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Colloidal nutrition science to understand food-body interaction

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ABSTRACT

Background: Food can be considered as a natural pool of biopolymer-based colloidal particles diverse in size, morphology, and functionalities. There remains considerable controversy on whether these particles can be absorbed from the intestinal lumen in their intact form even though numerous studies have confirmed the possibility of the absorption of intact nanoparticles across the intestinal wall.

Scope and approach: In this review, we comprehensively summarize the absorption process of nanoparticles, including mucus-penetrating, cellular uptake, and intracellular transportation. We then perform a detailed study on the absorption of food colloidal particles composed of protein, lipid and carbohydrate. The *in-vivo* transportation and biodistribution of nanoparticles is then summarized. We also specially discuss the dynamic colloidal aspects of food components which is of great importance to the food digestion and absorption. Finally, we analyze the safety issue of food nanoparticles since an increasing concern on this arises in the past decades.

Key findings and conclusions: External nanoparticles can be absorbed into cells through endocytosis, which can occur via different mechanisms. Like various fabricated nanoparticles, food colloidal particles potentially can also be absorbed in their intact form. However, previous studies rarely touch upon the absorption, biological fate, potential health effects, and safety of these colloidal particles. Their dynamic formation and disassembly process is also ignored. All these issues are of great importance to the food digestion and absorption mechanism and worth to be thoroughly studied. We attempt to coin all these relevant studies as "Colloidal Nutrition Science", which aim to understand the food-body interaction from colloidal aspects.

1. Introduction

Many chemicals naturally found in food matrix are present in a colloidal state such as globulins a few nanometers in diameter, starch granules (~100 nm), or fatty acids several nanometers in length. Traditional processing (e.g., emulsification, heating, or cooling) can generate a variety of multiscale colloidal structures such as micelles, emulsions, foams, gels, or dispersions (Bellmann et al., 2015). There are also endogenous colloidal nanoparticles physiologically produced from ions in the mammalian gastrointestinal tract (GIT) (Powell, Faria, Thomas-McKay, & Pele, 2010). All these colloidal structures generally act as the skeleton in foods. They not only maintain the stability, processing and texture characteristics of foods before consumption but also carry the sensory, digestion, and absorption attributes of foods after ingestion (Lu, Nishinari, Matsukawa, & Fang, 2020). Hence, to understand the interaction of food with the body from a perspective of food colloids is a key to completely uncover food digestion and absorption mechanisms, and thus provide essential basis for the development of functional food products that are applicable to common and/or specific populations (Dickinson, 2015).

The interaction between food colloids and the body starts from the moment when they enter the mouth where colloidal structures first affect the flavor perception during the oral processing (Gao et al., 2017). Food colloids then consequently determine the digestion and emulsification in stomach, the absorption in small intestine and thus the biological fate of food components (Acevedo-Fani, Soliva-Fortuny, & Martín-Belloso, 2017; Sarkar, Zhang, Holmes, & Ettelaie, 2019). The emerging interdisciplinary trend is driving the research of food colloids to go deeper and deeper into an "in-body" age, which pays more attention to the nutritional and health-beneficial aspects of food colloids (Li & Nie, 2016; Wijaya, Patel, Setiowati, & Van der Meeren, 2017). However, little is known about how these food-grade nanoparticles interact with the body and endow the nutritional and health-beneficial effects of foods. Many issues relevant to the interaction between food nanoparticles and the body remain to be answered, such as the absorption mechanism (in their intact form), intracellular fate (in a single cell), *in-vivo* transportation and biodistribution of these food-grade

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List of abbreviations

GIT	Gastrointestinal tract
CP	Conventional particles
MPP	Mucus-penetration particles
AML	Adherent mucus layer
BMDC	Bone marrow dendritic cell
132N1	Human glial astrocytoma cell line
A549	Human lung epithelium cell line
HepG2	Human hepatoma carcinoma cell line
MVB	Multivesicular body
A431	Human carcinoma cell line
IgG	Immunoglobulin G
BSA	Bovine serum albumin
GALT	Gut-associated lymphoid tissue
Caco-2	Human colorectal adenocarcinoma cell line
ODA-FITC	Otcadecylamine-fluorescein isothiocyanate
NRK	Normal rat kidney
CQDs	Carbon quantum dots
PEG	Polyethylene glycol
OVA	Ovalbumin
ROS	Reactive oxygen species

nanoparticles.

Here, we therefore review nanoparticle absorption process, which include mucus penetration, cellular uptake and intracellular transport. Then, we focus on the available studies on the absorption and biological fate of three main types of food-grade nanoparticles, protein, lipid, and carbohydrates nanoparticles. The *in-vivo* biodistribution and safety issue of naturally-occurred or engineered food nanoparticles was also discussed. We proposed this study with an objective to expand the perspective of exploring the interaction between food and body through a perspective of food colloids, which mainly concern about the absorption, transportation, and biological fate of colloidal structures in naturally or processed foods. We can coin a title for all these relevant research as "Colloidal Nutrition Science" and then arouse more researcher's interest and attention.

2. Food digestion

The food digesta can be considered as a mixture of both digestive products and original food components in any phase of digestion (Bornhorst, Gouseti, Wickham, & Bakalis, 2016). When reaching small intestine, it is generally believed that only certain groups of digestive products, e.g., free amino acids/short peptides, mono-/-oligo-saccharides, or free fatty acids/monoglycerides, can cross mucosa layer and then be absorbed by the body through small intestinal epithelium cells (Fig. 1). Therefore, food colloidal structures (e.g., protein, carbohydrate, or lipid particles) should be firstly degraded into small molecules (amino acids, monosugar, or free fatty acids), and then can be absorbed (Bhutia & Ganapathy, 2018). In fact, various naturally-occurred or engineered nanoparticles have been well proved to be absorbable by different species of cells (Salatin & Yari Khosroushahi, 2017; Teng et al., 2018; Xia et al., 2018). Further *in-vivo* studies have also shown that many engineered nanoparticles are capable of penetrating the intestinal mucus layer and then being absorbed in their intact form (Bellmann et al., 2015; Reitsma, Westerhout, Wichers, Wortelboer, & Verhoeckx, 2014; Trevaskis, Kaminskas, & Porter, 2015).

Based on these findings described above, we accordingly believe that a certain number of nanoparticles in foods potentially can escape the degradation process in GIT and be absorbed from the lumen in their intact form. However, there is still considerable controversy on this and the following discussions may provide some new clues for answering this question.

3. Absorption of nanoparticles

Nanoparticles that escape the general digestive degradation then can be absorbed in their intact form from the GIT lumen. These particulates should first penetrate across the intestinal mucus layer before approaching epithelium cell layer, where they are absorbed into the circulation or lymphatic system through paracellular or transcellular pathway (will be described later in Fig. 3).

3.1. Penetration across mucus

Mucus is a viscoelastic and adhesive gel that is composed of water (>95%), mucin (<5%), inorganic salts (~1%), carbohydrates and lipids (Bansil & Turner, 2018). Mucus can be considered as the first barrier between external environments and the internal milieu in GIT. Mucus is also responsible for nutrient absorption and waste secretion, which require a selectively permeable barrier.

Some external particles (conventional particles, CP) are mucoadhesive and cannot penetrate the mucus layer. Their diffusion is restricted to mainly stay on the surface layer of mucus and are easily cleared out (Fig. 2). Mucus-penetration particles (MPP) can readily penetrate across the luminal mucus and enter the underlying adherent mucus layer (AML) (Fig. 2). It is currently believed that colloidal particles transport in mucus via channeling through low viscosity pores. Saltzman and Cone's work pioneeringly found that some proteins and virus particles (30–55 nm) can diffuse nearly unhindered in cervical mucus and their penetrating rates in mucus were found to roughly equivalent to that in water (Olmsted et al., 2001; Saltzman, Radomsky, Whaley, & Cone, 1994).

