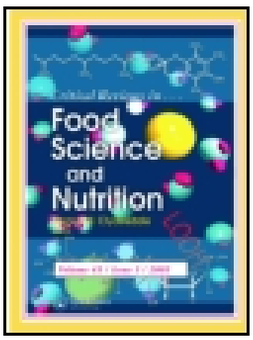

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CRITICAL REVIEWS IN FOOD SCIENCE AND NUTRITION
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REVIEW

Enhancement of bioavailability and bioactivity of diet-derived flavonoids by application of nanotechnology: a review

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ABSTRACT

Flavonoids, which are a class of polyphenols widely existing in food and medicine, have enormous pharmacological effects. The functional properties of flavonoids are mainly distributed to their anti-oxidative, anticancer, and anti-inflammatoryeffects, etc. However, flavonoids' low bioavailability limits their clinical application, which is closely related to their intestinal absorption and metabolism. In addition, because of the short residence time of oral bioactive molecules in the stomach, low permeability and low solubility in the gastrointestinal tract, flavonoids are easy to be decomposed by the external environment and gastrointestinal tract after digestion. To tackle these obstacles, technological approaches like microencapsulation have been developed and applied for the formulation of flavonoid-enriched food products. In the light of these scientific advances, the objective of this review is to establish the structural requirements of flavonoids for appreciable anticancer, anti-inflammatory, and antioxidant effects, and elucidate a comprehensive mechanism that can explain their activity. Furthermore, the novelty in application of nanotechnology for the safe delivery of flavonoids in food matrices is discussed. After a literature on the flavonoids and their health attributes, the encapsulation methods and the coating materials are presented.

KEYWORDS

Absorption; anti-cancer; antioxidant; flavonoid; health benefit; nanoformulation

Introduction

At present, more than 9000 kinds of flavonoids are reported and most of them widely distributed in the plant kingdom with a characteristic C6–C3–C6 structural backbone (Wu et al. 2018). They are classified into six main categories: flavone, isoflavone, flavan-3-ol, flavanone, anthocyanidin and flavonol.

Flavones such as tangeritin, apigenin and luteolin are abundantly presented in broccoli, apple, celery, grape and other food raw materials. Flavonols including quercetin, kaempferol and myricetin are mainly found in onions, lettuce, berries, tea, and red pepper. Flavanones give the special taste of citrus peel which are rich sources of eriodictyol, naringenin, and hesperitin. Isoflavones are a special kind of flavonoids extracted from soybean, mainly distributed in soybean seed coat, hypocotyl and cotyledon, there are three main isoflavones: genistein, daidzein and glycitein. Other flavonoids named flavan-3-ol (dihydroflavonols) such as EG, EGCG, EGC, ECG, and GCG are rich in black and green tea. The most commonly associated food with anthocyanins such as cyanidin, delphinidin, malvidin, pelargonidin, peonidin is berries including strawberry, blueberry and raspberry.

As a dietary component, flavonoids are thought to have beneficial effects on human health. Their health-promoting properties are always associated with anticancer, anti-inflammatory, and antioxidant effects (as shown in *Materials and methods*). Unfortunately, due to low solubility, poor absorption, and rapid metabolism, use of flavonoids in disease prevention is not satisfactory. In this regard, modern nanotechnology have been developed to overcome this obstacle. Although some flavonoid oral delivery approaches have been discussed in previous studies, the present review is intended to provide readers with an updated comprehensive catalog of these ongoing approaches, with the goal of harnessing the true potential of these agents in the food industry and clinical area. To comprehensively understand the application of these novel strategies in delivering flavonoids, we searched and collected related previous reports to date and generalized them from the following aspects: absorption enhancers, structural transformations, and pharmaceutical technologies. In addition, the bioactivities and structure-activity relationships, as well as possible limitations of nanotechnology are discussed. This work will provide some beneficial references for efficiently resolving the low bioavailability issue of these insoluble flavonoids.

Materials and methods

An electronic search was conducted using PubMed, Science Direct and Google Scholar by finding the keywords

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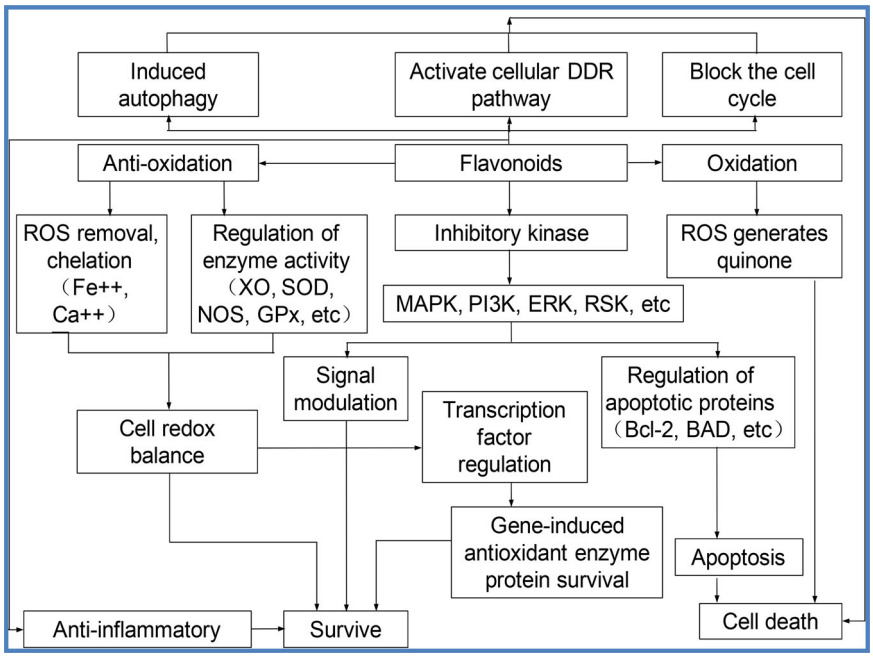

Figure 1. Interaction between various mechanisms of apoptotic cell death. Adapted from Zeng, 2016.

"Flavonoid" and "bioactivity" and "anticancer" and "anti-inflammatory" and "antioxidant" or "bioavailability" or "absorption" or "nanotechnology" in "Title/Abstract/Keywords", without date restriction, to identify all published studies (*in vitro*, *in vivo*, clinical and case-control) that have investigated the connection between lentils and their various beneficial effects. Health-promoting information was gathered and orchestrated in the suitable place in the review.

Bioactivities and structure-activity relationship

Anti-cancer activity

By far, as shown in Figure 1, flavonoids as well as their analogues have been explored in the treatment of liver, lung, blood, pancreatic and breast cancer. At the molecular level, various mechanisms have emphasized the effect of flavonoids in cancer intervention, including inhibition of proteasome and Nrf2 signaling, as well as induction of cell differentiation and cell cycle arrest (Lu et al. 2017; Madunić et al. 2018). Flavonoids can also effectively inhibit the activities of xanthine oxidase, cyclooxygenase (COX), Lipoxygenase (LOX) and other enzymes involved in inflammation and cancer pathology (Tavsan and Kayali 2019).

