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Bioavailability enhancement of EGCG by structural modification and nano-delivery: A review

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ABSTRACT

EGCG is an important bioactive component of green tea, which has the biological functions of antioxidant and antitumor. However, the stability of EGCG is poor, the absorption rate is low, and the bioavailability needs to be improved. In this study, the factors influencing the bioavailability of oral EGCG and the commonly used methods to improve its bioavailability were reviewed. The results showed that oral EGCG was not stable in intestinal and blood environment, most of EGCG was not absorbed, and its bioavailability was reduced. However, the bioavailability of oral EGCG could be significantly improved by modifying the structure of EGCG or the protection and delivery through nano-materials. It provided a reference for further research and development of tea polyphenol-related products.

1. Introduction

Green tea is a widely used traditional health drink, which contains a variety of nutrients and functional components, including tea polyphenols (Pasrija & Anandharamakrishnan, 2015). Flavonoids-3-alcohols is commonly known as catechins in green tea. Epigallocatechin gallate (EGCG) is the main ester catechins, accounting for about 40% of the catechins in green tea (Sharangi, 2009). The biological activity of EGCG comes from a large number of active phenolic hydroxyl groups with molecular structure, which are widely used in food industry. Especially in recent years, some studies have confirmed that EGCG has good health care effects, including antioxidant (Kim et al., 2018; Wolfe & Liu, 2007) and antitumor (Huang et al., 2017; Khan & Mukhtar, 2013). Many studies had confirmed that the bioavailability of EGCG was related to its stability. Poor stability was an important reason for the low utilization rate (Cao, Teng, & Selbo, 2017; Zhang & Zhang, 2018).

This paper reviewed the absorption, distribution and metabolism of oral EGCG in vivo, and introduced the methods to improve the bioavailability of oral EGCG by molecular structure modification and nanometer delivery technology. In addition, the challenges of oral administration of EGCG were discussed.

2. Main factors influencing the bioavailability of oral EGCG

The bioavailability of oral EGCG was relatively poor. Oral EGCG is usually absorbed into the blood through the gastrointestinal tract to play its biological role. It has been reported that the highest plasma concentration of EGCG was only 0.15 μM after two cups of green tea were taken into human body (Jia, Shufang, & Shu, 2013). The main factors limiting the intestinal absorption of oral EGCG were as follows: (1) the stability of the intestinal environment of EGCG was poor (Wang, Taylor, Wang, Wan, & Zhang, 2012), (2) the intestinal absorption was low (Smith, Giunta BBickford, Fountain, Tan, & Shytle, 2010).

2.1. Poor intestinal stability

Although EGCG has good biological activity, the effect of improving its oral utilization rate is not ideal. Some results had shown that EGCG is prone to oxidative decomposition under high temperature, neutral or weak alkali conditions, and the degradation rate accelerates with the increase of ambient temperature and oxidation concentration (Dube, Ng, Nicolazzo, & Larson, 2010). In addition, intestinal pH may be one of the important factors affecting the stability of oral EGCG. In particular, catechins in green tea are very unstable in the digestion of saliva,

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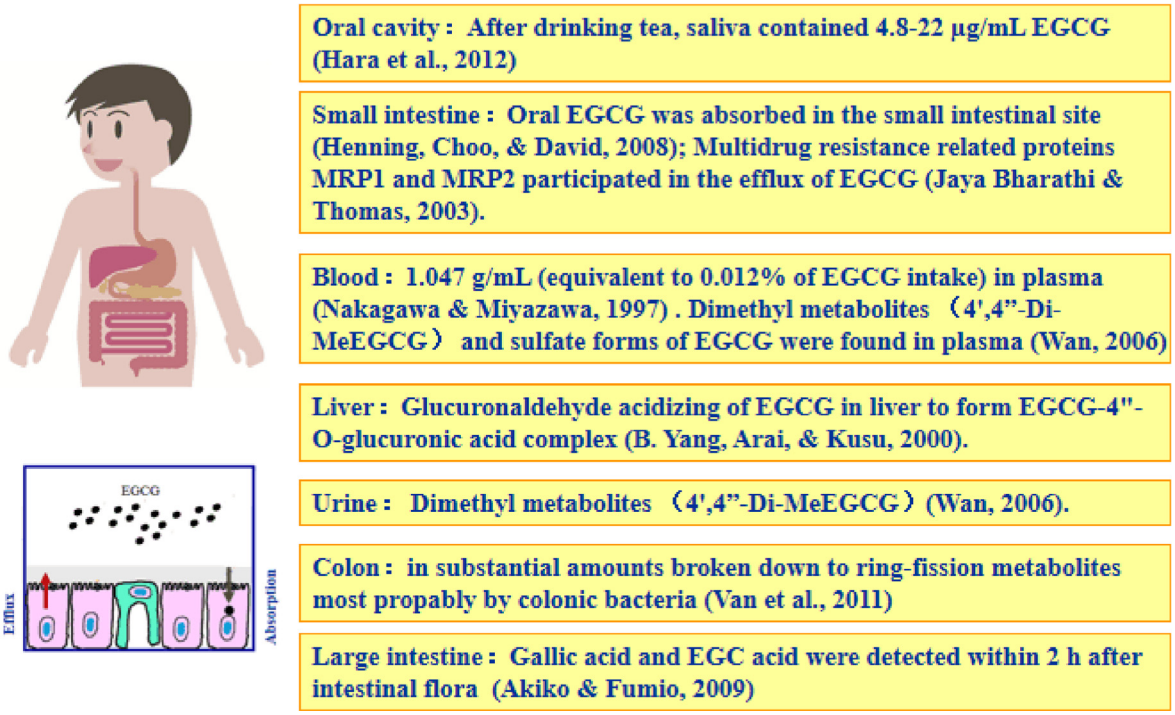