MPP always show the following characteristics: (1) Suitable size. The particle size is an important factor that determines the diffusion rate. Mucus always has a heterogeneous distribution of pore size depending on its origin. Human cervicovaginal mucus shows a mean pore size of 340 ± 70 nm (range approximately 50–1800 nm) (Lai, Wang, Hida, Cone, & Hanes, 2010) while intestinal mucus in porcine and murine have an average pore size of around 200 nm (Bajka, Rigby, Cross, Macierzanka, & Mackie, 2015). The smaller of the particles, the easier it is to penetrate the mucus. Particles less than 100 nm can effectively diffuse across the mucus layer and larger particles (>200 nm) demonstrate limited diffusion. However, nanoparticles of 500 and 200 nm in diameter can also effectively diffuse across the mucus if coated with polyethylene glycol (PEG) (Maisel, Ensign, Reddy, Cone, & Hanes, 2015); (2) Being negatively or nearly neutrally charged. Mucus is made of negatively charged glycoproteins, which can interact with positively charged particles and reduce their diffusion velocity across the mucus. Thus, negatively or neutrally charged particles always display a significantly higher diffusion coefficient in mucus than those positively charged (Rossi et al., 2019); (3) Hydrophilicity. Mucus can develop low-affinity interactions with the particulates through hydrophobic interactions. Particles with hydrophobic surfaces always show mucoadhesive properties and low mucus diffusion coefficient. Thus, a hydrophilic surface is always preferred to achieve an effective diffusion across the mucus layer (Khutoryanskiy, 2018); (4) Reduced adhesion to mucin fibers to avoid significant steric inhibition by the dense fiber mesh. Tethered chains on a particle surface can interpenetrate with mucin fibers, which accordingly hinder the transport of the particles in mucus layer. Hence, particles with constrictive structures are easier to diffuse across the mucus as compared with those having outstretched surfaces.

Many food-derived colloidal particles meet one or some of these conditions, which accordingly suggests that these food colloidal particles potentially can also penetrate the mucus and then approach the epithelium cell layer, where they are absorbed in their intact form. However, current research interest is mainly paid on how to fabricate

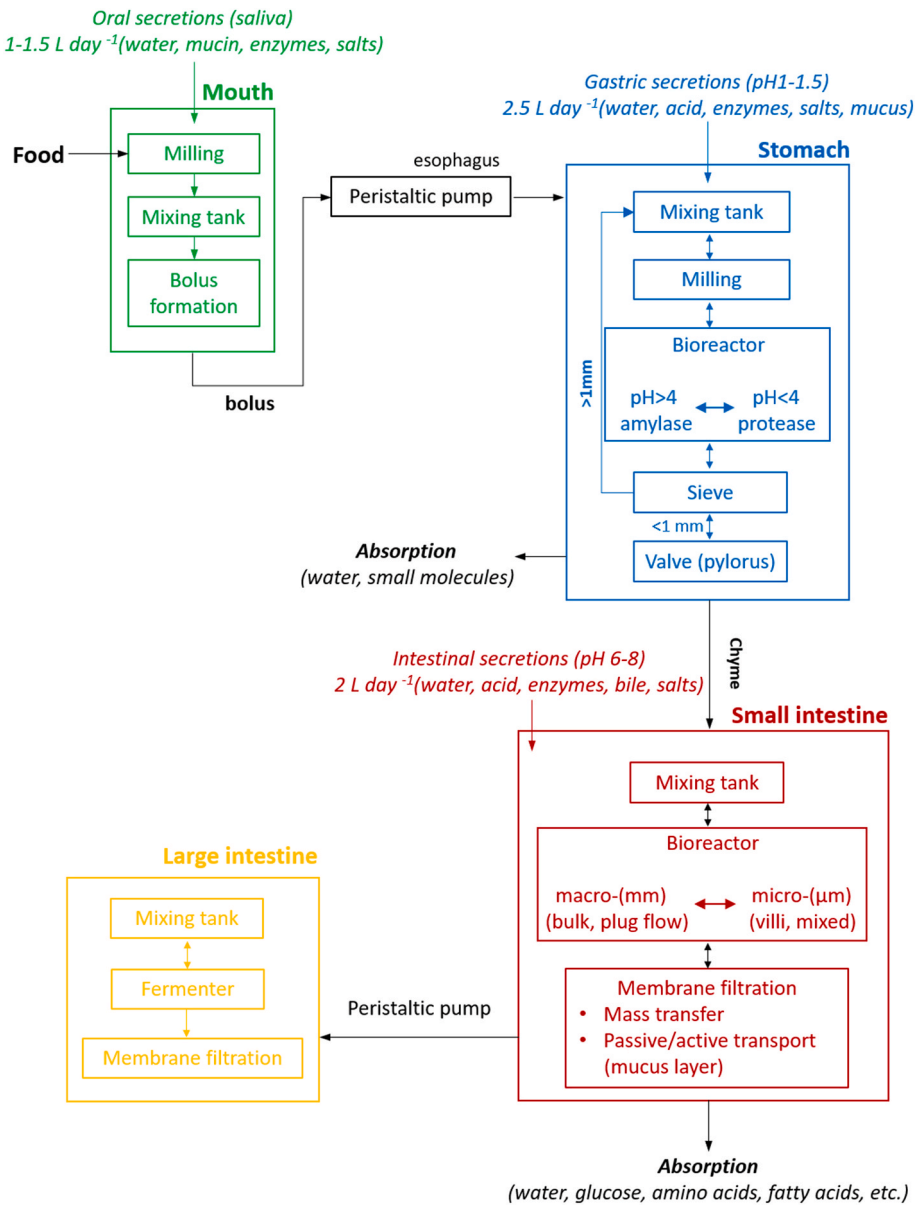

Fig. 1. Flow diagram of human food gastrointestinal digestion(Bornhorst et al., 2016). Ingested food enters the mouth and passes via the esophagus to the stomach, small intestine, and large intestine. The different boxes show the various unit operations that occur during each digestion process. In the diagram, the box for each organ (mouth, stomach, small intestine, and large intestine) is represented with a different colored line.

polymers-based nanoparticles with desired mucus-penetrating ability to develop ideal functional carriers (Liu, Zhang, Shan, & Huang, 2015; Rossi et al., 2019). Very little is known about the diffusion behavior of food colloidal particles in mucus even though this determines the subsequent absorption process of these particles. Relevant studies are therefore worth to be comprehensively carried out.

3.2. Pathway of absorption

After diffusing across the mucus layer, colloidal particles get close to the epithelium cell layer, where they can be absorbed from the lumen to the basolateral side through two main different pathways (Yu, Yang, Zhu, Guo, & Gan, 2016): (1) paracellular pathway through the tight junctions between adjacent epithelial cells (Fig. 3); (2) transcellular pathway through enterocytes or microfold cells (M-cells) (Fig. 3). Enterocyte-mediated transcellular pathway is the promising way for intestinal absorption of colloidal particles, and it enables particles to cross the intestinal epithelium, reach the *lamina propria*, and further enter the systemic circulation (Fig. 3). The intestinal barrier contains another cell type, M-cells, which are specialized epithelial cells with the ability to transport particulate matter from the lumen. They functionate as part of the mucosal immune system (Beloqui, Brayden, Artursson, Preat, & des Rieux, 2017). Hence, particles absorbed through M-cell--mediated transcellular pathway can be captured by macrophages and dendritic cells, and then delivered to the lymphatic system (Fig. 3). The earliest evidence of nanoparticle uptake was obtained from the observation that raw starch fed to rats was absorbed across the gut mucosa (Lu et al., 2012).