For structure-activity relationship, flavonoids such as natural flavone, isoflavonone, genistein, EGCG, or tea catechins and quercetin are emerging as candidates for anticancer drug and some of them have been applied to clinical practice. It seems that the presence of double bond between C2-C3 and a coplanar structure with free hydroxyl linkage of flavone at the C-7, C-3′, and C-4′ positions are required for tumor related protein kinase inhibitory effects. The important role of double bond presented as C2-C3 to the linkage between rings C and A/B, which is significant important for their anti-cancer activity. For example, apigenin and naringenin, a large number of studies conducted over the past decades have demonstrated that both of them have potential anticancer effect (Madunić et al. 2018; Choudhury et al. 2013; Hu et al. 2015). Additionally, for breast cancer and colon adenocarcinoma cells, the presence of double bond of C2 = C3 of flavonoids has been explored to enhance anticancer effects by in-depth analysis of gene expression (van Zanden et al. 2004; Isoda et al. 2014). In fact, a comparative study indicated that dihydroisorhamnetin with respect to unsaturated counterparts of 2, 3-dihydrochrysoeriol strengthened tumor inhibitory effects about 17% (Amrutha et al. 2014).

In another case of C-3-hydroxylation, for example, quercetin and kaempferol, of C-3-hydroxylation at the position of C2 = C3 has been considered as a decisive conjugation to enhance biological effects (Liao et al. 2016). Moreover, weakened inhibitory effect on protein kinase C (PKC) would occur with co-existence of C2-C3 saturation and two ring B hydroxyl groups (Kang, Howard, and Thurston 2003). Nevertheless, many publications have evidenced hydroxylation of flavonoids influences on tumor modulation (Kale, Gawande, and Kotwal 2008). Generally, the inhibitory effect of specific hydroxylated flavonoids on tumor cells was stronger than that of permethoxylated counterparts (Manthey, Guthrie, and Grohmann 2001). The auxiliary role of free hydroxyl substituents at the C-3′, C-4′ and C-7-positions has been revealed (Abotaleb et al. 2018; Wilsher et al. 2017).

It has been proposed that the substitution of B-ring, such as catechol, has an important enhancement of anti-cancer effect, and the additional hydroxyl substitution in the same posistion does not change the activity (Hitge et al. 2020). Kaempferol, gave another example, having C-3 hydroxylation with notably stronger antiproliferative effect than apigenin (Corina et al. 2017). On the other hand, flavonoid derivatives linked O-methylation at A ring are contributed to enhanced biological activity (Fig. 2). Polymethoxyflavones, in case of nobiletin and tangeretin, showed the most significant anti-

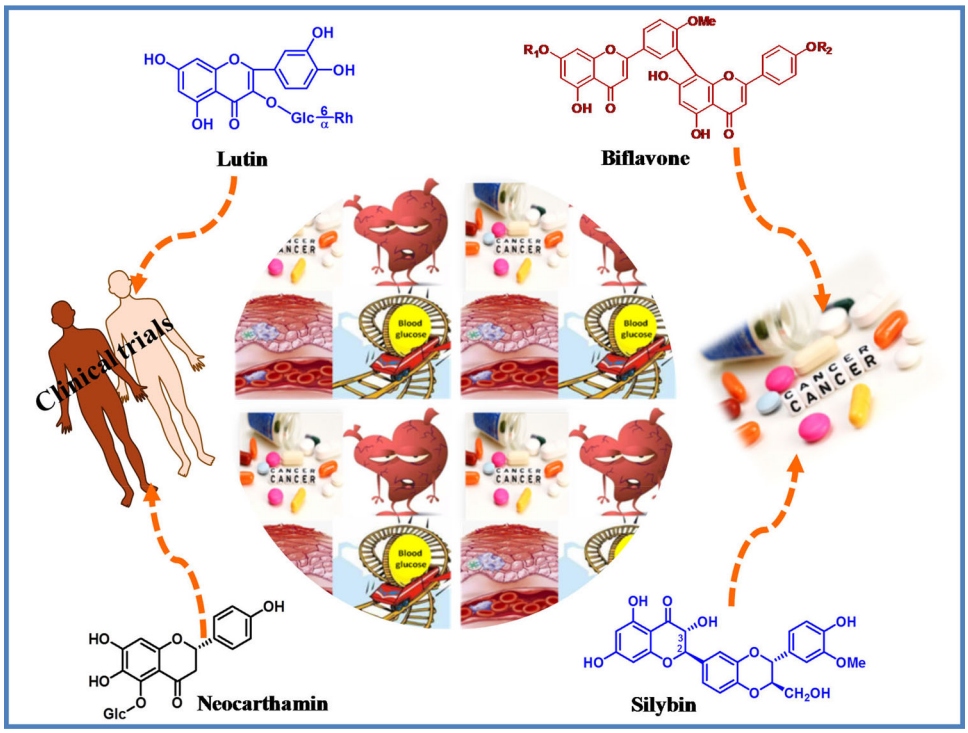

Figure 2. Proposed schemes for the extensive accumulation of the chemopreventive flavonoids.

proliferative effect in cell culture, also suggesting the importance of C_8 position in inihibitory activity (Surichan et al. 2018). In agreement with previous researches, flavonoid glycosylation seems not affect induction of cell differentiation (Cai et al. 2018). The weakened antiproliferative effects of flavonoid-goycosides (compared with aglycone of flavonoid) might be caused by steric blocking involved in cell entry and receptor binding (Özkan et al. 2019; Cai et al. 2018).

Anti-inflammatory activity

In fact, preventive role of flavonoids on inflammation which can be produced in tissues and organs of various parts of the body, such as folliculitis, tonsillitis, pneumonia, hepatitis, nephritis, etc. has been investigated (Liu et al. 2017; Feng et al. 2016). Among them, various inflammatory mediators including proinflammatory cytokines modulation, interleukin and nterleukins effect, as well as prostaglandins attenuation and its relevant signaling pathways have been concluded *in vitro* and *in vivo* (Liu et al. 2018;) . Quercetin, luteolin, fisetin, apigenin, isoliquiritigenin, rutin, chrysin, genistein, silymarin, and kaempferol are reported to have the abilities to inhibit NFκB, these flavonoids may modulate the expression of pro-inflammatory genes leading to the attenuation of the inflammatory responses underlying various cardiovascular pathology (Leyva-López et al. 2016; Gandhi et al. 2018; Aziz, Kim, and Cho 2018). In conclusion, the anti-inflammatory effect of flavonoids has been widely studied, and its specific mechanism may not be uniform, which increases the urgency of further study on its anti-inflammatory mechanism (Fig. 3).

For structure-activity relationship, in general, the preferred structural aspects of flavonoids with anti-inflammatory effects are summarized as follows: (1) the C2 = C3 double bond may be attributed to the molecular planarity. This double bond's absence always leads to a larger volume/surface ratio, as diosmin shows a stronger anti-inflammatory effect than hesperidin (Sahu et al. 2016). (2) Hydroxylation patterns, such as 3′-hydroxylation of phenacetin, and 5-hydroxylation of isoflavones, especially the cyclo-b-catechol fraction, provide the prefer effect on inhibitory effect on cell differentiation (apigenin) (Boisnic et al. 2018). (3) Methoxylation significantly enhances the anti-inflammatory effect, possibly through hydroxylation and a more pronounced NFκB signaling pathway inhibition (O-methylation of aspenin) (Wang, Li, et al. 2018). (4) The glycosylated forms of flavonoid have lower lipophilicity and possess lower anti-inflammatory activity (Xiao 2017). (5) Finally, the presence of C7-C8 double bond in A ring, C-butyrolactone and (or) C5-acetic acid/lactone group has been considered as a possible classification in treatment of inflammation (Xin et al. 2017).

