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REVIEW ARTICLE

A Review of Food–Drug Interactions on Oral Drug Absorption

Jianyuan Deng[1] · Xiao Zhu[1] · Zongmeng Chen[2] · Chun Ho Fan[1] · Him Shek Kwan[1] · Chi Ho Wong[1] · Ka Yi Shek[1] · Zhong Zuo[1] · Tai Ning Lam[1]

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Abstract Food effect, also known as food–drug interactions, is a common phenomenon associated with orally administered medications and can be defined as changes in absorption rate or absorption extent. The mechanisms of food effect and their consequences can involve multiple factors, including human post-prandial physiology, properties of the drug, and how the drug is administered. Therefore, it is essential to have a thorough understanding of these mechanisms when recommending whether a specific drug should be taken with or without food. Food–drug interactions can be clinically relevant, especially when they must be avoided to prevent undesirable effects or exploited to optimize medication therapy. This review conducts a literature search that examined studies on food effect. We summarized the literature and identified and discussed common food effect mechanisms. Furthermore, we highlighted drugs that have a clinically significant food effect and discussed the corresponding mechanisms. In addition, this review analyzes the effects of high-fat food or standard meals on the oral drug absorption rate and absorption extent for 229 drugs based on the Biopharmaceutics Drug Disposition Classification System and demonstrates an association between Biopharmaceutics Drug Disposition Classification System class and food effect.

Key Points

Food effect is a complicated interaction between food and drugs that depends on the type of food, the patient's post-prandial physiology, the nature of the drugs, and the manner they are administered.

Food effect can be reflected in alterations in both absorption rate and absorption extent, from the perspective of pharmacokinetics.

Some food effects are favorable and should be exploited, but others can be hazardous and should be avoided.

Although there may be a food effect between a specific drug and a particular type of food, it may not necessarily occur for all drugs or in all patients; even if a food effect exists, it may not necessarily be clinically significant.

The Biopharmaceutics Drug Disposition Classification System may be useful for anticipating potential consequences on the oral drug absorption rate and absorption extent of food effect from high-fat food or standard meals.

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✉ Tai Ning Lam
teddylam@cuhk.edu.hk

[1] School of Pharmacy, Faculty of Medicine, The Chinese University of Hong Kong, Shatin, New Territories, Hong Kong

[2] State Key Laboratory of Natural Medicines and Laboratory of Chemical Biology, China Pharmaceutical University, Nanjing, Jiangsu, People's Republic of China

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1 Introduction

Oral administration is the most convenient and cost-effective way for patients to consume drugs. However, interactions between food and drug, also called 'food effect', can hamper or facilitate the therapeutic efficacy of an orally administered drug [1]. A clear understanding of the factors that influence the time course of drug action may result in the rational use of drugs. Previous reviews have limitations in analyzing food effect in that they include few drug examples, do not examine the schemes that are used in food effect trials, or have little discussion of the differences between statistically significant and clinically relevant food effect. Therefore, this review summarizes common mechanisms for food effect and highlights the clinical significance of food effect. Furthermore, we also explored predicting food effect based on the Biopharmaceutics Drug Disposition Classification System (BDDCS).

We conducted a thorough literature search of food effect studies using Google Scholar, which is an academic search engine that has acceptable coverage and precision [2–4], using the keywords 'drug,' 'food or meal,' and 'absorption' for more than 900 drugs that are classified in the BDDCS [5], between 1 September, 2013 and 1 July, 2016, with periodic updates until 17 August, 2017. We retrieved and compiled literature reports and analyses on the observed food effects for 273 drugs that included detailed study designs, regardless of clinical relevance. A comprehensive analysis and generalization of possible food–drug interaction mechanisms are presented in Sect. 2. Section 3 presents considerations of, and factors that may lead to, clinically significant food effect. In addition, we analyzed the effects of high-fat food or standard meals on the rate and extent of absorption for 229 drugs to explore the relationship between BDDCS and food effect. A summary of the methods and results as well as references for the collected food effect studies are presented in the Electronic Supplementary Material (ESM). Table S1 of the ESM summarizes information on the designs of food effect studies and includes information on the dose of the tested drug, the number of subjects, and co-administered food types. Table S2 of the ESM lists the outcomes of the studies in Table S1 and focuses on changes in the rate and extent of absorption and their statistical significance.

Generally, food effect is investigated with a simple single-dose pharmacokinetic (PK) study. The presence of food effect is usually reflected in alterations of drug absorption rate and absorption extent, which can be quantified by measuring the rate and extent to which a drug is absorbed into systemic circulation [6]. Commonly used parameters for absorption extent are area under the concentration–time curve (AUC), including the AUC up to last measured concentration at time t ($AUC_{0\text{-}t}$) and the AUC extrapolated to infinity (AUC_{∞}), or oral bioavailability (F). The latter is possible when there is PK information on the intravenous dose. In a single-dose design, AUC_{∞} is preferred because this AUC predicts steady-state exposure. However, there are instances where $AUC_{0\text{-}t}$ is used when extrapolation is infeasible, as in cases of extended-release formulations, endogenous substances, poorly absorbed drugs, drugs with a long elimination half-life, and poor assay sensitivity [7]. For absorption rate, plasma or serum maximum concentration (C_{max}) and the time to reach C_{max} (T_{max}) are the indicators [8, 9]. In addition, our discussion in this review is limited to food effect of orally administered drugs expected to exhibit systemic exposure and exert systemic effect.

2 Mechanisms for Food Effect

Food effect is the consequence of interactions between food and drugs under certain physiological conditions. Food may directly react with drugs or indirectly affect oral drug absorption by changing the postprandial gastrointestinal (GI) tract environment. Moreover, these interactions further depend on factors that are related to food categories, drug properties, and dosage regimens. Thus, a single food effect may have multiple underlying mechanisms (Table 1).

2.1 Food Categories

Before discussing food–drug interactions, it is important to consider food categories. Not unexpectedly, owing to the complex nature of meals (including volume, mixture of solids and liquids, pH, osmolality, temperature, and caloric content), different foods lead to disparate changes in luminal contents and therefore have distinct outcomes from food effect.

