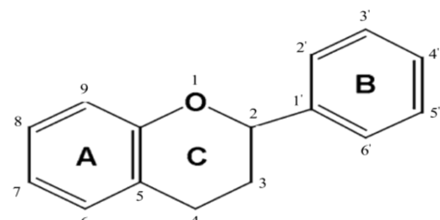


**Figure 2**. Basic chemical structure of flavonoids.

## 4. Encapsulation Systems for Flavonoids

Although flavonoids possess potential health benefits, their weak stability and insolubility are obstacles to their incorporation into foods. Also, flavonoids degrade in the extreme acidic pH of gastric juice resulting in low bioavailability and absorption [3]. Therefore, it seems that encapsulation can be an effective approach for the protection of these compounds. Numerous methods and coating substances are used for the encapsulation of bioactive components. The methods are classified into physical (spray drying, fluid bed coating, centrifugal extrusion, processes using the supercritical fluids), chemical (interfacial polycondensation, *in situ* polymerization, interfacial polymerization, interfacial cross-linking), and physicochemical (spray cooling, hot melt coating, ionic gelation, solvent evaporation extraction, simple or complex coacervation) [68, 69]. Delivery systems used for flavonoids are presented in the following sections. Table 3 represents some encapsulation approaches applied for flavonoids.

*4.1. Spray drying.*

Spray drying is a technique in which a fluid feed is atomized, evaporated, and converted to powder. It is widely used in the food industry because of its low production cost. The spray-dried powders are stable and resistant to microbiological and oxidative degradation and have low water activity due to low moisture and water activity and higher solubility and quality characteristics (color, flavor, nutrients) [84, 85]. However, the high temperature of the process (150-220ºC of inlet air and 50-80ºC of outlet air) has a detrimental effect on sensitive compounds such as vitamins, colors, lycopene, β-carotene, and polyphenols [84, 85]. Various coating materials, including maltodextrin, gum arabic, chitosan, and soy protein isolate, have been applied in microencapsulation of anthocyanins, quercetin, and catechins [86-88].

Hu *et al*. (2018) [12] encapsulated extracted flavonoids from citrus peels and encapsulated them in gum arabic and whey protein concentrate using spray drying. It was shown that microcapsules prepared with a mixture of gum arabic and whey protein concentrate had higher retention efficiency, encapsulation efficiency, and powder yield, and more stability. Interaction of polyphenols and protein was expressed as the probable reason for higher retention of flavonoids encapsulated in gum arabic and whey protein concentration. Naringenin and quercetin were encapsulated by spray drying (inlet temperature of 125ºC and outlet temperature of 78-80ºC) using cellulose acetate phthalate (CAP) and some surfactants (carboxymethylcellulose, sodium dodecylbenzensulfonate, and Tween 85) to enhance dissolution rate. The results indicated that microcapsules prepared by CAP and Tween had high encapsulation efficiency, homogenous dimensional distribution, and spherical shape [3].

In a study performed by Wu *et al*. (2014) [89], microcapsules from flavonoids extract of *Rhodomyrtus tomentosa* (Ait.) Hassk. were prepared by spray-drying (inlet temperature of 150ºC and outlet temperature of 100ºC) and response surface methodology with variables (maltodextrin to gum arabic ratio, solid content, glycerol monostearate, and flavonoids extract to coating material ratio. The highest encapsulation efficiency (91.75%) was obtained in conditions with maltodextrin to gum arabic ratio of 1:1.3 (w/w), solid content of 27.4%, glycerol monostearate of content at 0.25%, and core: coating ration of 3: 7. maltodextrin to gum arabic ratio and core to coating ratio was mentioned as the most substantial factors affecting encapsulating efficiency. It was noted that a large number of hydroxyl groups present in flavonoid extract could form hydrogen bonds with gum arabic retaining flavonoids throughout the spray drying. Furthermore, microcapsules' antioxidant activity remained unchanged and higher than citric acid and rutin at the same concentration.

Palma *et al*. (2012) [90] investigated the release kinetics of flavonoids (quercetin, naringenin, and epicatechin) microparticles prepared with inulin (lipid-insoluble) and Capsul® (lipid-soluble and as channelizing agent) in methyl linoleate. Higher encapsulation efficiency was reported for quercetin and epicatechin (> 60%) than naringenin (~ 40%) in microcapsules with and without channelizing agent that was ascribed to the higher number of hydroxyl groups in flavonoids structure.