Fig. 1. Distribution and metabolism of Oral EGCG.

stomach and upper intestine. Zou et al. (2014) reported that the total recovery rate of catechin was very low (5.3%), EGCG decreased significantly, and the recovery rate of digestive tract was 6.1%. Under the condition of simulated gastric juice for 3 h, the residual amount of EGCG solution reached 92.2%. In the process of simulating intestinal fluid, the residual amount of EGCG decreased by 50% in 0.5 h, but only 3.4% in 1.5 h. After two hours, EGCG content was not detected. In particular, EGCG is unstable and easy to decompose under intestinal pH condition. It has been reported that the retention rate of free EGCG in simulated intestinal pH digestion is less than 10% (Zagury, Kazir, & Livney, 2019). Some related studies showed that 49.03% of free EGCG was retained after digestion at simulated gastric pH, while 20% of free EGCG was retained after digestion at simulated intestinal pH. In addition, the effect of intestinal microorganisms on the stability of EGCG was also crucial. The results have shown that intestinal microflora could dissociate and degrade EGCG in vitro and in vivo. For example, in the pig cecum model, EGCG was almost completely metabolized in the pig intestinal microorganism within 4–8 h (Gordon & Hans-Ulrich, 2009). Another study reported that after 4 h of oral isotope-labeled EGCG, the radioactivity in the blood and most tissues of rats remained at a low level, increased after 8 h, and reached the highest level within 24 h (Kohri et al., 2001). In particular, EGCG was hydrolyzed into EGC and gallic acid by intestinal microorganisms. It was suggested that EGCG underwent intestinal microbial metabolism before absorption (Akiko & Fumio, 2009). Therefore, the chemical instability of EGCG would reduce intestinal absorption and affect its bioavailability.

2.2. Low intestinal absorption

Oral bioavailability is also related to intestinal absorption efficiency. The retention time and permeability of intestinal EGCG affect the absorption of EGCG (Shengmin, Mao-Jung, Zhe, Chi-Tang, & Yang, 2005). The poor permeability was due to the poor intestinal transport caused by passive diffusion and active outflow. No specific receptors carrying EGCG into cells were found on the surface of intestinal epithelial cells. Therefore, the transmission mechanism of EGCG through epithelial cells was mainly passive diffusion, including acellular and transcellular diffusion. After absorption, most of the EGCG was pumped back into the cavity through an active jet. A large number of studies had shown that there were some efflux proteins in the process of ingestion of EGCG by Caco-2 cells, which could excrete EGCG from cells and reduce the absorption of EGCG in cells (Chan & Zhang, 2010). For the way EGCG entering Caco-2 cells through mouth, many results indicated that EGCG has efflux effect and the expression of related efflux proteins was enhanced (Gordon & Hans-Ulrich, 2009; Zagury et al., 2019). It was clear that MRP1 and MRP2 were involved in the efflux of EGCG (Jaya Bharathi & Thomas, 2003).

2.3. Blood-brain barrier permeability

Blood-brain barrier (BBB) is a kind of selective diffusion barrier, which can restrict some substances in the blood to enter the brain tissue and maintain a relatively constant internal environment. After oral administration, EGCG was metabolized into GA and EGC in the small intestinal microbial environment, while the resulting EGC further divides into EGC-M5 in the large intestine environment. Unno et al. (2017) reported the results of BBB permeability of EGCG within 0.5 h. Compared with smaller molecular size GA (MW170.12), the BBB permeability of the molecular size EGCG (MW458.372), EGC (MW306.27) and EGC-M5 (MW208.07) were decreased by 57.54%, 47.35% and 43.31%, respectively. The results showed that the molecular weight of EGCG and its metabolites was smaller and its permeability was higher. In addition, the BBB permeability of EGCG may also be affected by hydrophobicity (Pervin et al., 2017); The less polar molecules were, the greater their absorption of brain tissue was Figueira et al. (2017), Squillaro et al. (2018). Therefore, the structural modification of EGCG could not only improve the stability of EGCG in gastrointestinal tract, but also affect its absorption.