Enterocytes was reported to endocytose nanoparticles in a low efficient way and majority of external particulates are absorbed through M-cell via phagocytosis and receptor-mediated endocytosis (des Rieux, Fievez, Garinot, Schneider, & Preat, 2006; Kadiyala, Loo, Roy, Rice, & Leong, 2010). In contrast, Singh et al. (Singh et al., 2015) found that the absorption of nanoparticles by M-cells can be restricted, because M-cells only account for approximately 1% of the total intestinal barrier and the absorption of nanoparticles by M-cells is lack of specificity. It is now

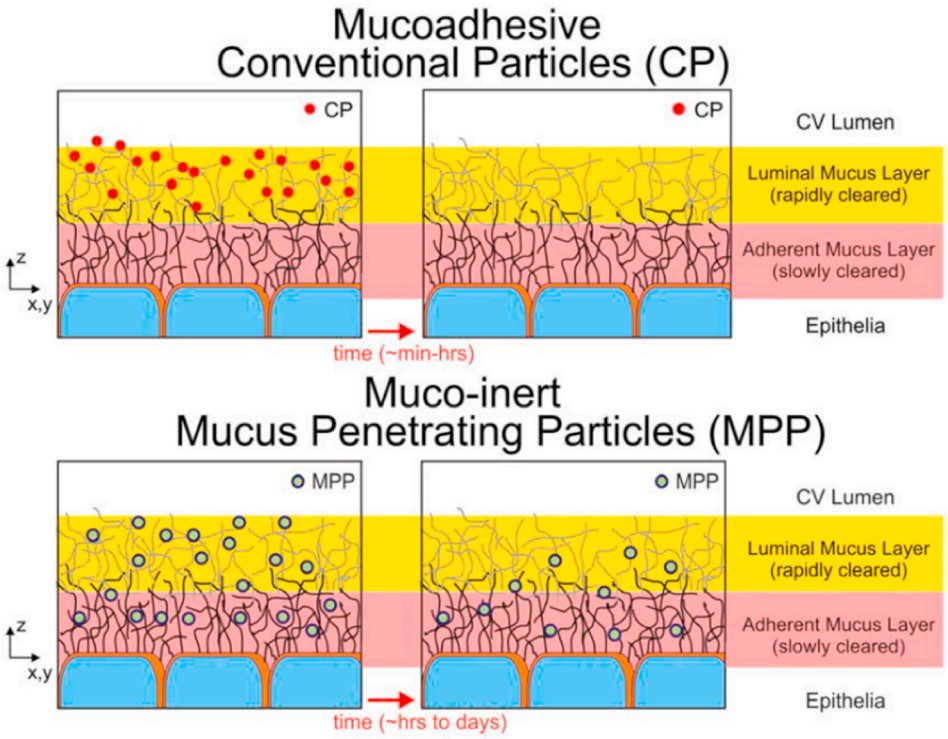

Fig. 2. Summary schematic illustrating the fate of mucus-penetrating particles (MPP) and conventional mucoadhesive particles (CP) administered to a mucosal surface. MPP readily penetrate the luminal mucus layer (LML) and enter the underlying adherent mucus layer (AML), showing a long retention time from hours to days. In contrast, the diffusion of CP in mucus is restricted and they are largely immobilized in the LML. CP can be easily cleared out of mucus after hours. This figure reproduced with permission from (Lai, Wang, & Hanes, 2009). The yellow and pink parts indicate the mucus layer. The blue part indicates the intestinal epithelium cell layer. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

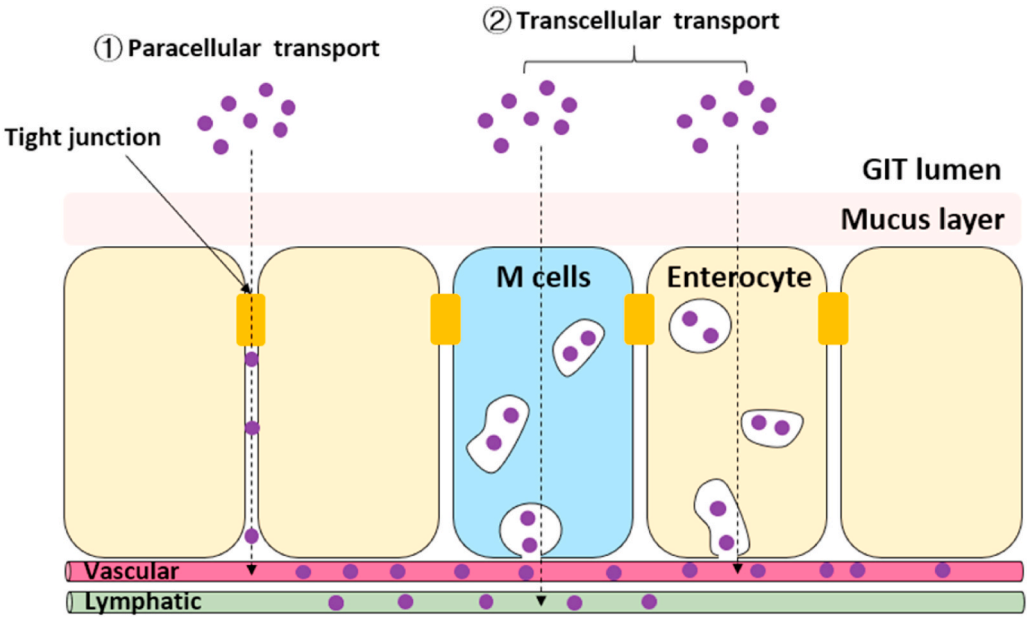

Fig. 3. Absorption pathway of nanoparticles from the GIT lumen. GIT indicate gastrointestinal track. Nanoparticles in GIT lumen can enter vascular or lymphatic system via paracellular (tight junction between epithelium cells) and transcellular pathway (enterocytes and/or M-cells). GIT indicates gastrointestinal tract. M cells indicates microfold cells.

generally believed that both enterocytes and M-cells involve the absorption of intact nanoparticles from the GIT lumen via endocytosis and enterocytes may dominate this uptake process since M-cells are only 1% of the total intestinal surface. However, more intensive works need to be done to further confirm this.

In addition, the degradation products (small molecules) of nanoparticles can be released from the surface of the particle and then absorbed into the body by conventional mechanisms. These absorbed degradation products, e.g., ions, can reconstitute into nanoparticles in tissue (Loeschner et al., 2011).

3.3. *Endocytosis of nanoparticles*

Transcellular absorption of colloidal particles mainly depends on the mechanism of endocytosis, which can be divided into two broad categories, phagocytosis and pinocytosis (Borel & Sabliov, 2014)(Fig. 4). Phagocytosis is responsible to the uptake of large particles (~20 μm) and generally happens in specialized cells such as macrophages, neutrophils,

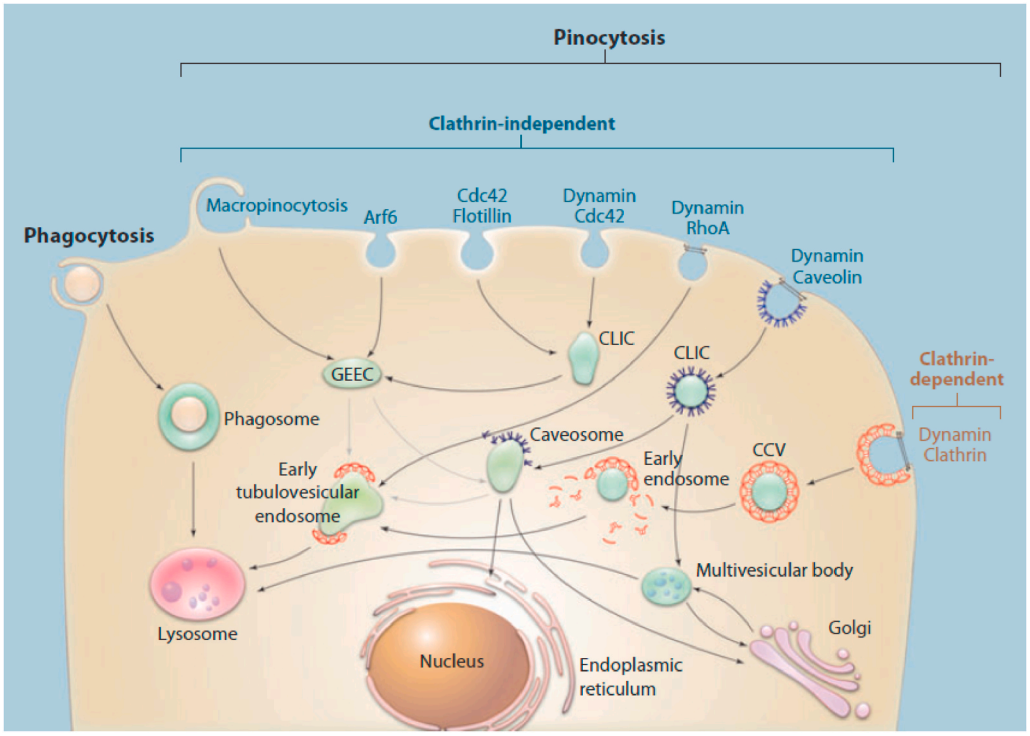

Fig. 4. Mechanisms of entry of nanoparticles into cells. Abbreviations: CCVs, clathrin-coated vesicles; CLICs, clathrin-independent carriers; GEEC, glycosylphosphatidylinositol-anchored protein-enriched compartment. This figure reproduced with permission from (Borel & Sabliov, 2014).

monocytes or dendritic cells. In contrast, pinocytosis is present in all types of cells and has multiple mechanisms dependent on the cell origin and properties of cargo, mainly including clathrin-mediated endocytosis, caveolae-mediated endocytosis, macropinocytosis, and caveolae/clathrin-independent endocytosis (Fig. 4).