Anti-diabetic activity

Nowadays, anti-diabetic agents derived from the food source attracted a lot of attention in the management of diabetes mellitus (Yunn et al. 2018). In terms of diabetes, the underlying mechanism of anti-diabetic action of flavonoids has been well investigated (Kawser Hossain et al. 2016) including the effect on various digestion enzymes and signaling pathways (Shahinozzaman et al. 2018). Subsequently, it becomes of great interest to declare that chalcones are demonstrated to be strong inhibitors of α-amylase and α-glucosidase, which are effective digestion enzymes on glucose homeostasis (Rocha et al. 2020; Chen, Cao, et al. 2018).

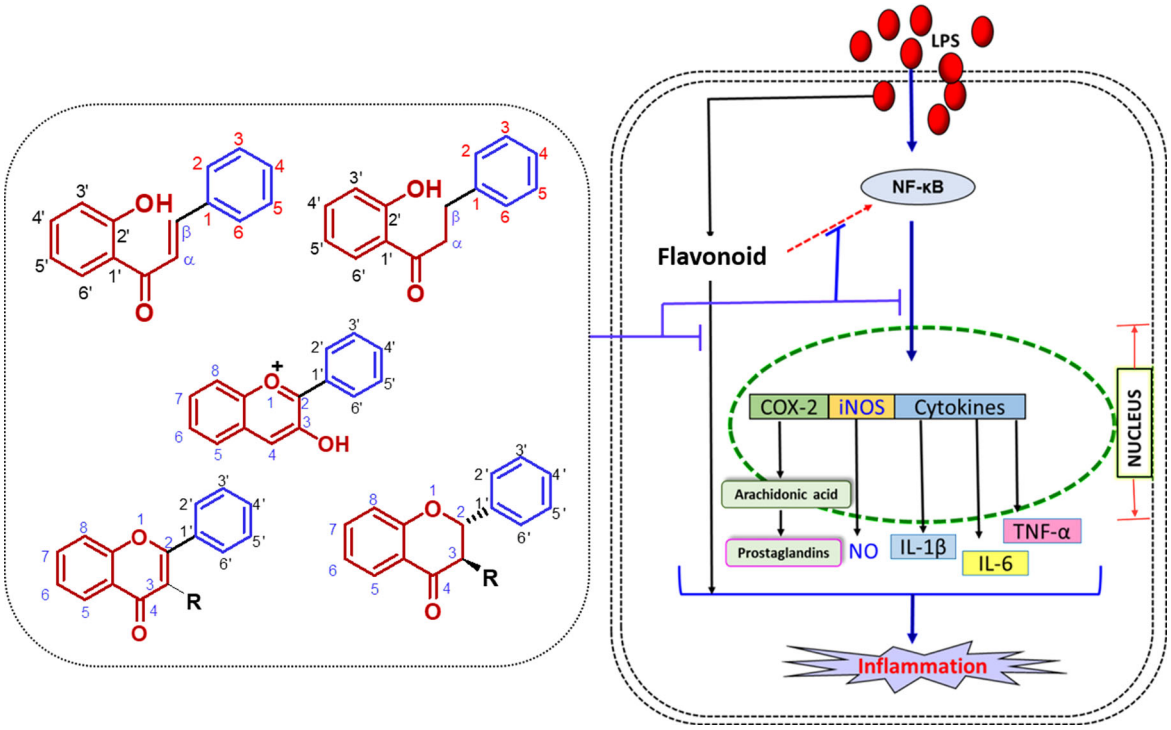

Figure 3. Anti-inflammatory effect of flavonoids.

Meanwhile, chalcone could exert these properties by acting on different therapeutic targets (Tripoli et al. 2007).

Interestingly, planarity and hydroxylation located in position C-7 on C ring in some flavonoids provide promising effect on peroxisome proliferators-activated receptor (PPAR) activation. Epidemiological studies have shown an inverse relationship between dietary hydroxylation flavonoid intake and a positive contribution of methoxylation with anti-diabetic effect (Tripoli et al. 2007). Regarding substitution of glycosylation presented in the aglycones of flavonoid, especially at C-3, has been demonstrated to show stronger effect on diabetes (Xiao and Kai 2012). More earlier, Zhang et al. (2005) found that the presence of C2-C3 double bond in ring C, ring B attached at position C2, hydroxylation at position C5, lack of hydroxylation at position C3 and hydrophobic substitution at positions C6, C7, C8 or C4', are important structural properties for anti-diabetic action of flavonoid (Zhang et al. 2005). Recently, quercetin-3-glucoside has been studied for its effects on regulating blood glucose and modulating β-cell function *in vivo* (Day et al. 2003). The underlying mechanism of 3-glucoside located at C3 position on regulatory effect of glucose consumption in diabetic rat further convinced the fact that flavonoid glycosides (or glucuronide) could enhance the anti-diabetic activity (de Araújo et al. 2013).

Collectively, the hydroxytoluene unit successfully explained the antidiabetic activity of flavonoids on the B-ring and A-ring. In addition, a comprehensive model of free radical scavenging reaction of flavonoids was established, which could explain the contribution of hydrogen atom and the termination of aryloxy radical, which was proposed to be effective for diabetes mellitus (Mbikay et al. 2014).

Antioxidant activity

There are two types of antioxidant systems in the body, the one is the enzyme antioxidant system including SOD, CAT, GST; the other is a non-enzymatic antioxidant system, for example, GSH. The NRF2/KEAP1 signaling plays an important role in maintenance intracellular redox homeostasis, and plays a vital role in a variety of cell types and organs in oxidative damage-related cardiac diseases, including myocardial ischemic disease, cardiac hypertrophy and diabetic cardiomyopathy. Up to date, numerous publications have attributed abroad function of flavonoids related to their antioxidant activities, and most were reported as free radical scavenging mechanisms (Lee, Koo, and Min 2004; Nemzer et al. 2019). However, these results are often ambiguous and incomparable based on different oxidant types or analytical methods. In general, the mechanism of antioxidant activity is scavenging free radicals and chelating activity of transition metal ions. With the delocalization of phenoxyradicals, flavonoids could provide hydrogen and therefore to prevent ROS from damaging many diseases (Piao et al. 2008). In addition, under abnormal conditions, flavonoids can chelate transition metals and promote the formation of hydroxyl radicals through Fenton reaction (Poprac et al. 2017).