2.4. Distribution and metabolism of oral EGCG

Oral EGCG entered the intestine through the stomach. Part of the EGCG that entered the intestine was absorbed into the blood and then transported to other organs or parts. Therefore, only part of EGCG could

play its biological function. Most EGCG entered the excretion system through bile and then was excreted. Most of the EGCG was not absorbed by the intestine, entered the large intestine and was excreted by feces. From oral administration to excretion, only a few EGCG have biological effects, as shown in Fig. 1. Some studies had shown that EGCG containing 4.8–22 g/mL was detected in saliva after drinking tea (Hara et al., 2012). EGCG could be absorbed by the small intestine (Henning, Choo, & David, 2008), and transformed into hepatic and intestinal cells. It was mainly caused by methylation, sulfation and glucuronic acid metabolites induced by metabolic enzyme II (Sang, Lambert, Ho, & Yang, 2011). Methylation of EGCG was catalyzed by catechol-O-methyltransferase (COMT) (Chen et al., 2005; Sang et al., 2011). In particular, EGCG was methylated by COMT to form 4′-O-methyl-EGCG, 4″-Omethyl-EGCG and 4′-4″-di-O-methyl-EGCG metabolites (Chen et al., 2005). EGCG was also shown to inhibit COMT activity in vitro (Lu & Meng, 2003; Nagai, Conney, & Zhu, 2004). However, a recent study of healthy volunteers taking a single dose (750 mg) of EGCG after one night fasting demonstrated that COMT activity measured in erythrocytes was not inhibited (Lorenz et al., 2014). Takagaki et al. (Akiko & Fumio, 2009) reported that EGCG was hydrolyzed into EGC and gallic acid by intestinal microorganisms. It was reported that the radioactivity of blood and most tissues was still low after 4 h of oral isotope labeled of EGCG in rats, increased after 8 h, and reached the highest level after 24 h (Kohri et al., 2001). Another study reported that the blood concentration of EGCG peaked from 1 to 2 h after ingestion, when oral EGCG was absorbed by the intestine (Law, Yao, Bi, & Lam, 2017). Nakagawa and Miyazawa (1997) reported that the highest concentration of EGCG in fasting rats and human plasma was 0.156 g/mL (equivalent to 0.32% of EGCG intake) and 1.047 g/mL (equivalent to 0.012% of EGCG intake), respectively. It was reported that EGCG was mainly in the form of sulfate in plasma samples (Lee et al., 1995). However, some studies had also confirmed the metabolic pathways of EGCG methylation, glucuronidation and sulfation in blood. Dimethyl metabolites of EGCG (4,4″-diMeEGCG) were found in plasma and urine. Especially, methylation was a major metabolic pathway. Its metabolites were 4′-O-methyl-EGCG, 4′,4′-dimethyl-EGCG-3′-glucuronate, 3′,4′- or 3′,5′-dimethyl-EGCG-4′-O-glucuronic acid (Wan, 2006). EGCG mainly existed in plasma samples in the form of sulfate. Some studies had found that only a small amount of EGCG (about 1% of the total oral dose) could enter the human circulatory system (Shpigelman, Israeli, & Livney, 2010). Some studies speculated that most of the EGCG ingested did not enter the blood, but first entered the colon from the gallbladder, and then exited the body (Cyril, William, Yukihiko, & Alan, 2008). In addition, due to the weak alkaline environment of blood, even EGCG entering the blood could not be fully utilized. EGCG acidified in liver to form EGCG-4″-O-glucuronic acid complex. EGCG may be removed from blood by the liver and secreted into the bile. EGCG passing the small intestine either unabsorbed or after enterohepatic recycling were then in substantial amounts broken down to ring-fission metabolites most probably by colonic bacteria (Lambert, Sang, & Yang, 2007; Van et al., 2011). Generally, nearly 50% of EGCG was recovered from ileal fluid, but it might not be absorbed at all. About 1% of ileal fluid was secondary conjugate, but it might be directly discharged from intestinal cells, rather than the result of intestinal-hepatic circulation. The main way to eliminate EGCG was bile excretion. The total amount of metabolites in urine was related to the maximum plasma concentration. The recovery rate of some tea catechins was 0.5–6% (Yang, Arai, & Kusu, 2000).

3. Improving oral bioavailability of EGCG by structural modification

In general, 2-phenyl-benzo-phenyl-benzene with molecular formula of $C_{22}H_{18}O_{11}$ and the structure comprises four ring cores of A, B, C and D, has important biological activity (Fig. 2 and Table 1). The biological activity of EGCG was derived from a large number of active phenolic hydroxyl groups in the molecular structure, but due to the A, B and D rings in the structure, eight phenolic hydroxyl groups were linked, so there were differences in fat solubility, low bioavailability and unstable neutral structure, which severely restricted the application and development of EGCG (Sang, Lambert, & Yang, 2010). Therefore, it was necessary to improve the oral bioavailability of EGCG by structural modification.