Endocytosis occurs in several steps. First, the particles contact with

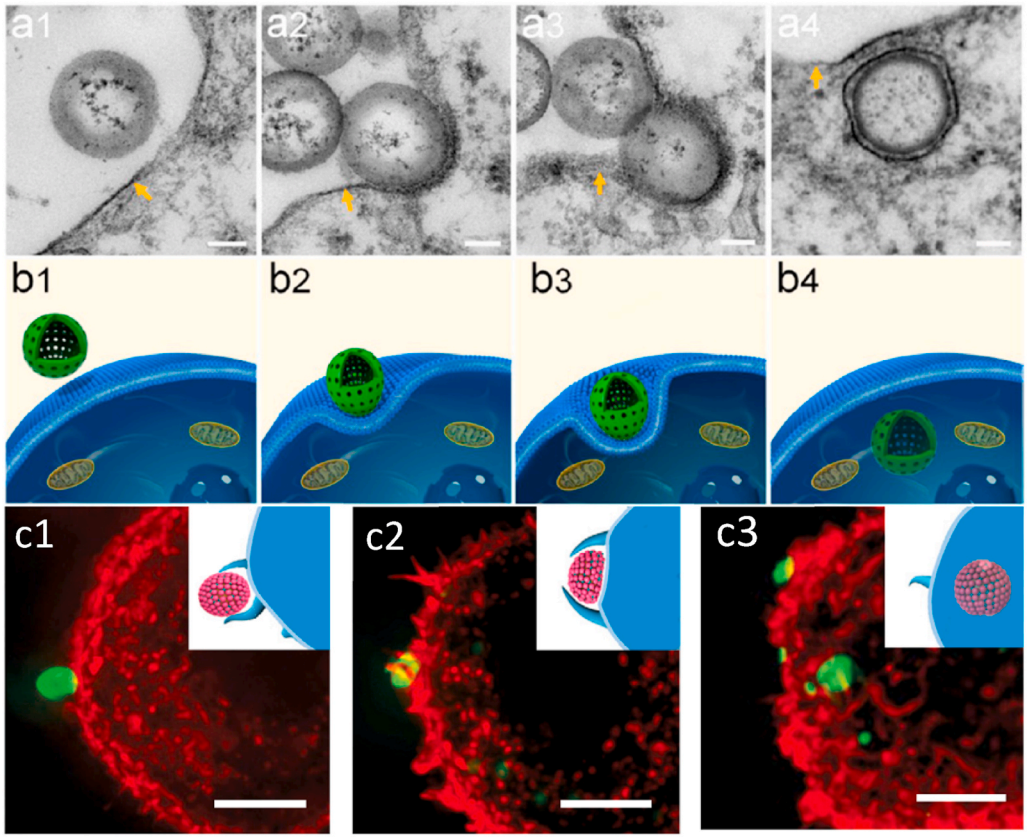

Fig. 5. The absorption process of external particles. (a1–a4) TEM images and (b1–b4) schematic illustration of the uptake processes of hollow periodic mesoporous organosilica nanocapsules by human breast cancer MCF-7 cells at 37 °C. The arrows indicate the cellular membranes. Scale bars, 100 nm; (c1–c3) The process of the phagocytosis of PLGA-stabilized Pickering emulsion droplets containing ovalbumin by bone marrow derived cells (BMDCs). Membrane actin and ovalbumin were labelled by rhodamine-phalloidin (red) and Alexa Fluor 488 (green), respectively. Scale bars, 5 μm a1–a4 & b1–b4 reproduced with permission from (Teng et al., 2018); c1–c3 reproduced with permission from (Xia et al., 2018). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

the cell membrane and deposit on the surface of membrane. Then, the particles are enveloped in membrane invaginations that are pinched off to form membrane-bound vesicles, also known as endosomes (or phagosomes in case of phagocytosis). Finally, the endosomes deliver the cargo to various specialized subcellular structures, which enables sorting of cargo towards different destinations (Sahay, Alakhova, & Kabanov, 2010) (Fig. 4). In addition, the physical characteristics (e.g., kinetics, energetics and forces) related to the interactions between the nanoparticles and the cell membrane are important to the subsequent endocytosis process since they can significantly influence the wrapping process of nanoparticles, and thus the mechanism, rate and amount of absorption. These kinetics and energetics parameters are dependent on the size, shape, and deformability of nanoparticles, cell membrane properties, and the local environment of the cells (Zhang, Gao, & Bao, 2015).

Several studies have captured the process of endocytosis. Xia et al. (2018) observed the endocytosis process of deformable Pickering emulsion droplets containing antigens by bone marrow dendritic cells (BMDC). The emulsion droplets were first deposited and deformed on the cell membrane by cellular wrapping (Fig. 5 c1-c2), which can increase the contact area between emulsion droplets and cell membrane. In the binding region of droplets and cell membrane, antigens inside the droplets were laterally streaming on the droplet surface to trigger the multivalent interactions and finally induced phagocytosis of the droplets. As compared with deformable droplets, control group of solid droplets, which did not have deformation ability, showed a significantly decreased endocytosis, suggesting that the deformability of the particle plays an important role in their endocytosis process. In another study investigating the cellular uptake of organosilica nanocapsules, authors found that hollow silicon nanoparticles had a spherical-to-oval deformation when entering the cells (Fig. 5 a1-a4, b1-b4), and this deformability of the nanocapsules can significantly contribute to their improved cellular uptake (Teng et al., 2018).

Many cells can employ different endocytotic pathways to internalize the same nanoparticle. For example, Human glial astrocytoma 132N1 cells endocytose carboxylated polystyrene nanoparticles mainly via clathrin-mediated mechanism, while Human lung epithelium A549 cells use a caveolae-dependent pathway (dos Santos, Varela, Lynch, Salvati, & Dawson, 2011). Caveolae-dependent endocytosis potentially make up over one third of the endocytosis in some tissues, especially frequent in smooth muscle, endothelial cells, adipocytes, fibroblasts, and type I pneumocytes (Parton & del Pozo, 2013). However, many other cells such as neurons, leukocytes, and HepG2 cannot internalize external particles through this way because they lack caveolae-1 protein.

4. Intracellular fate of endocytosed particulates

When a colloidal particle is absorbed into a cell's cytoplasm through endocytosis, it can have several biological fates: (i) be secreted back into the extracellular environment; (ii) remains in the cell and accumulates; (iii) be degraded in the cell; or (iv) be transported into systemic circulation. This process is usually determined by the intracellular sorting mechanisms mediated mainly by a network of cellular endosomes in conjunction with the Golgi apparatus, endoplasmic reticulum, and lysosomes (Behzadi et al., 2017).

Nanoparticles are usually first delivered to early endosomes, which are the main sorting stations in endocytosis. In the early endosomes, some particles are transported along with receptors to recycling endosomes and are subsequently excreted out of the cells; others that remain in early endosomes then mature and differentiate into late endosomes, which can either fuse with the plasma membrane (releasing their contents outside the cell in the form of exosomes) or fuse with lysosomes and form endolysosomes, where the colloidal particles are exposed to a variety of degradation enzymes. However, in some cases, the endocytosed particles can escape from the above-mentioned pathway at any stage. If such escape occurs prior to the fusion with lysosome, the particles will not go through lysosomal degradation and stay intact in the cytoplasm or in other subcellular structures (Dominska & Dykxhoorn, 2010; Martens, Remaut, Demeester, De Smedt, & Braeckmans, 2014).