**Table 3**. Summary of encapsulation methods for flavonoids.

| Type of flavonoid | Method of encapsulation | Results | Reference |
|---|---|---|---|
| Quercetin | Molecular complex with b-cyclodextrin (β-CD), hydroxypropyl-β-cyclodextrin (HP-βCD) and sulfobutyl ether β-cyclodextrin (SBE-βCD) | Higher scavenging capability than that of quercetin in water and quercetin-SBE-bCD complex was the most reactive form | [70] |

| Type of flavonoid | Method of encapsulation | Results | Reference |
|---|---|---|---|
| Quercetin | Molecular complex with b-cyclodextrin (β-CD), | Higher weight loading with a much lower release and also improved its solubility, antioxidant activity, and photostability properties. | [71] |
| Chrysin | β-CD | Increased the solubility of chrysin as well as its therapeutic efficacy | [72] |
| Rutin | HP-*β*-CD | Enhancement of the oral availability by the capsulation of rutin by HP-*β*-CD | [73] |
| Naringenin | *β*-CD | Enhanced water solubility and thermal stability of naringenin | [74] |
| Fisetin | sulfobutylether-β-cyclodextrin | Enhanced the aqueous solubility of fsetin | [75] |
| Apigenin | | Higher solubility and increased antioxidant activity | [76] |
| Genistein | *β*-CD, *β*-CD, HP-*β*-CD and RM-*β*-CD | Higher solubility in the case of HP-*β*-CD and RM-*β*-CD<br>Improvement of the ability to cross the biological membrane | [77] |
| Hesperetin and hesperidin | *β*-CD and HP-*β*-CD | Improvement on the solubility and chemical stability and better results were achieved in complex of HP-*β*-CD and hesperetin | [78] |
| Astilbin | α-, β-, and γ-CD | Solubility of astilbin in β-CD microcapsules prepared by the freeze-drying method was enhanced by 122.1-fold, and its dissolution profile was improved | [79] |
| Catechin | *β*-CD | Higher stability of catechins inclusion complexes in solid matrix compared to semi-solid and liquid matrix. Sensory evaluation showed that the inclusion complex masked the catechin's bitter taste without affecting the color and overall acceptance of the product. | [80] |
| Rutin | Chitosan-tripoyphosphate | High positive charge in optimized nanoparticles. Retaining rutin in SGF and 20% release in SIF. | [81] |
| Hesperetin | Nanostructured lipid carriers (NLC) and solid lipid nanoparticles (SLN) | NLC formulations with glycerol monostearate and 0.064 % hesperetin showed better size, zeta potential, encapsulation efficiency, stability, and hesperetin release. | [82] |
| Baicalein | self-microemulsifying drug delivery systems (SMEDDS) | Baicalein in SMEDDS had a higher release rate and bioavailability compared to baicalein suspension. | [83] |

The release rate constant was inversely related with the EE% and was higher in microcapsules with a channelizing agent that indicated the formation of channels inside the microcapsules resulting in diffusion of flavonoids into methyl linoleate. Furthermore, the release mechanism was independent of flavonoid structure and was only associated with the channelizing agent's presence. The authors pointed out that controlling the release of flavonoids from microcapsules as potential antioxidants can help prevent lipid oxidation in foods.

*4.2. Molecular complexes.*

The physical association of the active ingredient and the coating substance leads to molecular complexes' formation. Cyclodextrins (CD) are interesting molecules used in this context. They are naturally occurring cyclic oligosaccharides consisting of six (α-cyclodextrin), seven (β-cyclodextrin), eight (γ-cyclodextrin), or more glucopyranose units linked by (1,4) bonds [91, 92]. Cyclodextrins have a truncated cone shape with a hydrophobic internal cavity and hydrophilic external surface, which can enclose hydrophobic molecules inside their internal cavity and improve the dissolution rate, stability, solubility, and bioavailability of bioactive ingredients [87, 93, 94]. Various compounds, including flavors, volatile oils, sweeteners, and polyphenols, have been trapped in cyclodextrins [69, 91].

The majority of studies concerning to encapsulation of flavonoids by cyclodextrins have used β-cyclodextrin and its derivatives such as hydroxyproyl-β-cyclodextrin (HP-β-CD), methyl-β-cyclodextrin (M-β-CD), dimethyl-β-cyclodextrin (DM-β-CD), trimethyl-β-cyclodextrin (TM-β-CD), solphobutylether-β-cyclodextrin (SBE-β-CD), and glucosyl-β-cyclodextrin (G2-β-CD) [94, 95]. The cyclodextrins can interact with flavonoids conducting the B-ring toward the CD's secondary rim or heading the A-ring toward the CD's secondary rim [96].