3.1. Methylated modification

Methylation modification refers to a series of derivatives, also known as etherification, formed by converting all or part of the eight phenolic hydroxyl groups in the benzene ring of EGCG into methyl ether. In 1982, Japanese scholar saijo isolated EGCG3″Me (Saijo, 1982). The solubility and stability of EGCG were improved after methylation. Its stability in animal blood was significantly higher than that of EGCG, and its oral absorption rate was 9-folds higher than that of EGCG. In vivo activity test showed that when hydroxyl group was replaced by more stable lipophilic methoxy group, the stability and liposolubility of derivatives were also improved, so that the bioavailability of derivatives was significantly improved, showing a strong biological activity (Forester & Lambert, 2015). Other studies had shown that EGCG3”Me has a significant inhibitory effect on angiotensin l-converting enzyme activity with high absorption rate and blood stability (Ikuko, Mari, Hirofumi, & Masanori, 2010).

3.2. Acyclization modification

Acylation modification can selectively connect with acyl groups and form ester bond on eight phenolic hydroxyl groups of EGCG molecule. The chemical acylation method is mainly to react the phenolic hydroxyl groups in catechin molecule with acylation reagents such as acyl chloride to form phenolic esters, so as to reduce its water solubility and improve its fat solubility (Wang, Zhang, Ying, Perera, & Shahidi, 2016). Catechins have high phenolic hydroxyl content and low redox potential, which lead to rapid oxidation damage and short antioxidant aging. The stability of catechins increased and the aging time prolonged when the molecules were linked to aliphatic chains. The study on the activity of a large number of long-chain fatty acid acylated EGCG derivatives showed that with the increase of fat solubility, the antioxidant activity caused by the increase of cell membrane permeability also increased. The steric hindrance effect of long-chain acyl group would affect the participation of phenolic hydroxyl groups around the reaction. Long fat chain was easy to aggregate and precipitate, leading to the decrease of fat solubility of some long chain fatty acid acylated EGCG. Song et al. (2014) used vinyl ester as acyl group, obtained EGCG acylation products to increase its lipid solubility by enzymatic molecular modification. The acylation sites and the final product structures were determined by purification and structural characterization. The lipid solubility and antioxidant activity of acylated products were evaluated. The results showed that the antioxidant activity of acetylated EGCG in oil was higher than that of unmodified EGCG. Wai Har et al. (2004) used acetic anhydride to synthesize acetylated EGCG. Because of the protection of phenolic hydroxyl groups by acyl groups, the stability of totally acetylated EGCG was 6 folds higher than that of EGCG. The acetylated EGCG was gradually hydrolyzed into diester and monoester by esterase in biological cells, which made the activity of inhibiting proteasome and inducing apoptosis of MCF7 breast cancer cells stronger than that of EGCG. In particular, oral peracetylated EGCG increased plasma exposure of EGCG by 2.4 times.

3.3. Glycoside modification

Glycoside modification refers to the selective attachment of one or more hydrophilic monosaccharides to eight phenolic hydroxyl groups of EGCG. At present, the most common modification was the

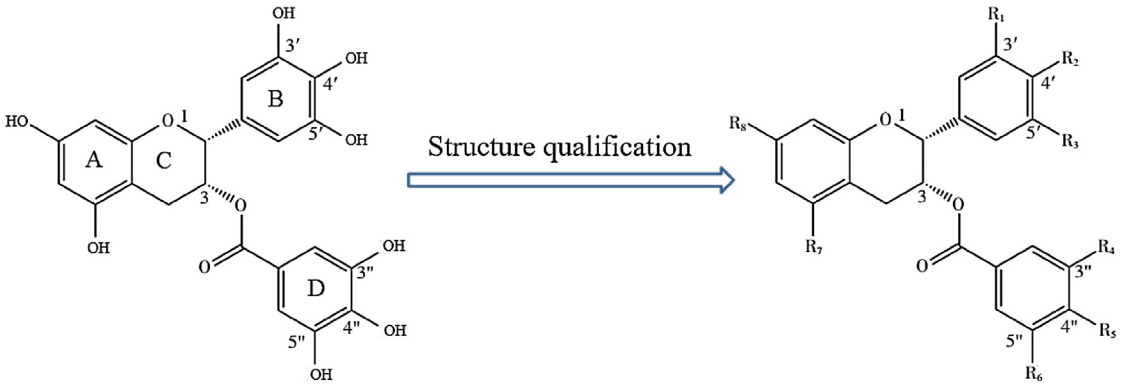

Fig. 2. Schematic diagram of EGCG structural modification.