2.1.1 High-Fat Food

A high-fat high-calorie meal is recommended by the US Food and Drug Administration as the test meal in food effect studies [10] because it will exert the largest effects on GI physiology and therefore may have the greatest impact on drug absorption and disposition. In a high-fat high-calorie meal, fat contributes to approximately 50% of the meal's total caloric content. Generally, high-fat food can significantly retard gastric emptying compared with a low-fat diet [11]. For example, fenofibrate had a prolonged T_{max} when co-administered with a high-fat diet compared

Table 1 Mechanisms for food effect

Mechanisms	Examples
Food categories	
High-fat food	High-fat food can significantly retard gastric emptying
	High-fat food can increase the absorption of hydrophobic drugs through enhanced solubilization
	High-fat food can decrease hydrophilic drugs absorption via stimulating the formation of drug-bile micelles
	High-fat food can induce bile secretion, which can interfere with epithelial membranes to enhance paracellular drug transport
	High-fat food can stimulate the intestinal lymphatic transport pathway for fat-soluble drugs
	High-fat food can inhibit epithelial efflux transporters for increasing the bioavailability of their substrates
	High-fat food may induce diarrhea to reduce drug absorption
High-protein food	Degraded protein segments can inhibit intestinal amino/peptide transporters responsible for absorbing specific drugs
	High-protein food can stimulate intestinal transporter systems
	Protein intake can stimulate hepatic enzyme activity and thus increase the speed of drug elimination
	High-protein food may exert effects beyond the GI system, such as the BBB
High-fiber food	Fiber can adsorb postprandial secreted bile acid to reduce the bile solubilization effect
	Fiber undergoing fermentation can decrease metabolism in the intestinal cavity
Metal-rich food	Metal ions can form complexes with specific drugs
Purine-rich food	Purine intake can inhibit the intestinal CNT2 transporters responsible for absorbing purine-like drugs
High-carbohydrate food	Carbohydrates have distinguishingly different food effects that primarily delay gastric emptying
Direct food–drug reactions	
Physical reaction	Drugs can be adsorbed by dietary fiber
Chemical reaction	Quinolones, bisphosphonates, and tetracycline antibiotics can form precipitates when encountering metal cations
Postprandial digestive system physiology	
Increased viscosity in the GI tract	Food can increase intestinal lumen viscosity
Retarded gastric emptying	Food can retard gastric emptying
Altered pH in the GI tract	Food can elevate postprandial pH in the GI tract
Increased splanchnic blood flow	Food can enhance splanchnic blood flow
Stimulated bile secretion	High-fat food can stimulate bile secretion
Stimulated lymphatic transport	High-fat food can stimulate the intestinal lymphatic transport of lipophilic drugs
Affected intestinal flora	High-fiber food undergoing intestinal fermentation can compete with specific drugs for specific enzymes
Inhibited transporters and enzymes	Apple juice can inhibit OATP1A2 and grapefruit juice can inhibit CYP3A4
Drug characteristics	
Absorption	Retarded gastric emptying can promote absorption of drugs with a specific absorption window in the upper GI tract
Metabolism	Drugs with high intrinsic clearance have increased metabolism with higher blood flow
Distribution	Administered lipids may occupy plasma protein-binding sites for specific drugs, and lead to concentration fluctuations
Excretion	Different food categories may lead to varied urine pH, and thus affect the elimination rate
Dosage regimens	
Drug-to-food time interval	The time interval between drug and food is crucial for determining food effect
Dose	Drugs given at different doses react differently to food intake
Water volume	The volume of co-administered water influences the outcomes of food effect
Formulation	Drugs with different formulations have different responses after food intake

BBB blood–brain barrier, *CNT2* concentrative nucleoside transporter 2, *CYP* cytochrome P450, *GI* gastrointestinal, *OATP1A2* organic anion-transporting polypeptide 1A2

with a low-fat diet or in a fasting condition [12]. Fat content also affects absorption extent. For example, a full meal increased the bioavailability of itraconazole, a lipophilic drug, to a more significant extent than a light meal [13], which is presumably owing to enhanced solubility by fat. For lapatinib ditosylate, a low-fat breakfast increased its AUC 2.67-fold, while a high-fat breakfast increased its AUC 4.25-fold [14]. High-fat food can provide a lipophilic environment that enhances the solubilization of fat-soluble drugs. A similar example is gefitinib, an anti-cancer agent with a high log partition coefficient (Log*P*) around 4 [15]. However, there are also examples in which high-fat food leads to a substantial decrease in systemic exposure, for example, tacrolimus and indinavir [16, 17].

Bile secretion can be stimulated after a high-fat meal, where components, such as bile salts, form micelles to solubilize drugs, which is helpful for rapid dissolution [18]. Fat-induced bile secretion can elevate the surface-active bile salt concentration, which interferes with the epithelial membrane and changes its permeability, thus increasing paracellular transport inclination and absorption [19]. Nevertheless, the effect of bile may differ if micellar complexes are formed with drugs trapped inside, which would result in less free fraction and compromised absorption [20]; this effect is more evident for hydrophilic drugs than lipophilic drugs because bile micelles are amphiphilic [21]. The net result is a decreased absorption extent after the intake of fatty food, such as the cases of ambenonium [22] and atenolol [23], both of which are hydrophilic drugs.

In addition, high-fat food can also stimulate the intestinal lymphatic transport pathway [24], which facilitates the absorption of highly fat-soluble drugs into the systemic circulation via the lymph: acitretin [25] and retinoic acid [26] are examples. It is possible, yet uncommon, for lipids from high-fat food to inhibit epithelial efflux transporters, such as permeability-glycoprotein (P-gp) [27], blocking the export of drugs and thereby resulting in increased bioavailability. Interactions with P-gp may involve a transporter-enzyme interplay [28], especially when the drug is a transporter-enzyme dual substrate. Finally, high-fat food may induce emesis or diarrhea, which can lead to reduced drug absorption.