Fluid particles are generally absorbed by large vacuoles through macropinocytosis. There is no consensus on the final destiny of particles captured in macropinosomes yet, but some studies have shown that this potentially depends on the cell type. For example, macropinosomes fuse with lysosome in macrophages or HeLa cells with high levels of c-Src kinase activity, whereas in human carcinoma A431 cells or human dendritic cells, most macropinosomes recycle back to the cell surface, fuse with the cell membrane (exocytosis), and release their contents into the extracellular space (Falcone et al., 2006; Kasahara et al., 2007; Mercer & Helenius, 2009).

The intracellular biological fate of absorbed nanoparticles is closely correlated to their endocytosis pathway (Behzadi et al., 2017). Particles absorbed via clathrin-mediated endocytosis first enter early endosomes with a low pH and then enter lysosomes where they will be metabolized. Nanoparticles endocytosed through caveolae-mediated pathway are fused with caveosomes or multivesicular body (MVB) that have neutral pH. This pathway appears to be slower than clathrin-dependent endocytosis, but it can bypass lysosomes in some cases, which sometimes is beneficial to the delivery of proteins or functional ingredients that need to escape the lysosomal degradation. Most substances endocytosed by caveosomes are eventually delivered to the endoplasmic reticulum or the Golgi apparatus.

To sum up, the properties (e.g., size, shape, or deformability) of colloidal particles can determine their endocytosis pathway, which accordingly affect their subsequent intracellular transportation and final localization. If colloidal particles are designed to serve as carriers of bioactive compounds, the functionalities of these encapsulated bioactive compounds will be also altered.

5. Absorption of food colloids

5.1. Food proteins

Protein-based nanostructures exist in various widely-consumed food products, such as casein micelles in cow milk, soy protein particles in tofu, or zein in many processed foods. It is generally believed that these dietary proteins are hard to be absorbed in their intact form owing to their enzymolysis and poor ability of transporting across the cell membrane. Most dietary proteins are degraded by gastric, pancreatic, and brush-border proteases. However, a small amount of intact proteins can escape protease degradation and then be absorbed by M-cells. These absorbed proteins can further cross the intestinal epithelial layer by transcytosis (e.g., apical endocytosis and basolateral exocytosis) (Perrier & Corthesy, 2011). This process was found by researchers who explored the reason why some dietary proteins can cause allergy after passing through GIT as early as in 1980s, and it is impossible to escape the conclusion that immunologically significant amounts of intact proteins have been absorbed (Gardner, 1988).

Generally, proteins are transported across the intestinal barrier via different routes, which appear to depend on the health status of the individual. Intact proteins are mainly absorbed via the paracellular (e.g., gap between M-cells and/or enterocytes) and transcellular (e.g., M-cells or enterocytes) routes (Fig. 3). Many *in-vitro* and *in-vivo* studies have shown the absorption of differently-sourced food proteins in their intact forms, including γ-conglutin, β-lactoglobulin, α-lactalbumin, IgG, ovalbumin, and rice protein (14–16 kDa) (Reitsma et al., 2014). Some other non-food related proteins were also shown to be absorbed such as horseradish peroxidase and bovine serum albumin (BSA). A study done many years ago showed that approximately 2% of intact BSA can reach the intestinal lymph and portal circulation under physiological conditions (Warshaw, AllanWalker, & Isselbacher, 1974).

However, a study referring to the *in-vivo* absorption of fabricated

sodium caseinate nanoparticles showed that the particles with mean diameter of 138 nm can be found in the stomach 2h after oral administration, and 24 h later, the particles can be observed in the distal part of GIT. After 48h of ingestion, the particles were eliminated from the body, suggesting that sodium caseinate colloidal particles were not absorbed and remain within the GIT until being excreted (Gil, Irache, Penuelas, Gonzalez Navarro, & Lopez de Cerain, 2017). However, the study is lack of quantitative analysis regarding its fluorescence and radio labeling tests, and the result of the amount of intact casein nanoparticles in rat feces was also not given. Thus, it is hard to exclude the possibility of a partial absorption of these casein nanoparticles. Anyhow, more work needs to be done on the absorption of food protein nanoparticles, especially their absorption mechanism and biological fate.

Many *in-vitro* studies demonstrated naturally-occurred or engineered dietary protein nanoparticles can also be absorbed by enterocytes. An *in-vitro* and *ex-vivo* study showed that engineered soy protein nanoparticles containing vitamins can be taken up by Caco-2 cells via clathrin-mediated endocytosis and macropinocytosis pathways. These nanoparticles were also shown to be permeable into the rat jejunum enterocytes after 2 h incubation with mucosal side of the jejunum, indicating that these nanoparticles could be absorbed by intestinal tissue (Zhang, Field, Vine, & Chen, 2015). Another study exploring the cellular uptake of caseinate-zein nanoparticles suggested that caseinate-zein nanoparticles can be endocytosed by Caco-2 cells through both paracellular route and energy-dependent transcellular route (Luo, Teng, Wang, & Wang, 2013). The findings shed new light on the cellular uptake strategy of hydrophobic protein nanoparticles.

5.2. Food lipids

Lipid particles are another type of important colloidal structures widely present in foods. Typical examples in natural food materials include lipid droplets in milk and plant oil body. In addition, many lipid particles such as oil-in-water emulsions (Lu, Kelly, & Miao, 2016) and solid lipid nanoparticles (Fathi, Mozafari, & Mohebbi, 2012), have been specifically fabricated as efficient delivery carriers to improve the solubility, stability and bioavailability of bioactive nutrients in food systems. Therefore, whether and to what extent these lipid nanoparticles can be absorbed integrally via oral delivery should be clarified because it is the basis for elucidation of absorption mechanisms.

In a pioneer work, approximately 30% of Otcadecylamine-fluorescein isothiocyanate (ODA-FITC) labelled stearic acid solid lipid nanoparticles were found to be efficiently absorbed in GIT after oral administration. These absorbed lipid nanoparticles were transported into the circulation system mainly via lymph (~77.9%) in their intact form. The rest ones directly entered blood circulation system through capillary vessel or paracellular pathway of enterocytes (Yuan et al., 2007). In another study using an *in situ* single-pass intestinal perfusion test, solid lipid nanoparticles were first proved to be endocytosed into enterocytes potentially through clathrin/caveolae-mediated pathway. Subsequent *in-vivo* test showed that numerous lipid particles could be rapidly absorbed into the enterocytes before degradation in the intestine lumen even though the diffusion of the fluorescent marker could not be excluded (Zhang et al., 2010).

Nevertheless, some researchers have doubts on these results and provide the evidence that does not support the absorption of the intact lipid particles after oral uptake. A study investigating the *in-vivo* fate of tween 80-stabilized solid lipid nanoparticles showed that these lipid particles were digested quickly in the intestine. Translocation of intact particles to other organs or tissues was not observed. The *in-situ* perfusion study showed that lipid nanoparticles can adhere to the intestinal mucus, but not penetrate the mucus layer. *In-vitro* test further proved that these solid lipid nanoparticles can be uptaken by Caco-2 cells but failed to penetrate the cell monolayer, mainly locating on the surface of the cell monolayers and are hard to be absorbed through paracellular pathway (Hu et al., 2016). All these evidences suggested that tween 80-stabilized solid lipid nanoparticles were mostly digested in the intestine and cannot be absorbed into circulation system in their intact form.

In the face of above-described inconsistency, more persuasive evidences are needed to further confirm whether lipid-based food nanoparticles can be absorbed from the lumen in their intact form.

5.3. Food carbohydrate

As far as is known, the earliest evidence of nanoparticle uptake was obtained from the observation that raw starch fed to rats can be absorbed across the gut mucosa (Lu et al., 2012). Although, it is hard to track the details on how this experiment was performed more than 80 years ago, the study at least told us that researchers at that time have already started to pay attention to how these food colloidal particles are absorbed.