Table 1
The structural modification of EGCG.

Structure	Group							
	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8
1	OH	OH	OH	OH	OH	OH	OH	OH
2	X	OH	OH	OH	OH	OH	OH	OH
3	OH	X	OH	OH	OH	OH	OH	OH
4	OH	OH	OH	X	OH	OH	OH	OH
5	OH	OH	OH	OH	X	OH	OH	OH
6	X	OH	OH	X	OH	OH	OH	OH
7	X	OH	OH	OH	X	OH	OH	OH
8	OH	X	OH	OH	X	OH	OH	OH
9	OH	OH	OH	X	X	OH	OH	OH
10	OH	OH	OH	X	OH	X	OH	OH
11	X	OH	OH	X	OH	X	OH	OH
12	OH	X	OH	X	X	OH	OH	OH
13	X	X	X	X	X	X	OH	OH
14	X	X	X	X	X	X	X	OH
15	X	X	X	X	X	X	OH	X
16	X	X	OH	X	X	X	X	X
17	X	X	X	X	X	X	X	X

Note: In the process of structural modification of EGCG, X represents methyl, acyl and glycosides, respectively.

modification of 3′-OH. The water solubility of the modified EGCG was enhanced, which could enrich the cytoplasm, eliminated the excess free radicals and promoted the cell metabolism (Spencer, 2003). Moon et al. (Young-Hwan et al., 2006) used sucrose-6-glucosyltransferase to catalyze the reaction of sucrose with EGCG, and obtained EGCG-7-O-alpha-D-glucopyranoside, EGCG-4′-O-alpha-D-glucopyranoside and EGCG-7,4′-O-alpha-D-glucopyranoside with the water solubility of 49, 55 and 114 folds higher than that of EGCG, respectively. Zhang et al. (2016) synthesized 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide by using D-glucose and EGCG as substrate. EGCG-4″-O-β-D-glucopyranoside (EGCG-G1) and EGCG-4′,4″-O-β-D-glucopyranoside (EGCG-G2) were obtained. In addition, the water solubility of EGCG glycosides increased: EGCG-G1 and EGCG-G2 were 31 and 15 folds higher than that of soluble EGCG, respectively. However, the scavenging ability of DPPH to free radicals was reduced.

4. Improving oral bioavailability of EGCG by food nano-delivery

Food nano-delivery is mainly based on the fact that some food nanomaterials embed bioactive substances or components into their interior or surface of the adsorption materials to protect them from the influence of gastrointestinal environment, so as to achieve the purpose of stable, sustained release and improve biological activity. At present, EGCG had been extensively studied through nanoparticle, nanoemulsion, nanoliposome or other wall materials embedding and nano-delivery. As shown in Table 2, these delivery technologies might be used to improve the bioavailability of EGCG.

4.1. Nanoparticles

The nanoparticle carrier had a large specific surface area, which was conducive to increasing the contact area between nutrients and adsorbed biofilm, improving the special surface properties of nanoparticles, and greatly prolonging the retention time of nanoparticles in small intestine (Raju et al., 2018). Nanoparticles had protective effect on nutrients and could significantly improve the absorption and bioavailability of nutrients. The stability of EGCG in the process of simulating gastrointestinal digestion was improved by coating EGCG with nanoparticles prepared by thermal modification of β-lactoglobulin (Li, Du, Jin, & Du, 2012; Shpigelman, Cohen, & Livney, 2012). Our research group (Liang et al., 2017) prepared embedding EGCG chitosan nanoparticles coated with zein. The composite nanoparticles played a role in controlling the release and better DPPH clearance activity. The protective effect of EGCG ferritin-chitosan double-layer nanoparticles and chitosan on ferritin was obvious, and the stability of EGCG molecule in ferritin-chitosan double-layer film coating was obviously improved. The transport results of Caco-2 cells showed that nanoparticles had a significant protective effect on ferritin. Especially, bilayer coating was more conducive to the ingestion of EGCG (Yang et al., 2018). Hu, Ting, Zeng, and Huang (2012) prepared EGCG containing chitosan-casein-phosphopeptide nanoparticles. The results of cell uptake with intracellular green fluorescence of Caco-2 confirmed that the nanoparticles loaded with EGCG were internalized into cells. The absorption of EGCG in the range of the incubation time and concentration was dose and time dependent. In addition, surface-charged chitosan and polyglutamic acid nanoparticles could rapidly open the tight junction between Caco-2 cells, increase the extracellular transfer of EGCG, and thus improve the utilization efficiency of catechin (Tang, Ho, Huang, Yu, & Hsieh, & Hao-Ying, 2013). Chitosan/trimeric phosphate nanoparticles significantly improve the gastrointestinal absorption of EGCG, thereby enhancing the bioavailability of EGCG (Admire, Nicolazzo, & Ian, 2010). After oral administration, the amount of EGCG exposed to the plasma and jejunum increased by 1.5 and 2.3 times, respectively (Admire, Nicolazzo, & Ian, 2011).