In summary, the effects of high-fat foods primarily include (1) delaying oral drug absorption through retarded gastric emptying, (2) enhancing absorption extent through the solubilization of lipophilic drugs, (3) stimulating bile secretion, which exerts a complex effect on oral drug absorption, (4) stimulating intestinal lymphatic drug absorption, (5) inhibiting epithelial transporters, which also results in a complex effect on oral drug absorption, and (6) causing GI tract irritations, such as diarrhea, which reduce oral drug absorption.

2.1.2 High-Protein Food

On the one hand, high-protein food can increase the splanchnic blood flow rate [29], and this increased blood flow usually favors drug absorption. On the other hand, high-protein food is digested into small peptides or amino acids whose absorption depends on intestinal peptide or amino acid uptake transporters; these products compete with peptide- or amino acid-like drugs for transporter-mediated absorption. For example, after the intake of a high-protein diet, uptake transporters, such as peptide transporter 1 (PepT1), which is responsible for carrying agents such as levodopa [30] and penicillamine [31], might be competitively inhibited because those drugs have similar structures to amino acids and short peptides. Similarly, absorption decreased for β-lactam drugs, such as cephalexin and cefadroxil [32], in in-situ perfusion experiments.

Interestingly, some investigators believe that the intake of high-protein food can stimulate up-regulation of the intestinal transporter systems, which may explain why gabapentin had an increased absorption extent after a high-protein meal [33]. In addition to transporter stimulation, high-protein food can simultaneously increase enzyme activity for metabolizing drugs and lead to increased intestinal metabolism for drugs, such as theophylline, which are substrates of these enzymes [34, 35].

Furthermore, consumed protein can exert effects beyond intestinal absorption. An intriguing example occurs when levodopa [30] was consumed with a low- or high-protein meal. Although there is no evidence to support that protein caused an impaired extent or rate of absorption, a beneficial response to a low-protein diet for treating Parkinson's disease was found, which might be attributed to reduced competition for levodopa transport across the blood–brain barrier. In addition, high-protein food can also influence urine flow during drug excretion, which, in turn, may affect the clearance of drugs and therefore disposition [36, 37].

In short, the effects of high-protein foods primarily include (1) increasing postprandial splanchnic blood flow to improve oral drug absorption, (2) competitively inhibiting uptake transporters after being digested into amino acids or short peptides, (3) stimulating up-regulation of the intestinal transporter system, (4) increasing drug-metabolizing enzyme activities, and (5) exerting effects beyond intestinal drug absorption.

2.1.3 High-Fiber Food

For humans, dietary fiber sources are fruits, vegetables, and grain products, which include several non-starch polysaccharide substances, such as cellulose, hemicellulose, and gums that have characteristic chemical structures and physical properties: (1) a large bulky volume, (2) viscosity,

(3) water-holding capacity, (4) adsorption, and (5) fermentation [38].

Although fibers are resistant to human digestive enzymes, high-fiber food can have a significant effect on drug absorption. As shown in both in-vitro and in-vivo studies [39], high-fiber food can adsorb postprandial secreted bile acid, which solubilizes lipophilic drugs and thus results in decreased absorption for lipophilic drugs. The highly lipophilic (Log$P > 5$) antiretroviral etravirine [40] demonstrated increased bioavailability after a high-fat meal. However, when taken after an enhanced-fiber breakfast, etravirine had decreased AUC and C_{max} compared with a standard light- or high-fat meal.

Although dietary fiber can prolong gastric emptying, high-fiber content further reduces the fluid volume available for drug dissolution in the upper GI tract and increases the viscosity of luminal contents, which can impede dissolution. Not coincidentally, a study that compared the effects of low- and high-fiber diets found that a higher content of dietary fiber increased the absorption rate of amoxicillin but decreased the amount of the drug that was absorbed [41]. A similar phenomenon is observed in metformin when it was administered with guar gum [42]. Adsorption to fiber may lead to decreased absorption, as in digoxin [43]. High-fiber food also undergoes fermentation in the GI tract by gut flora, and therefore, there is a reduction in drug-metabolizing activity by intestinal bacteria. This can affect drugs undergoing enterohepatic circulation and may lead to a reduced reabsorption percentage. In brief, a high-fiber diet has the following effects: (1) delaying gastric emptying, (2) reducing dissolution liquid volume, (3) decreasing free bile salts concentration, and (4) competing for gut flora fermentation.

2.1.4 Metal-Rich Food

Divalent metal ions, such as Ca^{2+}, Mg^{2+}, and Fe^{2+}, which are originated from dairy products [44], vegetables [45], and flesh foods [46], can form complexes with some drugs and then become either insoluble precipitates or soluble complexes, both of which are not absorbed. Examples include tetracycline antibiotics, such as tetracycline hydrochloride and minocycline hydrochloride [47], organophosphates such as risedronate [48], and quinolones, such as levofloxacin [49].

2.1.5 Purine-Rich Food

Foods such as organ meats, lentils, spinach, mushrooms, and especially seafood are infamous for their high-purine content [50]. Dietary purine nucleosides depend on active absorption by the intestinal concentrative nucleoside transporter 2 (CNT2) [51]. Drugs such as ribavirin [52], which have a purine-like structure, are also absorbed in the intestine by human CNT2. An in-vitro study found that the cellular uptake of ribavirin was strongly inhibited by purine nucleoside. A follow-up clinical trial investigating the effects of dietary purine on the pharmacokinetics of orally administered ribavirin [52] showed that after high-content purine intake, C_{max} and AUC were significantly lower than after a low-purine meal. This result is probably because dietary purines compete with ribavirin for absorption through CNT2, which indicates that dosage should be adjusted for patient groups that have a high-purine diet.

2.1.6 High-Carbohydrate Food

Dietary carbohydrates can be classified into monosaccharides, disaccharides, oligosaccharides, and polysaccharides that form three types of components: sugars, starches, and fiber, which undergo rapid, slow, or no digestion by pancreatic enzymes or colon fermentation depending on specific components and their physical size [53]. Owing to the complex nature of high-carbohydrate food, it has a less predictable effect on drug absorption compared with other food. For example, praziquantel [54], when taken with high-carbohydrate food, had an increased bioavailability compared with when it is consumed with a high-fat meal, although there is no clear reason for this phenomenon. Tacrolimus [16], when consumed with a high-carbohydrate meal, had an increased absorption rate compared with when it was consumed with a high-fat meal.