On the basis of the results given by Rasulev and coworkers in 2005 and Zhang, Sun, and Wang (2003), as well as recent publications (Mahfoudi et al. 2017; Soumya et al. 2019), it seems that the strongest inhibitory effect on lipid peroxidation are the structures with hydroxyl ord prenyl-group groups located at C3' and 4'-substitution, or the hydroxyl group at the C-3 position of flavonoids (Ahmed et al. 2018). It also should be noticed that, the lack of

hydroxy group on the B-ring gives a lower degree of stability on the flavonoid, due to the absence of electron delocalization and becomes a critical characteristic for the antioxidant activity (Nemzer et al. 2019). In this case, flavanones related to the favorable 3′, 4′-substitution pattern (hydroxyl and/or prenyl) on the B-ring demonstrated to have high antioxidant activities (Karas, Ulrichová, and Valentová 2017). The highest inhibitory effect of flavonoids on peroxidation of lipids presence the C-3 hydroxyl ord the 3′, 4′-dihydroxy occupied B-ring (Smith et al. 2019). Those obtained results are clear evidences of basic structural elements for available antioxidant activity of flavonoids.

Absorption

The absorption fate of the flavonoids has been investigated over the years. Although many results have been obtained, the accurate evidence is far from solved. It has been proposed that the highly polar flavonoids have to be hydrolyzed into aglycones by microorganisms or enzymes in the intestine, but not be absorbed directly after oral administration (Manach and Donovan 2004; Chen et al. 2021). Based on emerging evidence, researchers believed that flavonoid glycosides should be deglycosylated by enterobacteria and then be absorbed at large intestine, while small intestine is the effective absorption site for glycoside binding structures (Murota and Terao 2003; Teng and Chen 2019; Choi, Bae, and Lee 2017). This is due to the glycolysis activity of intestinal cells, and the glucose transport system can participate in the absorption of glycosides (Tang et al. 2016). Glycosides might be absorbed through sodium dependent glucose transporter 1 which located in the small intestine (Williamson and Clifford 2017). Several publications focus on the absorption and bioavailability of flavonoids has been illustrated (Chen et al. 2019). For example, hesperidin, which mainly found as hesperetin-7-*O*-rhamnoglucoside and rutinoside in citrus fruits, cannot pass through the small intestine epithelium and be absorbed by direct jejunal perfusion (Lascala et al. 2018). The consistency of findings of oral absorption of hesperidin, the combination of its sulfate and glucuronic acid were found in plasma, and Tmax was 4–6 h (Rothwell et al. 2016). On the other hand, when in the form of oral administration of hesperetin-7-*O*-glucoside, the same conjugates were present in plasma, but C_{max} was higher and T_{max} was much shorter, indicating intestinal absorption of hesperetin-7-*O*-glucoside (Lee et al. 2017). In fact, intact hesperidin cannot be absorbed passively, however, hesperetin lack of the two sugars, could be readily absorbed (Najmanová et al. 2019).

The pharmacokinetic curve of tea catechins indicated that these flavonoids do not need prior decompose by intestinal microbiota and could be directly absorbed in the small intestine (Borges et al. 2018). After dietary intake ECG, the 3′-O-glucuronide conjugate was found as the most abundant metabolite in plasma (Oya et al. 2017). Although different researchers have investigated in different experimental way and obtained various results, the predominant epicatechin metabolites in humans after oral consumption were basically unified as GC, ECG, and EGCG (Miklasińska et al. 2016; Kruger, Stuetz, and Frank 2019; Gomes et al. 2018). Matsuzaki et al. further proved that a considerable portion of epicatechin was not absorbed by the small intestine and reached the colonic flora, then converted into low molecular weight compounds (Matsuzaki et al. 2017).

Absorption and metabolism of flavonoids in stomach

It is well known that most phytochemicals are rarely absorbed in the stomach; few drugs with weak acid can be absorbed through the gastric mucosa (Schulz, Schütte, and Malfertheiner 2016). Due to the relatively small area of gastric mucosa, the amount of absorption is limited. At present, it has been found that a few flavonoids can be absorbed into the human body through the stomach, such as quercetin, genistein and daidzein (Takahama, Yamauchi, and Hirota 2016). The results obtained by Yang and coworkers showed that only 38% of quercetin disappeared after administration of quercetin, isoquercetin and rutin by gavage in rats, indicating that quercetin but not its glycoside could be absorbed by stomach (Yang et al. 2018). In addition, some anthocyanins can be absorbed rapidly in the stomach, which may be related to the bile transferase, but the absorption mechanism has not been clearly explained (Han et al. 2019).

Absorption and metabolism of flavonoids in small intestine

Flavonoid aglycone has a large hydrophobicity and a small molecular structure, which makes it directly absorbed by villous epithelial cells on the wall of small intestine through passive diffusion (Babadi et al. 2020). In fact, acid medium is favorable for flavonoids to pass through Caco-2 cell model (Wang et al. 2016). In the Caco-2 cell model, the most important factor for quercetin absorption is the pH value, but the change of pH value has little effect on genistein, apigenin and daidzein. Further study showed that the absorption of quercetin (5-hydroxy), luteolin (4-hydroxy), apigenin (3-hydroxy), genistein (3-hydroxy) and daidzein (2-hydroxy) decreased in turn when the pH value changed to be 5.5 (Tasdemir et al. 2006). It can be concluded that the number of hydroxyl groups located in the structure of flavonoid aglycone and the position of B-ring conjugation significantly affect the absorption of aglycone.

At present, there exist two main approaches on the absorption mechanism of flavonoid glycosides in the small intestine. One is that flavonoid glycosides can be hydrolyzed to aglycones by lactase phlorizin hydrolase (LPH), which exists in the margin of small intestine of mammals (Day et al. 2003) The absorption of flavonoid glycosides might be significantly influenced by LPH, for example, quercetin-β-glucoside and genistein-7-β-glucoside could be isolated from the intestinal LPH of experimental rat (Naim et al. 1991). Another approach is that flavonoid glycosides could be transported through Na^+ depdendent SGLT1 pathway across cell membrane to intestinal epithelial cells (Kottra and Daniel 2007). In addition, flavonoid glycosides could be