4.2. Nanoemulsion

Nanoemulsion is a transparent or translucent dispersion composed of oil phase, water phase, surfactant and cosurfactant. The particle size was usually ranged from 5 to 200 nm (David Julian & Jiajia, 2011). As a carrier, it could improve the solubility, stability and bioavailability of insoluble nutrients. Because of its special particle size distribution and structure, it also has sustained release and targeting effect (Fan, Liu, Gao, Zhang, & Yi, 2018). The slow released of EGCG loaded with nanoemulsion could be attributed to the protective effect of 1-Dodecyl

Table 2
The effect of nano-delivery system on oral EGCG.

Delivery system	Wall	preparation method	Characteristics	Effect on bioavailability of oral EGCG	Ref.
Nanoparticle	β-lactoglobulin	–	Size: < 50 nm; ZP: −40 mV; EE: 60–70%	Protect EGCG in stomach and released it continuously in intestinal tract.	Li et al. (2012), Shpigelman et al. (2012)
	Chitosan H-2 ferritin	Self-assembly	size: ~330 nm; ZP:- ; EE: 9.69%	Improve the stability of EGCG in simulated gastrointestinal tract based on Caco-2 cells.	Yang et al. (2018)
	Chitosan Casein phosphate peptide	Ionic gel	size: ~150 nm; ZP: ~32.2 mV; EE:-	Improve the intestinal permeability of EGCG and bioavailability based on Caco-2 cells, showed dose and time dependence on the absorption process.	Hu et al. (2012)
	Chitosan poly(gamma-glutamic acid)	Self-assembly	size:123.6 ~ 150.4 nm; ZP:22.9 ~ 35.6 mV; EE:-	Increased the extracellular transfer of EGCG, and improving the utilization efficiency of catechin	Tang et al. (2013)
	Chitosan tripolyphosphoric acid	Self-assembly	size:~440 nm; ZP:~25 mV; EE:-	Improve the intestinal absorption of EGCG. The amount of EGCG exposed to the plasma and jejunum chambers increased by 1.5 and 2.3 times, respectively.	Admire et al. (2010), Admire et al. (2011)
Nanoemulsion	Sunflower oil Tween 80	High pressure homogenization	size:~280 nm; ZP:- ; EE: 83.16 ± 1.12%	Slow and continuous release under SGF	Gadkari et al. (2017)
	Corn oil Polysorbate 80	High pressure homogenization	size: ~99.42 nm; ZP: −23.4 mV; EE:-	The absorption of EGCG in tea polyphenols loaded with nanoemulsion increased significantly by 28.6%.	Peng et al. (2018)
	Soy protein sunflower oil	High pressure homogenization	size:~260 nm; ZP:~28 mV; EE:-	The bioavailability of the main catechin nanoemulsification was more than 2.78-fold.	Bhushani et al., 2016
Nanoliposome	Dextran sulphate amphiphilic chitosan	Film evaporation	size: ~189.8 nm; ZP: −40.6 mV; EE: 90.8%	Showed a slow release performance and could effectively slow down the degradation of EGCG in SIF.	Zou et al. (2014)
	Phosphatidylcholine Cholestenone	Reversed phase evaporation	size: ~180 nm; ZP:- ; EE: 85.79 ± 1.65%	Had good gastrointestinal stability and were concentration dependent on the uptake of Caco-2 cells.	Xiaobo et al. (2014)
Double emulsions	glycerin monostearate polyglycerol polyricinoleate	High pressure homogenization	Size: ~507 nm; ZP:-; EE: > 80%	Increased the absorption of EGCG by Caco-2 cells and 1.93 times higher than that of EGCG in pharmacokinetic study of rats.	C. Hu, Wang, Zhao, Yao, & Xia (2016)

Note: ZP: Zeta potential; EE: Encapsulation efficiency; SIF: Simulated intestinal fluid.