Despite specific responses to the different diets that were discussed above, some food–drug interactions may not be sensitive to food categories. Cefpodoxime proxetil [55] had almost the same food effects in response to normal, low-/high-protein, or low-/high-fat foods. Another example is cinacalcet [56], which had no different food effects when consumed with either a high- or a low-fat meal. Both diets prolonged T_{max} and increased AUC. An additional example is quazepam [57], which had no difference in response to low- or medium-high-fat meals. The food effects that were associated with darunavir [58] did not vary with meal type, namely, standard, high-fat, high-protein, and coffee. It is suggested that this lack of sensitivity to food types indicates that there is less of a burden for patients to choose the correct accompanying food category, which may lead to better compliance, even if there are significant food–drug interactions.

2.2 Physical and Chemical Reactions between Food and Drugs

The simplest forms of food effect are direct physical and chemical reactions between drug molecules and food constituents. When drugs are taken orally, there may be

reactions between food and drugs once they meet in the digestive tract. For chemical reactions, quinolones [59], bisphosphonates [48, 60], and tetracycline antibiotics [61] form precipitates or complexes with divalent metal cations, such as Fe^{2+}, which is abundant in meat [46] and Ca^{2+}, which is usually present in dairy products, such as milk, yoghurt, and cheese [44]. Adsorption of drugs to dietary fiber represents the physical reactions between drugs and food, of which digoxin is one example [62]. Under these circumstances, precipitates or adsorbed drugs cannot be absorbed, and there will be reductions in bioavailability.

2.3 Postprandial Digestive System Physiology

In addition to direct food–drug interactions, food intake leads to postprandial physiological changes, which then indirectly affect drug absorption.

2.3.1 Increased Viscosity in the Gastrointestinal Tract

After food intake, lumen viscosity often increases in the first instance. Water-sensitive magnetic resonance imaging that was conducted with healthy subjects in both fasting and fed conditions revealed that fluid volume in the small intestine can be reduced by 50% as a result of meal intake [63]. Viscosity in the GI tract significantly increases as a prominent postprandial change, which slows the diffusion of drugs towards the absorptive epithelium [64, 65]. For example, lenalidomide [66] had a 20% decreased absorption extent immediately after a high-fat high-calorie breakfast owing to, among other reasons, food acting as a physical barrier because of the resulting high viscosity restricting drug permeation to the absorptive membrane in the upper intestine.

2.3.2 Retarded Gastric Emptying

Drugs are stored in the stomach after oral administration. Few drugs are absorbed in the stomach [67]; most drugs have to be extruded out of the stomach and absorbed in the intestine. Previous research has shown that the stomach moves in a set pattern that consists of three phases [68] and that the intake of solid food often prolongs the gastric emptying time [69] until nutritional solids (and drug particles) are broken down into a particle size of 1–2 mm [70]. Therefore, for most drugs, food intake can delay absorption because of retarded gastric emptying and postponed intestinal absorption. For example, capecitabine [71] had a 1.5-h delay in T_{max} after food intake; duloxetine hydrochloride [72] had a T_{max} prolonged from 6 to 10 h when food was present in the GI tract; and when ketoprofen [73] was taken with food, T_{max} increased from 2.8 to 7.1 h. However, retarded gastric emptying rarely causes an altered absorption extent. In other words, although many drugs have delayed T_{max} after food intake, often there are no changes in the fed condition's AUC. Examples include reboxetine [74] and amoxicillin [75].

There are some circumstances in which retarded gastric emptying can alter the absorption extent. The next three cases illustrate this event. First, some drugs are acid-labile, such as erythromycin stearate and midazolam. A prolonged stay in the stomach decreased the absorption extent of erythromycin stearate [76], which is susceptible to acidic degradation. Midazolam [77] also experienced reduced absorption because it would become a polar, less permeable, primary amine in an open-ring form in an acidic pH (pH < 6). Second, for drugs whose absorption site is in the upper intestine and exhibit active and saturable transport absorption, retarded stomach emptying can increase absorption. An example is chlorothiazide [78]. When gastric emptying occurs quickly, the drug passes through the absorption window without absorption because the absorptive transporters are saturated. By slowing down the speed at which drugs present to the absorption window through lengthened gastric retention, lower drug concentration is available for absorptive transporters, and therefore, these transporters may no longer be saturated. Third, prolonged residence in the stomach that is caused by food can lead to better absorption in the intestine for pro-drugs, such as cefpodoxime proxetil, because longer retention there can enable optimal de-esterification to its active moiety (cefpodoxime) by esterases, which is more effective when pH is low [55]. In these ways, retarded gastric emptying may affect the absorption extent.

In clinical studies that investigate the effect of gastric emptying on oral drug absorption, paracetamol (also known as acetaminophen) is often used as a marker for gastric emptying time [79] because it is assumed to be absorbed not from the stomach but quickly and exclusively from the small intestine. Therefore, the time to the first appearance of paracetamol in the blood can be taken as the time required for transit through the stomach. In a food effect study, co-administration of an object drug with paracetamol, with or without food, can shed light on whether the observed food effect for the object drug is associated with gastric emptying time. For example, when diclofenac and paracetamol were taken simultaneously with or without food, there were changes in the PK parameters of diclofenac in a fed condition, while there were almost no changes in those of paracetamol. Therefore, it can be concluded that the food effect of diclofenac is not caused by delayed gastric emptying [80]. One study of danazol [79] investigated the food effect on its absolute bioavailability, together with gastric emptying time. Danazol had a slightly increased T_{max} when taken with a lipid-rich meal, and gastric emptying time indicated by the

appearance of paracetamol in the blood was significantly prolonged. Thus, food effect on danazol can only be partially explained by gastric emptying. Nonetheless, it is important to note that paracetamol can exert effects on drugs that are undergoing sulfation during first-pass metabolism because paracetamol can saturate the sulfation pathway; an example is its interaction with phenylephrine [81].