Yang *et al*. (2019) [97] investigated the complexation of three flavonoids (taxifolin, quercetin, and morin hydrate) with propanediamine-β-cyclodextrin (DP-β-CD). It was stated that the water solubility of taxifolin, quercetin, and morin hydrate was enhanced 70-102 times after resulting in an inclusion complex with DP-β-CD. Also, the antioxidant activity of DP-β-CD/ taxifolin complex was better than that of taxifolin. It was declared that hydroxyl groups in taxifolin are close enough to secondary hydroxyl groups of DP-β-CD to form intramolecular hydrogen bonds, resulting in an increase of antioxidant activity.

Morin/hydroxypropy-β-cyclodextrin (1:1 molar ratio) inclusion complex was prepared, and it was demonstrated that dissolution rate, solubility, oral bioavailability, the antihyperalgesic and anti-inflammatory activity of morin was increased [98]. A flavonoid-rich, *Allium cepa* L. var agrogatum Don extract was encapsulated in β-CD (1:3 molar ratio), and the results showed that aqueous solubility and the bioavailability of the extract was improved and, according to *in vitro* skin permeation study, had the potential to be applied for transdermal delivery [99]. In a similar study, methanolic extract of *Hypericum perforatum* (St John’s wort) was encapsulated using β-CD (1:4 mass ratio). Encapsulation efficiency was reported as 27.5, 30, and 35% for catechin, epicatechin, and quercetin, respectively. Moreover, the differential scanning calorimetry test showed the preventive activity of β-CD against thermal oxidation in the encapsulated extract at temperatures as high as 300ºC [100].

*4.3. Liposome entrapment.*

Liposomes are non-toxic lipid vesicles composed of phospholipid bilayers organized in water to form an aqueous core surrounded by a lipidic bilayer [87, 101]. This structure can entrap water-soluble, lipid-soluble, and amphiphilic substances [19, 87]. Liposome properties are influenced by lipid composition, surface charge, size, and method of preparation. Therefore, the lipid components' choice defines the rigidity, fluidity, and charge of the lipid bilayer and, consequently, the properties of the liposome. Although liposomes have been studied extensively as suitable carriers for antioxidants, antimicrobials, therapeutic agents, and bioactive compounds [101], high-cost production, low physicochemical stability, drug leakage, and fast release of core substance in the gastrointestinal tract are the major disadvantages [19]. Some approaches have recently been explored to prevail these defects, such as protein coating, chitosan coating, encapsulation using ultrasound, and coating of micronized sucrose and pro-liposome hydration method [102-105].

In a study by Tao *et al*. (2014) [106], propolis flavonoids were encapsulated in a liposome that resulted in an increase of immunological activity due to enhancement of the phagocytic function of macrophages and the release of IL-1β, IL6, and interferon γ and in vivo by activation the cellular and humoral immune response, including inducing higher level concentrations of immunoglobulin (IgG), IL-4, and interferon γ.

According to the report of Mignet *et al*. (2012) [107], liposomal encapsulation of fisetin by Phospholipon® 90G and dioctadecyldimethylammonium chloride-glycin- poly(ethylene

glycol) 45, yielded liposomes with nanometer scale, high homogeneity, encapsulation efficiency, and stability as well as maintaining cytotoxic and morphological activities on endothelial cells. Similarly, fisetin's liposomal formulation was prepared using 1, 2- dioleoyl-sn-glycero-3-phosphocholine and dioctadecyldimethylammonium chloride-polyethyleneglycol-2000 with high homogeneity and high encapsulation efficiency, and it was demonstrated that the bioavailability was 47-fold higher in liposomal form compared to free fisetin. Furthermore, liposomal fisetin prevented the growth of Lewis lung carcinoma tumors for a longer period than free fisetin at the same level [108]. This is in consistent with the results obtained by Goniotaki *et al.* [109], who reported an increase in growth inhibitory activity of flavonoids entrapped in liposomes.

Quercetin was encapsulated in nanoliposomes using rice bran phospholipids and the thin film sonication method. The quercetin-loaded nanoparticles were spherical with a 157 nm mean diameter and encapsulation efficiency of 84.92%. Nanoparticles were stable regarding quercetin retention and antioxidant activity stored at 4 and 27ºC during six months. Release of quercetin from nanoliposomes was limited in SGF (20% after 4 h), while in SIF, an initial release of 60% after 2 h and sustained release of 70% until 24 h was an indication of an efficient delivery and absorption of quercetin in the intestine [110]. Likewise, quercetin was encapsulated in chitosan-coated nanoliposomes by the electrostatic deposition technique. Encapsulation yielded spherical nanoparticles with 71.14% encapsulation efficiency and enhanced DPPH antioxidant capacity, hydroxyl radical and superoxide anion radical scavenging capacity, and ferric reducing capacity [103].