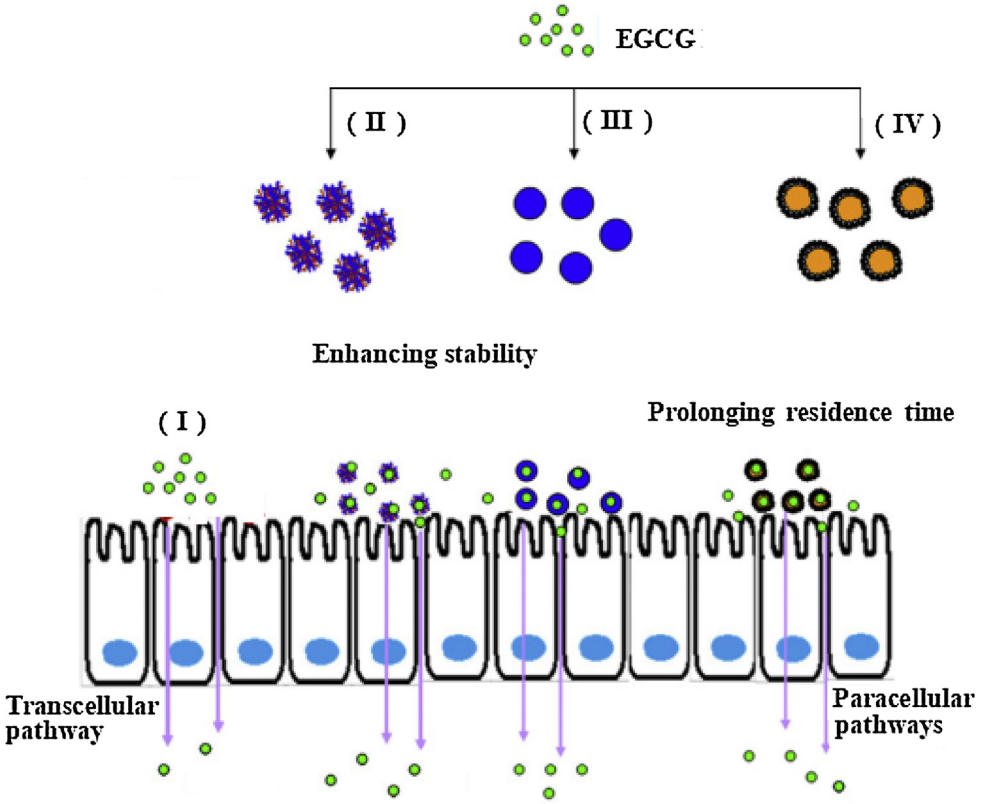

Fig. 3. EGCG and EGCG nano-delivery in simulated gastrointestinal digestion.

alcohol and soybean lecithin on EGCG under simulated gastric juice conditions (Gadkari, Shashidhar, & Balaraman, 2017). In the pharmacokinetics study of tea polyphenols, the absorption of EGCG in tea polyphenols loaded with nanoemulsion was significantly increased by 28.6% compared with that of tea polyphenols solution. The results showed that the absorption of EGCG could be enhanced by slow controlled release of tea polyphenols delivered by nanoemulsion system (Peng et al., 2018). Compared with the control group, the bioaccessibility of nanoemulsified catechin was 2.78 times higher than that of the control group, and the apparent permeability coefficient (Papp) of Caco-2 cells to catechin nanoemulsification was significantly higher than that of nonemulsified catechin (Bhushani, Karthik, & Anandharamakrishnan, 2016).

4.3. Nanoliposome

Nanoliposome is a bimolecular delivery system composed of phospholipid and cholesterol. Its structure and properties are similar to those of cell membrane. Nanoliposome could encapsulate hydrophobic nutrients in the lipid bilayer and hydrophilic nutrients in the middle hydrophilic cavity, improve the stability of nutrients and reduce the damage of gastrointestinal enzymes and acids to nutrients. Because of its special lipid structure, liposomes could easily fuse with intestinal mucosal cells, absorb and exchange lipids, which made the encapsulated nutrients easy to enter the body (He et al., 2018). The stability of EGCG in simulated intestinal fluid was significantly improved by nanoliposome encapsulation. In 1.5 h, the residual amount of EGCG was 31.2% and 47.7% respectively. While the residues of EGCG in EGCG solution were 3.4% and 3.5% respectively. Nanoliposomes encapsulation could effectively delay the degradation of antioxidant activity of EGCG in vitro (Zou et al., 2014). EGCG nanoliposomes were prepared with phosphatidylcholine and cholesterol as carriers. The results showed that EGCG nanoliposomes had good gastrointestinal stability. The absorption of EGCG nanoliposomes with different concentrations in Caco-2 cells was dose-dependent (Xiaobo et al., 2014).

4.4. Double emulsions

Double emulsion was also a better carrier delivery system, which could be generally divided into two species: water droplets-in-oil droplets-in-water (W/O/W) and oil droplets-in-water droplets-in-oil (O/W/O). Double emulsions are thermodynamically unstable emulsions. The key parameters affecting their stability are the composition of emulsion, emulsification conditions and osmotic pressure of inner droplets. However, they have several advantages over a single emulsion. For example, double emulsion may capture and protect various substances (e.g., hormones, vitamins, phenolic compounds, amino acids) and then control them to release from one phase to another. Thus, double emulsions are often used in the encapsulation and delivery of microcapsules, such as pharmaceuticals, nutrients and cosmetics. In the food industry, they could combine nutritional and bioactive compounds to create functional products with high efficiency (Muschiolik, 2007). In particular, in the protection study of EGCG, double emulsion had good entrapment efficiency (Evageliou, Panagopoulou, & Mandala, 2019). In addition, it had been shown that the double emulsion drug delivery system could increase the absorption of EGCG by Caco-2 cells. The pharmacokinetic study of rats showed that the absorption of EGCG by the double emulsion delivery system was 1.93 times higher than that of EGCG. Meanwhile, the prepared EGCG capsule could maintain the stability for 6 months (Hu, Wang, Zhao, Yao, & Xia, 2016).