2.3.3 Altered pH in the Gastrointestinal Tract

The postprandial GI tract can have changes in pH. In a fasting condition, the median pH in the human stomach is 1.7, while in the fed condition, the gastric pH increases to a median value of 5.0 [82]. However, the duodenal pH only mildly changes, from 6.1 to 6.3 [82]. In summary, food intake generally increases pH in the GI tract. Because most drugs are absorbed through passive permeation [83], the optimal absorption occurs when they are in a permeable non-ionized form. Consequently, altered pH in the GI tract can account for a food effect of ionizable drugs: acidic, basic, or zwitterionic. For ionizable drugs, especially weakly acidic drugs, such as griseofulvin [84], food can enhance the dissolution rate from a solid formulation by increasing the gastric pH and thus lead to increased and faster absorption. For weakly basic drugs, an elevated postprandial pH can lead to a larger percentage of drugs in a unionized form, which is beneficial for passive transport through the intestine epithelial membranes and can facilitate absorption of drugs such as chloroquine [85], the ionization of which decreases when pH increases.

Notably, food effect that is due to an altered pH also depends on the structural stability of test drugs. For drugs that are unstable in an acidic environment, elevated pH prevents degradation in the GI tract and thus increases absorption. Examples include leucovorin [86], which is unstable when the pH is less than 2.8, and bromazepam [87], which decomposes in acidic solutions at 37 °C. In addition, there are several drugs that are unstable in alkaline environments; thus, an elevated pH can lead to degradation and impede absorption. For example, after food intake, poor penicillamine [31] absorption could be attributed to reduced stability at a higher pH.

2.3.4 Increased Splanchnic Blood Flow

Splanchnic blood flow is usually augmented after food intake to accelerate the absorption of nutrients [88]. When mesenteric blood flow rises [89], drugs are delivered to hepatocytes at a higher rate. For drugs that have a very high intrinsic clearance and therefore undergo extensive hepatic metabolism, for example, high extraction ratio drugs such as labetalol [90], propranolol [91, 92], and metoprolol [92], increased splanchnic blood flow can boost metabolism—especially when the corresponding enzymes are not easily saturated—because the metabolic rate of these drugs is proportional to blood perfusion. Therefore, food intake decreases the bioavailability of these drugs with a concurrent increase in the metabolites' AUC of drugs, such as midazolam [77] and nefazodone [93], both of which have an elimination half-life of 2 or 3 h [94, 95] or, in other words, rapid metabolism. For low extraction ratio drugs that have low intrinsic clearance or whose metabolic enzymes can be saturated at a low concentration, such as atorvastatin calcium [96], increased splanchnic blood flow has no influence on first-pass metabolism. Another possible scenario is that the corresponding metabolic enzymes are saturated by a higher substrate concentration that results from increased postprandial blood flow. Consequently, extraction ratios can be reduced, thereby increasing the absorption extent in the fed condition. For example, when propranolol [91] and metoprolol [97] were given in immediate-release formulations [92], there was postprandial enhancement in the absorption extent, which may be the result of enzyme saturation. This enhancement disappeared when they were given in a slow-release formulation, which is most likely owing to a lower sinusoidal concentration resulting from slow release in the intestine. Thus, the enzymes are not saturated despite increased postprandial splanchnic blood flow.

2.3.5 Stimulated Bile Secretion

Bile salts, which are secreted by the gallbladder into bile, are responsible for micelle formation in the digestive tract and the subsequent solubilization of mono-glycerides and fatty acids, which allows them to penetrate the intestinal mucosa [98]. It is well known that bile micelle can enhance the solubility of lipophilic compounds, but it has also been proposed that bile micelles can decrease effective permeability because they reduce the fraction of free drugs at the epithelial membrane surface [21].

Food intake can influence the concentration of bile micelle. Bile secretion can be stimulated by ingesting high-fat food [20]. For example, phenytoin [99] had a food-induced absorption acceleration, and one plausible explanation is that the food-induced secretion of bile could enhance the dissolution of phenytoin, which is fairly lipophilic (Log$P$ = 2.47). In contrast, if co-administered food is rich in fiber, bile can be adsorbed by the fiber, which reduces the amount of available bile and leads to a negative effect on phenytoin absorption. Another example is carbamazepine [100], which also had an increased absorption extent that is accounted for by solubilization by

bile secreted after a meal. In addition, carbamazepine undergoes extensive bile-mediated enterohepatic circulation, which is reflected in fluctuations in plasma levels.

2.3.6 Stimulated Lymphatic Transport

The partitioning of highly lipophilic drugs (Log$P > 5$) in the intestinal lumen into the lymph is an alternative absorption pathway into the blood that bypasses first-pass hepatic extraction [101]. Although absorption via the lymph is negligible for many drugs owing to the low flowing rate of lymph fluid, lymph flow can be increased through the intake of high-lipid food. The intestinal lymphatic transport of lipophilic drugs can be strategically enhanced through the formation of lipoproteins [102, 103]. For example, cyclosporine can be absorbed via the lymphatic system [104]. In one food effect study, cyclosporine, which was mixed with chocolate milk [105], had an increased absorption extent with the consumption of a high-fat meal. The researchers suggest that one possible mechanism for this increase is an elevated intestinal lymph flow by fat [106]. In fact, one of the reasons that long-chain triglycerides are used for self-emulsifying drug-delivery systems to load highly lipophilic drugs, such as cyclosporine (Neoral®), ritonavir (Norvir®), and saquinavir (Fortovase®), is that these lipids can enhance their absorption into lymphatic circulation [107]. Other plausible explanations include enhanced solubility and the inhibition of efflux transporters.