### *4.4. Polymer nanoparticles.*

Polymer nanoparticles can be manufactured using a variety of ingredients such as natural polymers (proteins and polysaccharides), synthetic polymers (polylactide (PLA), poly lactide-co-glycolide (PLGA), poly glutamic acid, poly (vinyl alcohol)), and inorganic materials [87, 111]. Encapsulation of quercetin via BSA (bovine serum albumin), zein, chitosan-alginate, PLGA nanoparticles, PLA, Poly (caprolactone, PCL), and glycerol diglycidyl ether (GDE) have been reviewed by [87].

Pool *et al.* [112] utilized PLGA nanoparticles and the solvent displacement method to encapsulate catechin and quercetin. Polymeric nanoparticles with a mean diameter of 400 nm and encapsulation efficiency of 79% were produced. *In vitro* release study revealed that flavonoids release was pH-dependent, and higher liberation was observed at acidic pH as a consequence of PLGA degradation. Quercetin showed a slower release compared to catechin, which can be attributed to the carboxyl-carbonyl interactions of the polymer and quercetin. Also, an increase in antiradical and chelating properties of flavonoids was reported by incorporating them into nanoparticles. Pectin nanoparticles containing citrus peel extract were prepared by the ionic gelation method. The obtained nanoparticles had an average size of 271.5 nm, and the release profile in simulated gastric fluid demonstrated 73% and 28.78% release from the free extract and encapsulated extract, respectively, after 2 h. The releasing rate of flavonoids reached 91.47% from nanoparticles after 24 h in the simulated intestinal fluid (SIF). Furthermore, the encapsulated extract showed higher antioxidant activity than free extract according to DPPH and ABTS assays [113]. In another study by [114], whey protein concentrate was utilized to encapsulate mandarin peel extracts through ionic cross-linking. It was declared that extracts were entrapped in nanoparticles via hydrophobic interactions or hydrogen bonds. Encapsulation of extracts decreased the release rate of flavonoids in

gastrointestinal fluids and improved antioxidant activity in SIF. Fisetin was nano encapsulated using PCL and poly (D, L-lactic-co-glycolic acid)-block-poly (ethylene glycol)-carboxylic acid (PLGA-PEG-COOH). Nanoparticles had a mean diameter of 140-200 nm and EE% of 70-82%. Higher content of PCL in particle formulation yielded higher encapsulation efficiency due to the hydrophobic nature of both fisetin and PCL. Results of *in vitro* release indicated < 15% in SGF during 2 h in all formulations, while in SIF, formulation with a higher content of PLGA-PEG-COOH showed 70% release after 7 h and complete release after 24 h. In nanoparticles prepared by the only PCL, 54% and 70% release after 7 h and 24 h was observed, respectively [115].

### *4.5. Other types of delivery systems.*

Fisetin was encapsulated by osmoporation using Saccharomyces cerevisiae cells, and the effects of concentration, osmotic pressure, and temperature on the encapsulation and internalized fisetin content were studied. The results illustrated that osmoporation significantly increased EE% and entrapped fisetin [116].

Akhtar *et al*. (2014) [117] produced microcapsules containing rutin and Hibiscus anthocyanins in multiple emulsions using a spinning disk reactor (SDR). Using this technology, an emulsion premix was transmitted through a rotating disk at a regulated flow-rate and disk rotation speed which provided controllable and low shear conditions for the preparation of secondary emulsions. It was stated that using 2 wt.% emulsifier polyoxyethylene (20) stearyl ether produced W/O/W emulsion with fine droplets (13-15 nm) and EE of > 80%. The utilization of SDR efficiently encapsulated rutin and anthocyanins within multiple emulsions with a high retention and protection degree.

Onion-type multilamellar vesicles (MLVs) were applied in the entrapment of rutin and naringenin. It was announced that the encapsulation efficiency of naringin was low (< 10%) and was greatly adsorbed on MLV surface (> 60%), while rutin showed higher efficiency (> 60%). No rutin release was observed in the concentrated MLVs phase during 30 days, and 16% release was detected in MLVs dispersion after 31 days [13].