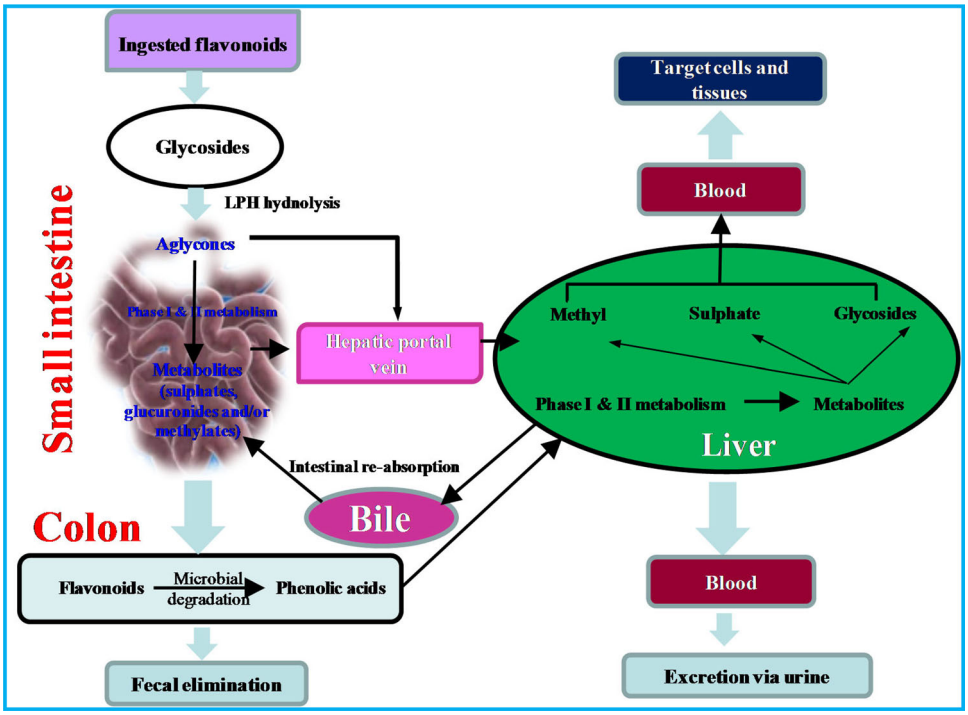

Figure 4. Proposed digestion, absorption, and bioavailibities of diatery flavonoids.

directly hydrolyzed into aglycones by β-glucosidase, then transported to intestinal epithelial cells through SGLT1, and finally entered into the circulatory system in the form of aglycones or conjugates. (Wolffram, Block, and Ader 2002). However, a drug delivery pump may also affect SGLT1 mediated absorption. Further studies showed that quercetin-4′-β-glucoside could not be absorbed through the Caco-2 monolayer cell model due to the "pump effect" of MRP2 (Alvarez et al. 2010). So far, only quercetin-glucosides can be transported by SGLT1 (Alvarez et al. 2010).

Taken together, both of the intestinal absorption mechanism revealed that flavonoid glycosides enter the body should be hydrolyzed into aglycones, rather than in the form of its prototype, except for rutin which can be absorbed in the small intestine of rats in the form of its glycosides (Carbonaro and Grant 2005). Furthermore, the absorption difference of flavonoids in the small intestine mainly depends on the type, number and position of glycosyl (Fig. 4). Firstly, the different types of glycosyl linked to flavonoid are critical factors affecting the absorption. After taking quercetin-4′-β-glucoside and quercetin-3-β-glucoside in the same dose, the maximum blood concentration of them were similar (Steffansen 2016), while quercetin-3-β-galactoside, 3-β-rhamnoside and 3-α-arabinoside could be absorbed poorly by rat intestine (Morand et al. 2000). Secondly, the different glycosylation may be another important factor influence the absorption of flavonoid glycosides in the small intestine. Flavonoid aglycones are more easily absorbed than flavonoid glycoside. For instance, quercetin-3-O-β-D-glucoside, quercetin-4′-O-β-D-glucoside, quercetin-3, 4′-O-β-D-glucoside and other glucosides could not penetrate the monolayer membrane (Kawabata, Mukai, and Ishisaka 2015). Fang et al. (2018) showed that the absorption of luteolin glycoside was significantly higher than that of luteolin, and the combination of baicalin and luteolin was significantly lower than that of luteolin, indicating that the amount of conjugated sugar affects its absorption, and the type of conjugated sugar affects the absorption of flavonoid glycosides (Fang et al. 2018).

Development of flavonoid-based nanoparticles

As shown in Table 1, recently, nanotechnologies are developed rapidly in the food and pharmaceutical industry. One of the main applications is nano encapsulation of bioactive compounds in addition to its biological activity protection and bioavailability (Ezhilarasi et al. 2013; Shishir et al. 2018; Wen et al. 2017).

Liposome

Liposomes consist of a single or multiple layered spherical structures composed of phospholipids. According to the amphiphilicity of phospholipid molecules, the hydrophobic area in the bimolecular layer can be used to load non-polar substances. Meanwhile, the phospholipid bilayer of liposome is easy to be absorbed by tissues and could be used to improve the biological accessibility and absorption of nutrients (Rezaei, Fathi, and Jafari 2019). Dammak, Lourenço, and do Amaral Sobral (2019) reported that liposome prepared by thin-layer evaporation was used to load hesperidin, which kept hesperidin stable in plasma for a long time without degradation, and had better drug release characteristics (Dammak, Lourenço, and do Amaral Sobral 2019). The antiproliferative activity of hesperidin liposome complex in H441 and MDA-MB-231 cells was significantly higher than that of hesperidin or liposome alone, which may be due to the better fusion of lipid with cell membrane,

Table 1. Nano-formulation of flavonoids reviewed in present study.