2.3.7 Affected Intestinal Flora

Enterohepatic circulation may be disrupted when intestinal flora is affected by food. The process of enterohepatic circulation typically consists of two stages: biliary excretion after hepatic conjugation and intestinal reabsorption after de-conjugation by intestinal microbial flora [108]. For drugs that undergo enterohepatic circulation, such as bromazepam [87] and piroxicam [109], it is necessary to have the intestinal microbial flora to reduce them to their original form to be reabsorbed because more hydrophilic conjugates are much less permeable. However, after food intake, sometimes, the metabolic function of the intestinal flora can be dented when high-fiber food is consumed because fibers are fermented by intestinal flora and therefore act as a competitor to drugs undergoing recycling [110]. As a result, if a drug requires intestinal flora to facilitate recirculation, the competition for intestinal flora that is caused by fiber may affect its systemic exposure, which is illustrated in the observation that a high-fiber diet is associated with diminished intestinal reabsorption of estrogen undergoing enterohepatic circulation [111].

2.3.8 Inhibited Transporters and Enzymes

In special cases, when drugs are administered with fruit juice instead of water, some components from the juice can inhibit the uptake transporters and enzymes that are responsible for drug disposition. For example, apple juice significantly reduced the systemic exposure of atenolol, which is a substrate for organic anion-transporting polypeptide 1A2 (OATP1A2) [112, 113]. In addition, grapefruit juice can inhibit OATP2B1 [113] as well as intestinal cytochrome P450 monooxygenase 3A4 (CYP3A4) [114]. Please see reference [114] for a detailed review on the effects of grapefruit juice.

2.4 Drug Characteristics that Influence Food Effect

In addition to physiological changes in the GI tract, the PK properties of drugs may also complicate the outcomes of food effect.

2.4.1 Absorption

During GI tract absorption, some drugs may show region-specific absorption [69] owing to differing solubility, permeability, and stability along the tract in which they experience changes in lumen pH, degradation by enzymes, and active transport. It is well known that pH varies along the intestine [98]. The absorption of drugs can also depend on intestinal enzymes, such as CYP3A4 and transporters, including PepT 1 and P-gp, which also have non-uniform expression levels on different segments [115, 116]. Therefore, oral drug absorption does not uniformly occur along the tract. For most drugs, there is an optimal region for absorption, which is called the 'absorption window.' For drugs such as chlorothiazide, which have an absorption window in the upper intestine that exhibits active or saturated transport absorption, retarded stomach emptying after food intake can actually promote absorption [78] because the limited absorptive efficiency as a result of saturation of absorption is ameliorated. In contrast, for drugs whose absorption is not dependent on a specific absorption window, retarded gastric emptying does not act as an enhancing factor. For example, one study on absorption in intestinal regions found that indomethacin had a similar absorption rate in both the large and small intestines, while paracetamol was absorbed more rapidly in the small intestine. Thus, food intake delayed the rate of indomethacin but did not change its absorption extent, while paracetamol suffered a reduced absorption extent [117, 118]. Other drugs that have a specific absorption window in the upper and lower GI tract include acyclovir, captopril, furosemide, metformin, gabapentin, levodopa, ciprofloxacin, ofloxacin, trospium chloride, and metoprolol

[119–126]. Notably, hydrophilic drugs often have a restricted absorption window in the upper GI tract, including the duodenum and proximal part of the jejunum.

2.4.2 Metabolism

When an orally administered drug is well absorbed in the intestine, hepatic first-pass metabolism is a primary factor in determining its bioavailability. Drug metabolism in the liver depends on the efficiency of removing drugs. The fraction of the presented drug being metabolized is known as the extraction ratio; the extraction ratio is further determined by two important parameters: fraction unbound and intrinsic clearance [127]. On the one hand, when a drug's intrinsic clearance is low compared with the liver's blood flow, its clearance by the liver is directly proportional to the degree of protein binding in the blood and the activity of its metabolizing enzymes, regardless of liver blood flow. Examples include theophylline [128], diazepam, antipyrine [129], and atorvastatin calcium [96]. Thus, even when there is enhanced postprandial blood flow, there is no reduction in the absorption extent. On the other hand, when the intrinsic clearance is much higher than the liver's blood flow, the liver can remove almost all the presented drug. Even protein-bound drugs can be stripped in one pass. In this circumstance, hepatic blood flow is the major determinant of systemic clearance. Consequently, increased postprandial splanchnic blood flow may lead to an increased metabolism extent and reduced bioavailability. However, there are cases, including propranolol and metoprolol [92], in which the corresponding enzymes are easily saturated. Thus, when blood flow increases, part of the hepatic metabolism can be circumvented, and absorption can be enhanced despite high clearance. Specifically, if a drug is susceptible to hepatic metabolism, yet relevant enzymes are not readily saturated, then food intake may decrease bioavailability during the postprandial period and increase the metabolite's AUC, which occurred in midazolam [77] and nefazodone [93].

2.4.3 Distribution

After a drug enters the body, distribution has an important role. Distribution is the reversible transfer of a drug between one compartment and another, which is primarily affected by plasma protein binding. The major drug-binding proteins in plasma are albumin, α1-acid glycoprotein, and lipoproteins. Albumin is responsible for binding long-chain fatty acids and acidic drugs, such as warfarin, phenylbutazone, diazepam, and ibuprofen [130]. α1-Acid glycoprotein is an acute-phase reactant with one binding site that is selective for basic drugs, such as verapamil, disopyramide, and propranolol [131]. Lipoproteins, which are responsible for carrying lipids, can also bind with some hydrophobic drugs, such as amiodarone, clozapine, and cyclosporine [132]. Hence, if a food component can bind to the same sites as the drugs, then they may be displaced from the binding site and have an altered PK property, such as fluctuations in the volume of distribution and bioavailability, which was observed in cyclosporine (in a well-dispersed chocolate emulsion) [133]. However, for most orally administered drugs, there appear to be few clinical effects of altered plasma protein binding [134].