Currently, studies mainly focused on the cellular uptake or *in-vivo* absorption of carbohydrate-based nanocarriers developed to improve the stability and oral bioavailability of functional nutrients and drugs (Liu, Jiao, Wang, Zhou, & Zhang, 2008; Salatin & Yari Khosroushahi, 2017), and the results showed that various food polysaccharides-based nanoparticles such as alginate, chitosan, dextran, pullulan, and pectin, can be absorbed by cells mainly through clathrin-/caveolae-mediated endocytosis and/or macropinocytosis. A favorable cellular uptake efficiency of polysaccharides-based nanoparticles is potentially attributed to their mucoadhesive nature (Salatin & Yari Khosroushahi, 2017), which can improve the residence time and thus increase their binding/uptake efficiency at the absorption site. Moreover, polysaccharides such as hyaluronic acid, pectin, and heparin can bind with cell membrane receptors (Lemarchand, Gref, & Couvreur, 2004), which can be applied to enhance the preferential uptake and intracellular accumulation of functional ingredients.

However, very few researchers have considered to dig deep the possibility of the absorption of carbohydrate biopolymers in their intact form and choose to believe that these biopolymers should be degraded into mono-, or disaccharides in the intestine first and then be absorbed from the GIT lumen. Little is known about the absorption process and intracellular fate of intact carbohydrate nanoparticles. Hence, this process worth to be intensively explored with an attempt to clarify the absorption mechanism of food carbohydrate particles.

In addition to above-mentioned protein, lipid, or carbohydrate nanoparticles, there was a study investigating the uptake of porcine bone soup derived colloidal particles containing lipid, protein and carbohydrate by murine peritoneal macrophages. The isolated colloidal particles with mean diameter of 275 ± 2 nm could be internalized by peritoneal macrophages and the engulfment did not influence the normal cells, but prevent them from peroxyl radical induced membrane hyperpolarization, mitochondria malfunction and phagocytosis suppression (Wang et al., 2019). The results suggest that there exist food colloidal particles containing multiple components (e.g., protein, lipid, and/or carbohydrate) and their absorption, biological fate and health benefits cannot be ignored.

Above all, the chemical characteristics, absorption and potential toxicity of food biopolymer-based colloidal particles were summarized in Table 1. Although there are some useful clues revealing the possibility of the absorption of food colloidal particles (e.g., protein, lipid, and carbohydrate), whether these particles can be generally absorbed from the GIT lumen in their intact form remains controversial. Many details regarding this process need to be further studied, including but not limited to how the colloidal particles in food matrix are absorbed, the absorption ratio, the biological fate of absorbed particles and their potential effect on the cell metabolism and human health. The illustration of these issues accordingly can contribute to drawing a complete picture of food digestion and absorption process, providing a new perspective of understanding the interaction between food and body.

Table 1
Chemistry, absorption and toxicity of main types of colloidal particles in natural and processed foods.

Colloidal particles	Chemical characteristics	Absorption	Toxicity	Reference
γ-conglutinβ-lactoglobulinα-lactalbuminOvalbuminRice proteinProtein nanoparticles	*In-vitro* test: these intact proteins can be absorbed by Caco-2 cells; intact absorbed proteins was recycled or transported via transcytosis while the others were degraded; *In-vivo* test: orally-fed intact proteins were shown to be absorbed into the blood of healthy adults and some animals (e.g., piglets, rats, and mice	Potentially can cause allergy		Reitsma et al. (2014)
Sodium caseinate nanoparticles		*In-vivo* test: absorption of intact nanoparticles was not observed	No toxicity with daily orally-administered particles below 150 mg/kg in rats	Gil et al., 2017
Soy protein isolate nanoparticles		*In-vitro* test: be uptaken by Caco-2 cells via clathrin-mediated endocytosis and macropinocytosis pathways; be permeable into the rat jejunum enterocytes	Not toxic to cultured Caco-2 cells	Zhang, Field, Vine, and Chen (2015)
Caseinate-zein nanoparticles		*In-vitro* test: cellular uptake of caseinate-zein nanoparticles by Caco-2 cells exhibited an energy dependent endocytosis, and the energy route and endocytosis pathway require further investigation	No cytotoxicity for Caco-2 cells for 72 h	Luo et al. (2013)
Otcadecylamine-fluorescein isothiocyanate labelled stearic acid solid lipid nanoparticles (SLNs)	Lipid nanoparticles	*In-vivo* test using SD rats: absorption efficiency of SLNs by oral administration was 30%; absorbed SLNs were transported into systematic circulation via lymph (~77.9%), capillary vessel or intestinal epithelial cells by paracellular pathway; PEG-coated SLNs can also be absorbed in GIT and achieve a prolonged blood retention		Not tested Yuan et al. (2007)
Simvastatin-loaded oleic acid SLNs		*In-situ* test: SLNs could be uptaken into the enterocytes through both clathrin and caveolae mediated endocytosis pathways	Not tested	Zhang et al. (2010)
Tween 80-stabilized SLNs		*In-vivo* test: quickly digested in the intestine and translocation of intact particles to other organs or tissues was not observed;*In-situ* test: SLNs can adhere to the intestinal mucus, but not penetrate the mucus layer; *In-vitro* test: be uptaken by Caco-2 cells but failed to penetrate the cell monolayer, mainly locating on the surface of the cell monolayers; hard to be absorbed through paracellular pathway	Not tested	Hu et al. (2016)
AlginateChitosanDextranPullulanPectin	Carbohydrate nanoparticles	Absorbed by cells mainly through clathrin-/caveolae-mediated endocytosis and/or macropinocytosis; the favorable cellular uptake efficiency is potentially attributed to their mucoadhesive nature	Not clear	Salatin & Yari Khosroushahi, 2017
Nanoparticlesin porcine soup	Containing lipid, protein and carbohydrate	*In-vitro* test: isolated colloidal particles ($d = 275 \pm 2$ nm) could be internalized by peritoneal macrophages	Not toxic to the cells	Wang et al. (2019)
Fluorescent nanoparticles in Coke and Pepsi	Containing H, C and O three elements	Penetrated the living cells and accumulate in cytoplasm; absorbed in the small intestine and colorectum, and mainly distributed in the heart and brain	did not significantly show *in-vitro* and *in-vivo* toxicity in mice	Li et al. (2018)
Fluorescent nanoparticles in pizza	Containing C, O, N, and S elements	Entered the normal rat kidney (NRK) cells; entered the tissue and organs of *Caenorhabditis elegans*,	induced the NRK cell apoptosis at high dose;	Cong et al. (2019)

(*continued on next page*)

Table 1 (*continued*)

Colloidal particles	Chemical characteristics	Absorption	Toxicity	Reference
		and accumulated in the liver, lung and kidney of mouse		
Carbon quantum dots in roasted salmon	Mainly composed of C, O, and N elements	Entered the cytoplasmic and nuclear regions of NRK cells; absorbed in the small intestine and accumulated in the mouse brain	Caused autophagosome formation in NRK cells	Song et al. (2019)

6. *In-vivo* transportation and biodistribution

After absorption from the gut, nanoparticles can enter different transportation pathways (Fig. 6). Hydrophobic nanoparticles absorbed through the gut-associated lymphoid tissue (GALT) are transported to the lymph and reach lymphoid circulation while others can be sent to the liver, where they are processed and sent to systemic circulation (Chen, Sonaje, Chen, & Sung, 2011). Nanoparticles absorbed into lymph can escape first-pass effect by the liver and be delivered to systemic circulation through the caudal vena cava. Upon reaching systemic circulation, nanoparticles are transported to various organs such as the heart, lung, spleen, kidney, liver, and potentially the brain (Aillon, Xie, El-Gendy, Berkland, & Forrest, 2009) (Fig. 6). Those particles that are not absorbed in the intestine or metabolized after absorption will be excreted in urine or feces. A main *in-vivo* journey that colloidal particles in food may go through after ingestion is shown in Fig. 6.