5. Limitations of EGCG delivery by nano-delivery

At present, more and more nano-delivery had been used in order to improve the utilization of EGCG. Different nano-delivery carriers could be selected according to the properties and purpose of wrapping materials. As showed in Fig. 3, the nano-delivery carriers could enhance

the intestinal stability of EGCG, prolong the intestinal retention time and promote intestinal absorption (Oehlke et al., 2014; Reis, Neves, Frias, Granja, & Pinheiro, 2017). Chitosan nanoparticles had good adhesion to intestinal mucosa, which prolonged the contact time between the embedding material and intestinal epithelium (Feng et al., 2013). Some studies had shown that EGCG entered intestinal cells in the form of passive diffusion. EGCG could be pumped out of the cells by efflux related proteins during the transport process of EGCG. However, EGCG loaded with nanocarriers could promote intestinal absorption by changing the way EGCG enters cells. However, different nanocarriers had different limitations. Due to the limitation of small particle size and large specific surface area, the encapsulation efficiency of bioactivity was low and appeared to release abruptly. Some studies had shown that the nanoparticles formed by intermolecular interaction was prone to change under the influence of excessive ions, gastrointestinal pH and different digestive enzymes. Therefore, EGCG could not be well protected from degradation and oxidation in the process of delivery (Granja, Pinheiro, & Reis, 2016; Zheng, Hong, Xu, & Gu, 2015). Another limitation that cannot be ignored is the chemical functionalization of nanoparticles, because the function of biological macromolecules needs to be retained in and after the conjugated process. For example, aqueous and buffered media, additional surface protection, three-dimensional molecular structure and orientation should ensure the functionalization of biomolecules in their nanoparticles (Oh, Park, Joo, & Lee, 2015). Other studies had shown that nanoparticles could interact with circulating substrate, protein and other molecules in the blood, all of which might limit their therapeutic effects (Subbiah, Veerapandian, & Yun, 2010).

The stability of nanoemulsion was also affected by temperature, salt ion concentration and pH (Silva, Cerqueira, & Vicente, 2012). In order to enhance the stability of oral nanoemulsion, some high concentrations of surfactants and cosurfactants were usually used. However, the current research on the formation mechanism of nanoemulsion and the role of surfactants, as well as the negative effects of oral nanoemulsion were not clear.

The formation mechanism of nanoliposomes was the van der Waals force and hydrophilic-hydrophobic interaction between phospholipids and water molecules (Khorasani, Danaei, & Mozafari, 2018). Because nanoliposomes were dynamic structures that were easy to aggregate and/or fuse, the liposomes prepared in nanoscale may eventually become microliposomes. In addition, in order to prevent the aggregation, fusion and precipitation of nanoliposomes, cationic or anionic phospholipids could be used to generate repulsive electrostatic charges on the surface of vesicles. It was generally believed that when zeta potential was higher than 30 mV and less than −30 mV (Mozafari, Johnson, & Demetzos, 2008), the random threshold of lipid vesicles was positive and stable. However, in the preparation of nanoliposomes, the added organic solvent could not guarantee their complete removal, which might lead to the potential toxicity of oral nanoliposomes (Amoabediny et al., 2017).

6. Future perspectives

In recent years, many studies on improving the bioavailability of oral EGCG had been reported. However, there were still some problems: (1) how to improve the intestinal stability of oral EGCG more effectively; (2) how to influence the intestinal absorption of oral EGCG remained unclear, which need further study; (3) simulated in vitro absorption model, including animal model, valgus intestinal cyst and Caco-2 cell model, had been widely used to simulate in vitro absorption, but there were more complex transport mechanisms in the human gastrointestinal tract. In vitro tests might not fully reflect the normal absorption of human gastrointestinal tract. Therefore, the absorption, distribution, metabolism and excretion of EGCG in animals need further study. Up to now, the structural modification of oral EGCG, nano-delivery system and other related technical to improve oral EGCG were still limited, which might not improve the bioavailability of oral EGCG more effectively. It was necessary to study its pharmacokinetics and pharmacokinetics in vivo in order to improve the bioavailability of oral EGCG.

Ethics statements

Our manuscript was a review and it did not include any human subjects and animal experiments.

Declaration of Competing Interest

We declare that we have no financial and personal relationships with other people or organizations that can inappropriately influence our work, there is no professional or other personal interest of any nature or kind in any product, service and/or company that could be construed as influencing the position presented in, or the review of, the manuscript entitled.

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