2.4.4 Excretion

The final stage of disposition is excretion, which primarily includes bile and kidney excretion. Biliary secretion can be stimulated by high-fat meals, and therefore, bioavailability, as well as systemic exposure, can be reduced by food. The integrin very late antigen-4 antagonist HMR1031 [135] provides an interesting example. Formulated as a dry powder, HMR1031 is indicated for treating asthma and is administered by inhalation. However, disposition in the GI tract amounts to 75% of the administered dose, and oral absorption significantly contributes to plasma concentration. It was found that food significantly decreased both C_{max} and AUC, which was apparently owing to both increased liver blood flow and biliary excretion. In urinary excretion, low-sodium diets can lead to less excretion and increased lithium toxicity [136], which is reabsorbed with sodium. For some acidic or basic drugs that rely on tubular reabsorption through a passive permeation mechanism, reabsorption and bioavailability can be affected if the consumed food changes the urine's pH. For example, high-protein food tends to make urine more acidic, while high-carbohydrate food tends to make urine more basic [137]. Consequently, if urine is acidic, then weakly acidic drugs tend to be more easily reabsorbed, while weak bases tend to be reabsorbed better when urine is alkaline. Therefore, manipulating urine's pH can be used to adjust the total systemic exposure for re-absorbable ionizable drugs [138]. Because systemic exposure is determined by both bioavailability and clearance, a food effect may manifest in both absorption and elimination.

2.5 Drug Dosage Regimens

The drug dosage regimen refers to the method of administering drugs, including the formulation, route of administration, dose strength, and dosing time [139]. Across different clinical studies on food effect, varied regimens have been implemented, and these have constituted a source of variation in food effect.

2.5.1 Drug-to-Food Time Interval

When reviewing food effect, the time interval between administration of a drug and intake of food is often overlooked. Notably, a drug can be taken with different timing relative to the intake of a meal. For example, bevantolol [140] was investigated for its food effect on bioavailability under fasting conditions, shortly before, and after a standard breakfast. When bevantolol was administered in the absence of food or 15 min before breakfast, absorption was rapid, as comparative C_{max} was observed within 1 h. However, T_{max} significantly increased when bevantolol was taken 15 min after the meal compared with a fasting condition. These results show that the difference between the presence and absence of the food effect can be due to the timing of a dose as little as 15 min before or after a meal. Another example is esomeprazole [141]. In one clinical study, test subjects received esomeprazole 15 min before a high-fat meal and 4 h before (fasting) a non-high-fat meal. The results showed that when taken 15 min earlier, food impaired the systemic exposure of esomeprazole as a result of the retarded gastric emptying caused by food. Because esomeprazole is acid-labile, a prolonged stay in the stomach leads to more degradation. This also verifies that a 15-min interval can be enough to cause a food effect.

Meanwhile, a study on the food effect of quazepam [57] had nine healthy male volunteers take a single oral 20-mg dose of quazepam in a fasting condition, 30 min or 3 h after a standard meal. For the food treatments at 30 min and 3 h before dosing, both C_{max} and AUC increased compared with the fasting condition. Interestingly, there was no difference for any of the PK parameters between these two treatments, which indicates that the food effect may persist for up to 3 h. A study on the food effect of midazolam [77] that gave a single dose of 15 mg of midazolam to test subjects 1 h before, with food (0 h), and 1 h after a standard meal, as well as in a fasting condition, found no significant changes in the PK parameters AUC, T_{max}, or C_{max} when midazolam was taken 1 h before or with a meal compared with the fasting condition. However, when midazolam was ingested 1 h after a meal, there were significant changes in C_{max}, T_{max}, and AUC for both midazolam and its metabolite. Another study on risedronate [142] was conducted in healthy volunteers with different meal timings: namely fasting, 1 h before, 0.5 h before, and 2 h after a standard dinner. The extent of risedronate absorption was similar in subjects who were dosed 2 h after and 0.5 h before eating. Nonetheless, a significantly greater extent of absorption occurred when it was given in the fasting condition and 1 h prior to a meal. Administration 0.5, 1, and 4 h prior to a meal resulted in a significantly greater rate of absorption, with C_{max} respectively, 2.8-, 3.5-, and 4.1-fold greater than administration 2 h after dinner.

In summary, administering drugs 1 h before or within 3 h after a meal can lead to a food effect. However, if the food effect is small in the first place, the effect of the time interval between the food and drug can even be negligible. This is the case with ciprofloxacin [143]. When given as an oral 750-mg dose immediately or 2 h after a standard breakfast, its PK parameters remained unchanged compared with a fasting condition. The resistance of ciprofloxacin to a food effect is reflected in the absence of a food effect even when it was co-administered with a high-fat high-calcium meal [143].

2.5.2 Dose

Dose is another important factor for food effect. In a study of a food effect on ketoconazole [144], a broad range of doses (namely, 200, 400, 600, and 800 mg) were given to test subjects in both a fasting and a fed condition. The results showed that at 400 and 600 mg, food appeared to enhance absorption. However, this effect disappeared at 800 mg. The disappearance of the food effect at 800 mg may be explained by the limited solubility of ketoconazole. When a sufficiently large dose is given to attain the solubility limit, there is no difference whether enhanced solubilization or dissolution exists. Another example is aprepitant [145], which is a substrate and inhibitor of CYP3A4, for which the food effect differs when it was dosed at 80 and 125 mg. When dosed at 125 mg, the intake of a high-fat meal caused a 20% increase in the systemic exposure of aprepitant, while there was only a 9% increase in AUC when aprepitant was dosed at 80 mg. This disproportionate food effect can be attributed to the saturation of metabolism by CYP3A4 at the higher dose, which suggests that dose strength can influence food effect outcomes.