Quercetin from dry onion peel crude extract was encapsulated in reassembled casein particles, effects of pH, casein levels, and additives such as salts and Cetyl trimethylammonium bromide (CTAB) on EE% were studied. The highest EE% (97%) was achieved by 0.5% (w/v) sodium caseinate, 0.1 M of calcium chloride, 0.5 M of dipotassium hydrogen phosphate, 0.1 mM CTAB and 1 M of sodium citrate at a pH of 7 [118]. In another study by Horincar *et al*. (2019) [119], flavonoids were extracted from yellow onion skins and microencapsulated in whey protein isolate and combinations of chitosan, maltodextrin, and pectin. It was observed that a combination of whey protein isolate, maltodextrin, and pectin resulted in higher EE% (71%) compared to whey protein isolate and chitosan combination (59%). Also, it was emphasized that flavonoids interacted with whey protein isolate through van der Waals and hydrogen bonding. Ban *et al*. [120] used nanoparticles made up of physiological lipids to protect flavonoids (naringenin, quercetin and hesperidin) from the digestive system's harsh conditions until their absorption into enterocytes, thereby improving their bioaccessibility.

## 5. Considerable Aspects of Flavonoid Encapsulation

### *5.1. Biological fate.*

One of the key characteristics of an encapsulation system is not having an adverse effect on flavonoids' bioavailability. Various factors, including size, morphology, composition, and interfacial properties, can influence flavonoids' bioavailability [121]. These characteristics are changed during transit of particles from mouth to colon due to the presence of mucin, salts, digestive enzymes, buffers, and acids that affect flavonoids release rate and region [122]. Flavonoids are absorbed in the small intestine in the form of aglycons or are metabolized by intestinal microbiota and absorbed in the colon [33]; hence designing a delivery system that allows the release of flavonoid glycosides in the large intestine is indispensable. Starch-based wall materials used for entrapment of flavonoids are degraded in the mouth by the activity of α-amylase. Protein-based delivery systems are hydrolyzed in the stomach exposed to acidic pH and the enzyme pepsin. Lipid-based particles usually release the core substances in the small intestine [123]. Therefore, the physicochemical features of the substances used to develop flavonoid encapsulates and their digestibility in the gastrointestinal tract and the bioactive ingredient's action site are considerable issues that should be notified.

### *5.2. Incorporation into food matrices.*

Although numerous studies have been conducted regarding the encapsulation of flavonoids, few of them reported the stability and effect of their addiction to food matrices. By incorporating microcapsules, appearance, rheology, texture, and sensory properties of food may be altered. Some flavonoids are colorless, and some are yellow, and it is important to consider the point that if the emergence of color in the product is required or not. The incorporation of particles with different sizes, refractive index, and concentration causes changes in foods and beverages' appearance. In transparent food products, delivery systems generating small particles ($d<50$ nm) should be applied while particles with diameters $> 50$ can be used in products whose clarity is not required [122]. In addition, the microcapsules produced using gelling materials such as gellan, xanthan, or alginate are usually greater than 100 μm and do not provide acceptable mouthfeel and texture in the food formulation [124]. Particles obtained by spray drying are below 40 μm and generate a desirable mouthfeel in food products [125]. Furthermore, food products possess various pH and ionic strength and may undergo harsh processing conditions (freezing, heating, mixing, shearing, and dehydration), leading to the disintegration of microcapsules that should be considered in the design and fabrication of delivery systems [122].

### *5.3. Safety.*

The safety of materials utilized in the encapsulation process is of paramount importance. In this respect, a very limited number of coatings and excipient materials have been approved for food use. In some encapsulation methods, the residue of non-food grade solvents and detergents may pose health problems [126] that should be considered in selecting the technique for flavonoid encapsulation. Another challenge is the effect of nanoparticles on the body, dependent on factors including size, composition, surface properties, and their ability to cross the biological membranes [127, 128]. It has been speculated that reduced-size particles have a detrimental impact on the biological system. Nanoparticles might increase the

bioavailability of bioactive substances and induce health risks [121]. There are still unanswered questions regarding the interaction of nanoparticles and the biological system and their potential toxicity. It is not possible to elucidate the safety of nano-scale encapsulation.

## 6. Conclusion and Future Perspective

Flavonoids are important constituents of many fruits and vegetables, which provide various health benefits that can be extracted from these sources and be utilized to develop functional foods. However, they are sensitive to light, heat, and oxygen. Their poor bioavailability after oral administration and degradation under acidic pH of stomach limit their successful application. In this respect, different encapsulation systems were introduced in this review that can resolve the mentioned shortcomings. Encapsulation can improve the stability of flavonoids as well as solubility, controlled release, and bioavailability. However, each encapsulation method has its advantages and disadvantages that should be considered in selecting the specific system for the special application field. Based on the collected data, the future development of delivery systems for flavonoids should be centralized on applying food-grade ingredients as coating materials, other encapsulation methods with higher efficiency, and investigation of the application of microcapsules and their effects in food products.

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## Conflicts of Interest

The authors declare no conflict of interest.

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