6.1. Nanoparticles in processed foods

Little has been known about the *in-vivo* transportation of natural food-grade nanoparticles after oral administration. Previous studies focused more on the processed foods since food processing can also produce some colloidal structures that can be absorbed and cause biological effects (Table 1). For example, Li et al. (2018) first reported the presence of fluorescent nanoparticles in Coke and Pepsi. These particles can penetrate the living cells and accumulate in cytoplasm while did not significantly show *in-vitro* cytotoxicity, and *in-vivo* acute toxicity in mice. They were absorbed in the small intestine and colorectum, and mainly distributed in the heart and brain, suggesting they can cross the blood-brain barrier. A class of water-soluble fluorescent nanoparticles ($d = 3.3 \pm 0.76$ nm) were also found in the charred part of pizza (Cong et al., 2019). These nanoparticles were shown to enter the normal rat kidney (NRK) cells and induce the cell apoptosis. They can also enter the tissue and organs of *Caenorhabditis elegans*, and accumulate in the liver, lung and kidney of mouse. The origin of these nanoparticles is probably attributed to the complex physicochemical conversion of pizza ingredients like proteins, lipids and carbohydrates during the baking process. In another study by the same group, researchers found that roasted salmon contained carbon quantum dots (CQDs) with different particle size, surface groups, and fluorescence property. These nanoparticles can enter the cytoplasmic and nuclear regions of *in-vitro* cultured NRK cells, while they were shown to be absorbed in the small intestine and accumulated in the mouse brain (Song et al., 2019).

Nevertheless, whether these nanoparticles produced in the food processing have impact on the health of humans is not clear. Rigorous *in-vivo* test is therefore needed to further confirm their potential health or toxic effect.

6.2. Nanosized food additives

Many nano-sized food additives have been widely used in the food industry to improve the taste, color, texture, processing suitability, nutritional values, and shelf-life of food products. These food additive particles are ingested together with the food matrix by the body. Thus,

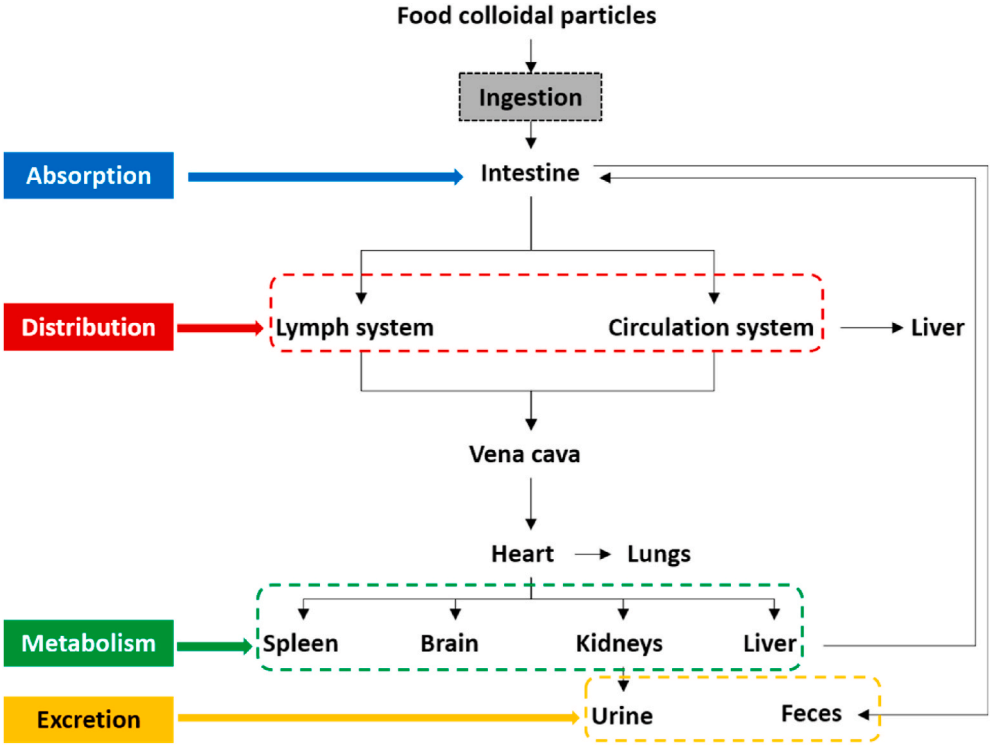

Fig. 6. A nanoparticle's path through the body from ingestion to excretion.

the illustration of their absorption and transportation seems to be very important since the widespread use and end-of-life disposal of food-grade colloidal particles can lead to unexpected human exposure and environmental contamination, which raise concerns about their potential toxicity.

Currently, nano-sized SiO_2 is one of the most widely utilized food additive particles in various food sectors. After oral administration, silica nanoparticle accumulation can be found in kidney, liver, lung, brain and spleen, and their organ biodistribution is potentially dependent on their shape, mesoporous, or surface chemistry (Bourquin et al., 2018; Chen, Chen, & Shi, 2013; McCracken, Dutta, & Waldman, 2016). It was reported that the organ distribution of silica nanoparticles significantly changed with the extension of observation duration but the distribution did show organ targeting (Kim et al., 2014). 75–80% of the orally ingested silica nanoparticles are excreted in the feces, while 7–8% are excreted via the urine, and a longer retention can be observed in the liver and kidneys than in the lungs and spleen (Lee et al., 2014).

A study investigating the absorption and biodistribution of another food additive calcium carbonates particulate showed that orally ingested calcium carbonates particles mainly distributed in lung, followed by the blood, brain, liver, spleen, and kidney of rats after 14 days of daily treatment (Lee et al., 2015). A very high distribution in the ovary of female rats was also observed. In addition, there was a significant increase in total calcium concentration in spleen and no accumulation was observed in any other organ.

6.3. *Particle characteristics affecting their biodistribution*

The blood residence time and organ specific accumulation of nanoparticles can be significantly influenced by their particle characteristics, including composition, size, shape, core properties, surface chemistry (chemical modifications and/or surface charge), and elasticity (Aaron et al., 2015; Bourquin et al., 2018). All these factors have been shown to substantially affect the biodistribution and blood circulation half-life of nanoparticles by reducing the level of nonspecific uptake, delaying opsonization, and/or increasing the extent of tissue specific accumulation. Some other factors such as interaction with biological barriers and inflammation status of the host (Chen et al., 2015) can also influence the biodistribution of absorbed nanoparticles.

However, this does not mean that any of these factors can affect the biodistribution of all the nanoparticles. For example, several studies concluded that the biodistribution of silica nanoparticles is not significantly size dependent (Lee et al., 2014, 2017) while the particle size can significantly influence the biodistribution of iron oxide magnetic nanoparticles (Yang et al., 2015). It is therefore important to first confirm whether a factor (e.g., size, shape, or surface charge) can affect the organ distribution of a nanoparticle, and then achieve a specific biodistribution of the nanoparticle by controlling this factor.

7. Dynamic formation and disassembly process of food colloids

All above-mentioned studies can be considered as a static absorption process of colloidal particles present in GIT lumen. In fact, there exist dynamic formation and disassembly of food colloids under the drive of physical and chemical effects during the digestion process. This *in-vivo* dynamic process creating or breaking-up food colloidal structures is crucial to the digestion and absorption and thus the biological effect of functional food components. For example, food proteins tend to aggregate into large clusters in stomach owing to the low pH environment and gastric enzyme hydrolysis (Lu, Zheng, & Miao, 2018; Mulet-Cabero, Mackie, Wilde, Fenelon, & Brodkorb, 2019; Mulet-Cabero, Rigby, Brodkorb, & Mackie, 2017). When entering intestine, these large protein particles can be broken up by protease hydrolysis. In addition, proteins can interact with physiological surfactants in GIT and form protein nanoparticles with different size and surface chemistry (Mackie & Macierzanka, 2010). Protein can also absorb onto the surface of oil droplets and act as stabilizer. All these events occurring in the food digestion process can be considered as a dynamic formation or disassembly of food protein colloidal structures. These dynamic processes can significantly influence the digestion of proteins through affecting the accessibility of cleavage site to the intestinal protease or altering the flexibility of protein molecular structures.

Another example is the lipid digestion process. Lipids are essential nutrients and insoluble in the aqueous phase. They have to form a variety of colloidal structures that can stably disperse in water in order to be processed, digested and utilized since the human body relies largely on the aqueous phase for transporting essential nutrients around the circulatory systems (Wilde & Chu, 2011). Most dietary lipids are first emulsified into oil droplets. The lipase then adsorbs onto the surface of the formed oil droplets and promotes the lipolysis. Free fatty acids released by lipolysis then interact with bile-salt and form micelles. The formed micelles will move to the surface of epithelium cells, where micelle structures disassembly and free fatty acids are released and then absorbed. These dynamic colloidal processes including emulsification, hydrolysis, and micellization determine the digestion and absorption efficiency of dietary lipids. A deep insight into these dynamic processes is of significant meaning to the food digestion and absorption process.