	Substitutions				
Name	OH	OCH3	Others	Nano-formulation for major purpose	References
Apigenin	5,7,4′			Anticancer Tissue damage↓ ROS↑, Bax↑, Bcl-2↓, Cyt C↓, cleaved caspase-9 and 3↑, stability↑	Das et al. 2013; Abcha et al. 2019
Chrysin	5,7			Anticancer FTO↑, BRCA1↑, hTERT↑, solubility↑	Eatemadi et al. 2016
Hispidulin	5,7,4′	6		NC	
Wogonin	5,7	8		Anticancer PI3K/AKT/mTOR pathway↓	Sabra et al. 2018
Wogonoside	5	8	7-O-glucuronide	NC	
Baicalein	5,6,7			Anticancer ROS↑, Bax↑, Bcl-2↓, cleaved caspase-9 and 3↑	Kavithaa et al. 2016
Baicalin	5,6		7-O-β-D-glucuronide	Anti-inflammation IL-1β↓, IL-6↓, IL-8↓	Li et al. 2017
Luteolin	5,7,3′,4′			Anticancer Growth of H292↓, SCCHN↓ Tu212↓.	Majumdar et al. 2014
Luteolin-7-O-glucoside	5,3′,4′		7-O-glucoside	NC	
Tangeretin		5,6,7,8,4′		Regulation of cell apoptosis Matrix metalloproteinase (MMP)2↓, MMP9↓, markers of metastasis↓, vascular endothelial growth factor (VEGF) ↓	Roshini et al. 2018
Nobiletin		5,6,7,8, 4′,5′		Anti-inflammation TNF-α↓, IL-1β↓, IL-6↓, PGE2↓, iNOS↓, COX-2↓, NF-κB↓, JNK↓, ERK↓, P38↓	Liao et al. 2018
Galangin	3,5,7			Regulation of cell apoptosis AKT↓, ROS↓, p38↓, caspase-3↓, mitochondrial membrane potential↓	Li, Jin, et al. 2018
Kaempferide	3,5,7	4′		NC	
Kaempferol	3,5,7,4′			Anti-osteoporosis Bone marrow↑ osteoprogenitor cells, osteogenic genes in femur↑, bone formation rate↑, and trabecular micro-architecture stimulatory effect↑	Kumar et al. 2012
Quercetin	3,5,7,3′,4′			Antioxidant↑, anticancer↑, anti-inflammation↑	Rasaie et al. 2014; Chakraborty et al. 2012; Minaei et al. 2016
Quercitrin	5,7,3′,4′		3-O-β-D-glucoside	Osseointegration↑, MMP1↓, TIMP1↓ mRNA↓, COX2↓, PGE2 ↓	Gomez-Florit et al. 2016
Myricetin	3,5,7,3′,4′,5′			Antioxidant DPPH↑, oral bioavailability↑	Chakraborty, Basu, and Basak 2014
Myricetrin	5,7,3′,4′,5′		3-O-rhamnoside	Hepatic concentration↑	Wei et al. 2019
Rutin	5,7,3′,4′		3-α-L-rham-1,6-D-Glc	Anti-hepatocellular carcinoma and antioxidant hepatic nodules↓, necrosis formation, infiltration of inflammatory cells↓, blood vessel inflammation↓, cell swelling↓	Ravi et al. 2018; Pandey et al. 2018
Formononetin	7	4′		Anticancer tumor inhibition rate↑	Liu et al. 2018; Cheng et al. 2016
Genistein	5,7,4′			Anticancer cell proliferation↓ apoptosis↑, caspases-3↑, 7↑, and 8↑, cytosolic cytochrome c↑, caspases-9↑	Si et al. 2010; Pham, Grundmann, and Elbayoumi 2015
Daidzein	7,4′			NC	
Daidzin	4′		7-glucoside	Bioavailability↑	Zou and Gu 2013
Genistin	5,4′		7-glucoside	NC	
Biochanin A	5,7	4′		Anticancer cytotoxicity↑	
Puerarin	7,4′		8-C-glucoside	Anti-inflammation IL-10↓, TNFα↓, NFκB↓,	Singh et al. 2013
Sophoricoside	5,7		4′-O-glucoside	NC	
Tectorigenin	5,7,4′	6		NC	
Naringenin	5,7, 4′			Anticancer and antidiabetic P-gp efflux inhibition↑, anti-proliferative activity↑, apoptosis↑, dyslipidemia↓, hyperglycemia↓	Sandhu et al. 2017; Raeisi et al. 2019; Maity et al. 2017
Naringin	5,4′		7-neohesperidose	NC	
Hesperidin	5,7, 3′	4′		Anti-bacteria and anti-arthritic TLRs mRNA↓, paw thickness↓, bone damage↓, tissue degeneration and bone erosion↓, cellular infiltration and granulamatous inflammation↓	Rao et al. 2018; Sahu et al. 2016
Hesperitin	5,3′	4′	7-α-L-rham-1,6-D-glc	Anticancer cytotoxicity↑, apoptosis-inducing activities↑, better cancer targeting and accumulation↑	Zhen et al. 2017
Dihydromyricetin	3,5,7,3′,4′,5′			Antidiabetic AMPK↑, AKT↑, ERK↓, JNK↓	Chen et al. 2019
Gallocatechin gallate	5,7,3′,4′,5′		3-gallate		

(*continued*)

Table 1. Continued.

Name	Substitutions			Nano-formulation for major purpose	References
	OH	OCH3	Others		
				Antioxidant, antidiabetic, anticancer, anti-aging, skin permeation↑, Wound healing ↑, immunoreactivity of Ki-67↑, CD31↑, α-smooth muscle actin↑	Kim et al. 2008; Avadhani et al. 2017; Siddiqui et al. 2009
Epigallocatechin gallate	5,7,3′,4′,5′		3-gallate	Antidiabetic Wound healing ↑, immunoreactivity of Ki-67↑, CD31↑, α-smooth muscle actin↑	Kim et al. 2008
Epicatechin gallate	5,7,4′,5′		3-gallate	Antioxidant	Wang, Li, et al. 2018
Epigallocatechin	3,5,7,3′,4′,5′			Antiinflammation Inflammatory↑ response in human dermal fibroblasts↑.	Wu et al. 2017
Epicatechin	3,5,7,4′,5′			NC	
Catechin	3,5,7,4′,5′			Antioxidant, antidiabetic, anticancer, anti-aging	Ahmad et al. 2019

making the inclusion complex more easily absorbed by cells (Wei, Keck, and Müller 2017; Pisoschi et al. 2018). Pleguezuelos-Villa et al. (2018) prepared liposomes by film hydration dispersion and loaded naringin with a loading rate of 72.2% showed that the release rate of naringin liposome complex was significantly higher than that of free naringin. Furthermore, the liposome delivery system could improve oral bioavailability of naringin by about 13.44% (Pleguezuelos-Villa et al. 2018). In short, liposome delivery system might be an excellent method to improve the solubility and bioavailability of naringin.

Emulsion

The emulsion delivery systems, which mainly include water/oil (W/O), oil/water (O/W), oil/water/oil (O/W/O), water/oil/water (W/O/W) in modern food industry, always used to protect the active ingredients, prevent degradation, improve solubility, as well as improve the oral bioavailability of bioactive compounds (Luo et al. 2012; Macedo et al. 2014; Cefali et al. 2019). For example, Akhtar et al. (2014) used the emulsion delivery system to prepare flavonoids fractions, and found the anti-proliferative activity in cancer cell lines was significantly improved (Akhtar et al. 2014). By constructing cancer mice model, the emulsion delivery system containing baicalein can effectively enhance the effect against colon cancer (Kulbacka et al. 2016). Both *in vitro* and *in vivo* experiments confirmed that the emulsion delivery system was an effective option to improve oral bioavailability of flavonoids (Stelinski, Lapointe, and Meyer 2010; Ting et al. 2015). Similarly, Silva et al. (2018) prepared quercetin and gallic acid nanoemulsion by high pressure emulsification technology, which greatly improved the solubility of quercetin in water and effectively prevented its degradations (Silva et al. 2018). In this line, emulsions have been promisingly applied in the control of bioavailability and functionality of flavonoids and have obtained many achievements. However, the applications of emulsions to the control release of flavonoids are still in the preliminary stages, unknown health outcome of nanomaterials may limit their wide applications in food security.

Nano encapsulation

Nano encapsulation is to encapsulate materials into vesicles or wall materials with nano (or submicron) size. Nano encapsulation protects functional compounds and elements, such as selenium, antioxidants, and vitamins, as well as nutrients, and enhances the functionality and stability of functional foods. As a new delivery system, polymer nanomicelles can be used for encapsulation of phenols with poor water solubility and amphiphilicity. They have a copolymer diblock structure of hydrophilic shell and hydrophobic core. Encapsulated quercetin with poly (lactide) (PLA), the particle size was 130 nm, which enhanced the solubility and stability of quercetin.

Nanoformulation to enhance bioactivity

As shown in Table 1, nanoformulation containing flavonoids have been used in food industry with high encapsulation efficiency and prolong systemic circulation in animal models (Sabra et al. 2018). For example, baicalein loaded protein nanoparticles exhibited significant effect on up-regulation of pro-apoptotic proteins and down-regulation of the anti-apoptotic Bcl-2 proteins, which evidenced by Kavithaa et al. (2016).Nano particles of baicalin could more effectively down-regulate the IL-1β-induced expression of IL-6 and IL-8 in human gingival epithelial cells (Li et al. 2017). Another comparative study carried out by Majumdar et al. (2014) revealed that nano-protein particles of luteolin exhibited strong inhibitory effect on the proliferation of lung cell lines (Majumdar et al. 2014). Interestingly, nanoparticles of pH sensitive quantum dots of tangeretin exerted stronger apoptotic effects than free tangeretin in metastatic lung cancer (Roshini et al. 2018). Study on Chen et al. (2014) suggested protein-based nanoparticles could also be used to encapsulate tangeretin to increase stability under simulated gastrointestinal conditions.

Recently, a useful nanoemulsions was developed by Liao et al. (2018) to enhance the anti-inflammatory activity of nobiletin in LPS-induced RAW264.7 cells with a decrease in expression of pro-inflammatory cytokines and mediators (Liao et al. 2018). Moreover, in order to overcome the

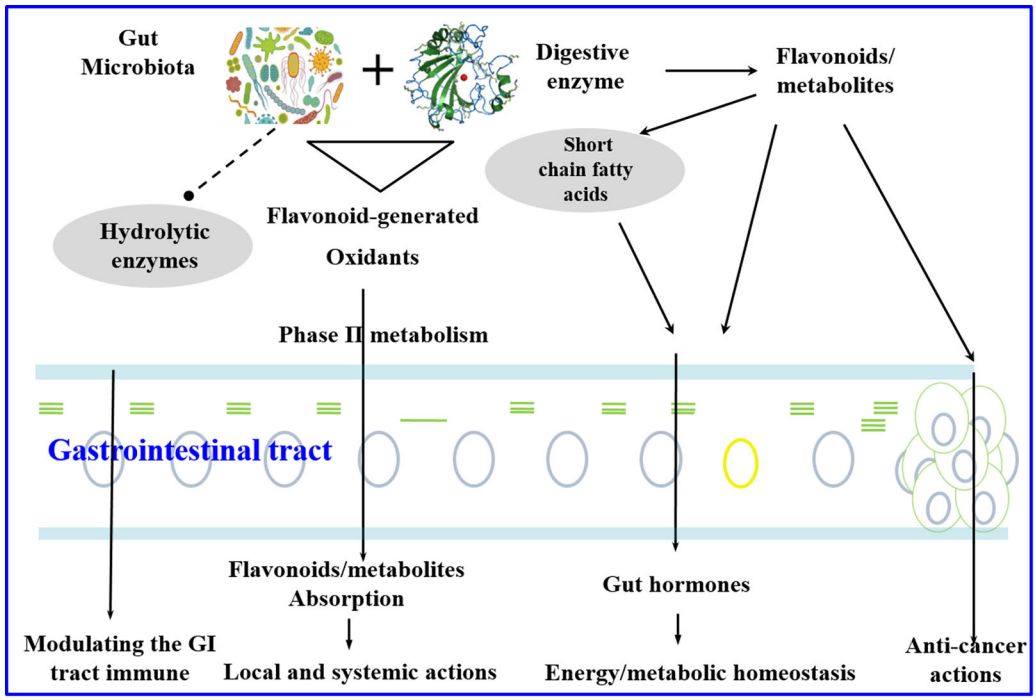

Figure 5. Effect of gut microbiota on metabolism of diatery flavonoids. Adapted from (Oteiza et al., 2018).

obstacles of galangin (insolubility in water), Patil et al. (2019) conducted galactosylated pluronic F68 polymeric micelles of galangin and found nanoformulation could significant improve in the amount of in liver (about 2.6 folds as compared to free galangin) (Patil et al. 2019). On the other hand, to improve the anti-cancer activity of galangin, Li and coauthors developed an aqueous nanoparticle to embed it and found the caspase-3 activity of HepG2 was significantly enhanced (Li, Jin, et al. 2018). In addition, the developed layer-by-layer nano-matrix could also enhance anabolic effect of kaempferol *in vivo* through increased stimulatory effect in osteoblasts (Kumar et al. 2012). Alternative quercetin formulation strategies like liposomes, nanocapsules and microsphere have been developed to improve the therapeutic efficacy including antioxidant, anticancer and anti-inflammatory effects (Rasaie et al. 2014; Chakraborty et al. 2012; Minaei et al. 2016). Among different strategies, nanocapsules can protect flavonoid from gut microbiota on metabolism (Fig. 5). Moreover, Gomez-Florit et al. (2016) reported that nanocoated quercitrin decreased initial bacterial adhesion while increased human gingival fibroblasts attachment. Furthermore, quercitrin-nanocoated particles increased collagen mRNA levels and decreased matrix metalloproteinase-1/tissue inhibitor of metalloproteinanse-1 mRNA ratio, which under basal and inflammatory conditions (Gomez-Florit et al. 2016). Another publication investigated the bioavailability of vitamin Ed-α-tocopheryl polyethylene glycol 1000 succinate (TPGS)-loaded myricetrin micelles, the results showed that myricetrin-loaded-micelles accumulated well in the liver tissue, indicating a promising carrier for liver targeting with improved hepatic concentration of myricetrin (Wei et al. 2019). Preclinical evaluation of anticancer effect of rutin-poly (lactic co-glycolic acid-nanoparticles) through oral route exhibited significant improvement in live protection. Similarly, formononetin-TPGS micelles significantly improved anti-proliferatory effect on cancer cell lines compared to that observed with free formononetin in tumor-bearing mice (Cheng et al. 2016).

For isoflavones, the effects of free genistein and Fe3O4-genistein nano-conjugate on the proliferation and apoptosis of gastric cancer cell line SGC-7901 were investigated by Si et al. (2010), the results indicating that nano-conjugate system is a promising for isoflavones in magnetic hyperthermia therapy (Si et al. 2010). In addition, genistein-nanoparticles treatments ultimately lead to distinct activation of intrinsic apoptotic pathway markers. Nevertheless, zein nanoparticles have been recently reported to encapsulate daidzin, an isoflavone glycoside, and improved the oral bioavailability of daidzin (Zou and Gu 2013).

A self-nano-emulsifying drug delivery system was also employed to enhance bioavailability of naringenin in female Wistar rats (Sandhu et al. 2017; Raeisi et al. 2019). Other studies further proved that polymeric formulations are quite effective for oral delivery of the naringenin as a therapeutic agent in the treatment of diabetes (Raeisi et al. 2019; Maity et al. 2017). Considering the anti-arthritic effect of hesperidin; Rao and coauthors developed an AgNPs formulation for the better therapeutic activity of hesperidin. It was also observed that AgNPs- hesperidin showed significant reduction in paw thickness along with minimal arthritic score, decreased bone damage, tissue degeneration and bone erosion(Rao et al. 2018). Nano- and micro-particle systems have been used wildly to stabilize tea catechins including gallocatechin gallate, epigallocatechin gallate, epicatechin gallate, epicatechin gallate, epicatechin gallate, epigallocatechin, and epicatechin, when exposed to adverse environments and to improve their bioactivities such as