When some nanoparticles travelling in the circulation system, their colloidal status can also be dynamically changed. In biological fluids, proteins can bind to the surface of inorganic nanoparticles to form a coating known as the protein corona, which can critically affect the interaction of nanoparticles with living systems (Chen et al., 2017; Tenzer et al., 2013). Protein corona can further lead to the aggregation and nonspecific adsorption of these inorganic nanoparticles, and consequently affect their blood retention time and biological fate. Thus, this process is not always favored by inorganic nanoparticle especially those designed to act as functional delivery carriers. Strategies to reduce the protein corona formation and thus improve the delivering and targeting efficiency of inorganic nanoparticles have been accordingly widely studied, one of a promising way is coating the nanoparticle with hydrophilic polymers such as polyethylene glycol (PEG) (Ke, Lin, Parak, Davis, & Caruso, 2017).

Above all, the dynamic formation and disassembly process of food colloidal structures can influence not only their digestion and absorption in GIT but also their transportation in circulation systems and final biodistribution. Previous studies did not pay much attention on the correlation of this dynamic process with digestion, absorption, and health-benefits aspects of food, and relevant studies are worth to be comprehensively deepened.

8. Safety issue

There is increasing concern about the potential toxicity of the application of nanotechnology in foods since nanotechnology has been widely used to design smart food systems by enhancing solubility, improving bioavailability, facilitating the controlled release and maintaining the stability of micronutrients in food products (Das, Saxena, & Dwivedi, 2009; McClements & Xiao, 2017). Nanoparticles present in foods can be generally classified into two main groups based on their compositions, inorganic nanoparticles and organic nanoparticles. Inorganic nanoparticles mainly consist of inorganic materials, such as silver, iron oxide, titanium dioxide, silicon dioxide, or zinc oxide (Pietroiusti, Magrini, & Campagnolo, 2016) while organic nanoparticles are composed of organic macromolecules, such as proteins, lipids, and/or carbohydrates. We then summarize the safety issue of food inorganic and organic nanoparticles in this section.

8.1. *Inorganic food nanoparticles*

Inorganic nanoparticles are found to accumulate in various organs after ingestion, including liver, kidney, stomach, intestine, spleen, lung, and heart. They can cause toxic effects on different organs and/or tissues

when consumed at a high dose, such as intestine dysfunction, hepatic injury, nephrotoxicity or myocardial damage (McClements & Xiao, 2017). Inorganic nanoparticles arouse these adverse health effects mainly via the mechanism of generating reactive oxygen species thereby promoting oxidative stress, which consequently cause damages to cell membranes, organelles, and the nucleus, such as silver (Sharma, Siskova, Zboril, & Gardea-Torresdey, 2014), zinc oxide (Sirelkhatim et al., 2015), iron oxide (Wu, Yin, Wamer, Zeng, & Lo, 2014), titanium dioxide (Frohlich & Frohlich, 2016), and silicon dioxide (Yang et al., 2016) nanoparticles. The toxic effects of inorganic nanoparticles have also been shown as their accumulation within specific tissue, interference with normal GIT function and gut microbiota (McClements & Xiao, 2017).

8.2. Organic food nanoparticles

We found very limited reports on adverse effects of organic food-grade nanoparticles. They are generally believed to be safe and less toxic than inorganic ones since they are often fully digested within the human GIT (McClements & Xiao, 2017; Yokooji, Noum, & Matsuo, 2014). There may be certain circumstances where they could cause toxicity. For example, some emulsion droplets contain indigestible oil phase or indigestible interfacial layers, all of which can prevent the enzymatic hydrolysis of the droplets. These unhydrolyzed droplets potentially can be absorbed in their intact forms. Their biological fate are not clear and they may have some potential toxic effects (McClements & Xiao, 2017). In addition, protein or polysaccharide nanoparticles can also arouse potential adverse health effect if absorbed in their intact form, such as ovalbumin (OVA) (Yokooji et al., 2014). These organic nanoparticles can interact with the gut microbiota, leading to some unforeseen effects.

The most important issue regarding the potential toxicity of organic nanoparticles is their using as delivery carriers for functional substances. The use of organic nanoparticle-based carriers potentially can alter the digestion and release site of functional substances or cause an excessive release and absorption of these compounds thereby inducing adverse effect on the body health. For instance, multilayer-coatings of oil droplets by biopolymers can inhibit the digestion rate and extent of the oil droplets through different mechanisms, e.g., hindering the adhesion of lipase and bile salts to the droplet surface (Li, McClements, Liu, & Liu, 2020). Hence, high levels of undigested lipids reach the colon, where they are fermented by the colonic bacteria and thus cause gastrointestinal problems. In addition, enhanced bioavailability of bioactive nutrients through incorporating them into organic nanoparticles sometimes can become a safety issue, because a high exposure level of these compounds have potentially adverse health effects and can be toxic even if they are health-beneficial at a suitable level (Taylor & Davies, 2018).

Many characteristics of food nanoparticles can affect their potential toxicity, including compositions (inorganic or organic), dimensions (particle size or shape), interfacial properties (surface charge, hydrophobicity/hydrophilicity, thickness of corona) or aggregation state (single particle, or clusters) (McClements & Xiao, 2017). Furthermore, the interaction of food nanoparticles with complex food matrices and the GIT should not be ignored since they can significantly influence the biological fate and thus the toxic effect of food nanoparticles.

An increasing concern on the safety issue of food-grade nanoparticles has been considerably observed in the past few years. Relevant studies have some insights into the type of food-grade nanoparticles that may cause adverse health effects, as well as into the possible mechanisms (Jain, Ranjan, Dasgupta, & Ramalingam, 2018). However, there remains lots of contradictory results and unanswered questions in this area. For example, some studies suggested that nano-sized titanium dioxide (TiO_2) in food does not produce toxicity, whereas others showed that they are toxic (Winkler, Notter, Meyer, & Naegeli, 2018). Moreover, little is known about the GIT fate and toxicity of most types of food-grade nanoparticles at present, and more works need to be done to evaluate the safety of different types of food nanoparticles and corresponding mechanisms to their toxicity.

9. Conclusions and future trends

Numerous *in-vitro* and *in-vivo* tests have shown an indisputable fact that a variety of naturally-occurred and engineered colloidal particles can penetrate the mucus layer and be absorbed from the GIT lumen in their intact forms via endocytosis. The endocytosis pathway consequently determines the intracellular transportation route and *in-vivo* biodistribution of absorbed particles. Factors such as size, shape, composition, and surface chemistry of nanoparticles are shown to significantly affect their endocytosis, intracellular transportation and the final biodistribution.

Nevertheless, there remains confusions or even controversies about that of food nanoparticles. Understanding how these food nanoparticles are absorbed and metabolized is considerably important since this can elucidate whether they have effect on the cell and body health. Many contents therefore need to be comprehensively studied, such as the absorption process of food nanoparticles (e.g., casein micelles, oil droplets, or rice starch particles), their intracellular and *in-vivo* biological fate as well as the biodistribution and potential effects on cell metabolism and body health. Furthermore, a deep insight into the dynamic formation and disassembly process of food colloidal structures can also contribute to a whole picture of food digestion and absorption.

Moreover, nanoparticle potentially can arouse some adverse health effects due to their small size and accumulation in tissues and organs. They can produce *in-vivo* toxicity and cytotoxicity through different mechanisms (e.g., generating Reactive oxygen species (ROS), or disturbing gastrointestinal functions). Organic nanoparticles present in food are believed to be less toxic than inorganic ones since they are generally degraded into small molecules. Little has been done on the biological fate of intact food nanoparticles and there has been no hard evidence that confirms the general toxic effect of most food-grade nanoparticles. Their safety issues need to be further studied.

All these described topics can be grouped by defining them as a new research direction entitled “Colloidal Nutrition Science”, which aims to get deep insight into the nutritional effects of colloidal particles and thus thoroughly uncover the complicated interaction between food and the body from a perspective of colloidal science.

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Declaration of competing interest

The authors declare no competing interests.

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