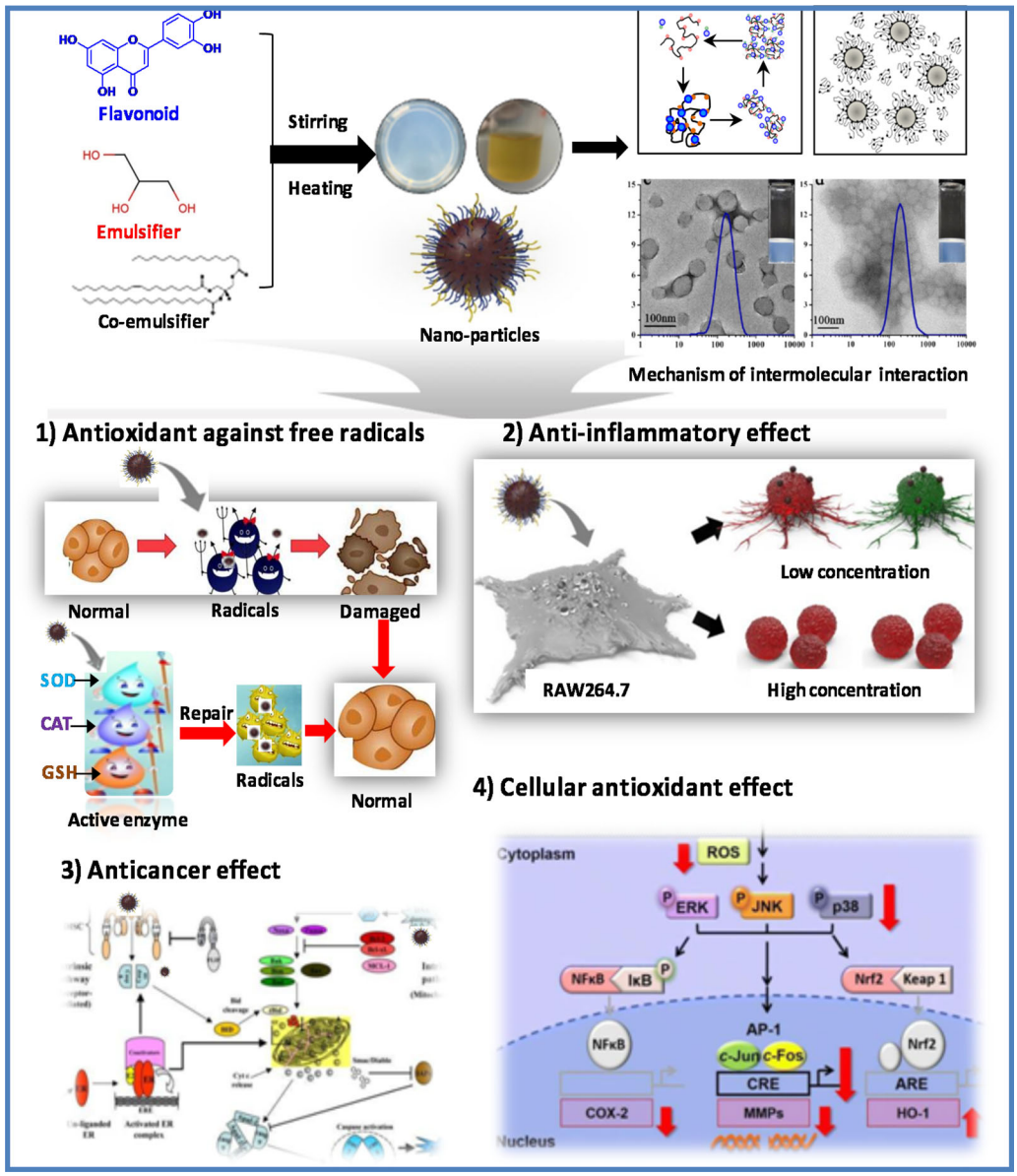

Figure 6. Proposed flavonoid-grafted nanoformulation for enhanced bioactivities.

antioxidant, antiidabetic, anti-aging, anti-inflammatory effects etc upon ingestion (Kim et al. 2008; Avadhani et al. 2017; Siddiqui et al. 2009; Wang, Li, et al. 2018). Bioactive properties were retained at higher level in encapsulated catechin compared to free catechin (Ahmad et al. 2019).

Prospect of nanoformulation for the delivery of flavonoids

As shown in Figure 6, at present, nano embedding technology has shown a broad application prospect in the field of food and medicine. Usually, nano particles can be used to embed nutrients, bioactive substances, drugs and so on. In the field of food, many nutrients and bioactive substances are hydrophobic, which limits their application in food industry. When these active substances are embedded in nanoparticles, not only the solubility could be significantly improved, but also the storage stability and slow-release effect can be ensured. Some studies have shown that the nanoparticles formed by embedding nutrients with lipid materials have slow-release function, and their retention time *in vivo* is prolonged by multiple times, and they are not easy to be destroyed by various intestinal biological factors. Moreover, the particle size of the composite particles is small, which is conducive to the absorption of human body, and the bioavailability can be increased by few times. In the field of medicine, the traditional technology of drug delivery cannot achieve the goals of high efficiency, stability and targeting. Using nanoparticles as drug delivery carrier is conducive to improve the stability of drugs, prolonging the time of drug action, and therefore enhances drug efficacy and reducing adverse reactions]. The application of embedded drug nanoparticles has become a research hotspot. Nanoparticles can carry drugs to break through the cell barrier by loading drugs, combining with drugs or indirect

reactions, and even can break through the complete epidermis to deliver large hydrophilic drugs. Moreover, nanoproducts are not labeled as such, and consumers who wish to avoid these food products are not being given this option. Thus, mandatory testing of nano-modified product is desirable before they are allowed on the market. New approaches and standardized test procedures to study the impact of nanoparticles on living cells are urgently needed for the evaluation of potential hazards relating to human exposure to nanoparticles. It is widely expected that nanotechnology-derived food products will be available increasingly to consumers worldwide in the coming years.

Conclusion and future trends

Flavonoids are active compounds synthesized by plants, however, their limited stability ord solubility, often combined with a poor bioavailability. Up to date, many formulation approaches such as absorption enhancers, structural transformation, and pharmaceutical technologies have been developed to overcome this issue of low bioavailability of flavonoids by enhancing their solubility and dissolution rate, increasing their mucosal permeation, preventing their degradation or metabolism in the gastrointestinal tract and delivering them directly to the physiological tract. However, the applications of present formulations for delivering flavonoids still suffer from the following challenges: (1) the physical instability and low drug loading is probably caused by the required abundance of pharmaceutical adjuvants and/or reaction steps and the tedious preparation methods, and (2) the undesirable side effects arise from the nonselective distribution of oral formulations and the generation of the byproducts, as well as the incomplete degradation of the carriers. With regard to this, the following several aspects should be considered in future studies to break through the barriers and consequently expedite their development. First, more efforts should be focused on modifying the existing drug delivery systems for flavonoids by exploring some convenient and safe techniques and procedures and by using some biocompatible natural materials or carriers. Second, the design of some new drug delivery systems can be triggered remotely to obtain flexible control of dose magnitude and timing by combining interdisciplinary knowledge, including polymer chemistry, materials science, biology, and pharmacy might provide feasible to further improve the oral absorption of flavonoid compounds. Third, many related studies are still kept at the lab level; in this case, translating laboratory achievements into products and then propelling the related food industry or clinical trials is highly desired. We are convinced that with rational design and continuing studies, a bright future can be foreseen for these insoluble active flavonoids for the effective treatment of various human diseases.

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