2.5.3 Water Volume

The co-administered water volume is an indispensable factor for the food effect of some poorly soluble drugs. According to the US Food and Drug Administration guidance, subjects should be administered drug products with 240 mL of water [10]. However, in actual food effect studies, water volume intake varies from study to study (ESM), which can influence outcomes of food effect. For example, both mefenamic acid, an anti-inflammatory analgesic, and danazol, an anabolic steroid, are lipophilic poorly soluble drugs that have enhanced solubilization by food intake. In one study, mefenamic acid [146] was administered in capsule form to patients under fasting and

fed conditions with 50 mL of water. The results showed that when taken with 50 mL of water immediately after ingesting a standard breakfast, the bioavailability of mefenamic acid did not change compared with that in subjects in a fasting condition. Nonetheless, when danazol [79] was administered with a high-lipid meal and 200 mL of water, its bioavailability increased from 11 to 44%. These different responses can be explained by the difference in water volume. In the danazol study, there was a sufficient amount of water. However, in the mefenamic acid study, owing to the limited amount of water that was available in the GI tract, the total amount actually solubilized is limited. In summary, for food effect in low-solubility drugs, co-administered water volume can be an important factor because the prerequisite for enhanced solubilization is that there should be enough water to act as a dissolving medium.

2.5.4 Formulation

A proper formulation sometimes helps a drug avoid a food effect. Ciprofloxacin, formulated as a suspension in a 500-mg dose, was given to test subjects under fasting and fed conditions. The study's outcomes showed that food did not alter its bioavailability [147]. Hydralazine hydrochloride [148], when formulated in two different preparations: Apresoline ® and sustained-release hydralazine had different food effect results, although the C_{max} of both preparations decreased after food intake, T_{max} was delayed in sustained-release hydralazine but did not significantly change in Apresoline, and the AUC was reduced by 44% in Apresoline but was not significantly altered in sustained-release hydralazine. This might be explained by the dissolution profiles of these two different formulations. For methylphenidate [149], when it was administered in immediate- and sustained-release formulations to investigate a food effect, there was a comparable increase in C_{max} and AUC with food, while the T_{max} of the immediate-release formulation was significantly prolonged and there was no effect on the sustained-release formulation.

Particle size might be another determining factor of food effect. When indomethacin, prepared in capsules with two different particle sizes, was administered to test subjects under fasting and fed conditions, AUC and C_{max} of both formulations were not statistically significantly altered. The T_{max} of indomethacin administered in a larger particle size was significantly prolonged, whereas the drug administered in a fine particle size remained unaffected after food intake [118]. Likewise, griseofulvin [84] had a higher peak serum concentration after food intake when formulated as a polyethylene glycol, ultra-microsize tablet than it did as a commercial microsize product. However, in the fasting condition, the microsize product showed higher serum concentrations than the ultra-microsize with a comparative AUC. In-vitro tests showed that an ultra-microsize formulation may produce larger particles or agglomerates when disintegrating in the fasting condition; but in the presence of food, further disintegration and de-aggregation of those particles can be accelerated. An interaction between food and formulation effect can therefore be observed. In addition, single- vs. multiple-unit dosing may also make a difference [150] because the transit of multiple-unit pellets is significantly slower than that of single-unit tablets because of the smaller size [151].

Different formulations generate specific dissolution profiles, whereas components in food participate in the dissolution process, diminishing or exaggerating the formulation effect even more. For instance, fat in food negated dissolution differences of nitrofurantoin from two formulations [152]. Another case is oxycodone [153], a strong opioid agonist. When formulated as an immediate-release solution, its AUC was increased and C_{max} was decreased by food; on the contrary, when formulated as a controlled-release tablet, no food effect was observed. Nevertheless, a modified-release form does not guarantee a drug devoid of food effect. For example, buflomedil hydrochloride, even if formulated in a controlled-release form, still had a statistically significant food effect [154]. Diltiazem showed no sensitivity to food effect regardless of formulation as a conventional or slow-release tablet [155].

3 Food Effect of Clinical Significance

3.1 Consequences of Food Effect

Food intake can alter absorption rates or absorption extents of many drugs, and some of them are clinically insignificant for patients. Taking abacavir sulfate [156] as an example, food statistically significantly prolonged T_{max}, but did not affect efficacy because food only delayed the onset of its anti-human immunodeficiency virus activity, which is less of an issue in long-term dosing. Meanwhile, even though the absorption extent in some drugs might be decreased by food, their clinical efficacies are retained. For instance, food decreased cilazapril [157] AUC significantly, but only by 14%, thus it is believed to be of little clinical consequence. Upon administration of roxithromycin [158], an antimicrobial agent whose efficacy is dependent on both concentration and time [159], overall plasma concentration declined after food intake but was still higher than the minimum inhibitory concentration,

maintaining therapeutic efficacy. Furthermore, for drugs such as tolterodine [160], while bioavailability increased significantly after food intake, therapeutic efficacy remained the same because the metabolite is the active moiety and is free of a food effect, meaning effective exposure is unchanged. In contrast, if a drug's metabolite is toxic, such as that of oral idarubicin, the food effect in metabolism should be noted because of possible consequences of clinical relevance [161].

3.1.1 Food Effect to be Avoided

Undesirable food effects on the extent or rate of absorption occur in two primary areas: (1) increased toxicity owing to a higher peak concentration or exaggerated exposure, and (2) diminished therapeutic efficacy owing to a lower peak concentration or insufficient exposure. These food effects should be avoided, and the drugs should not be administered with food or therapeutic effects can be suboptimal. Hydrocortisone [162] had delayed absorption in the non-fasting compared with the fasting conditions, with reduced C_{max} and prolonged T_{max}. Hence, to optimize the consistency of patient responses to oral hydrocortisone therapy, this drug should be routinely administered on a fasting stomach, early in the morning before breakfast, to simulate the physiological cortisol peak. The bioavailability of trospium chloride [163] significantly decreased with concomitant food ingestion. Consequently, it should be administered before meals or on an empty stomach. Phenytoin sodium [99], which is an anticonvulsant drug that has a narrow therapeutic window, had an enhanced absorption when taken with a standardized breakfast. Therefore, to avoid fluctuations in the plasma phenytoin concentrations and related toxic effects, it should always be taken in combination with meals.

3.1.2 Food Effect to be Exploited

Food effect can also be exploited to produce desirable after-effects. One of the most desirable effects is more consistent bioavailability when given with food, and an example is rivaroxaban. Food may improve the efficiency of oral absorption, as well as reduced inter- and intra-individual variability at the same time. At a 20-mg dose of rivaroxaban, food intake increased both AUC_{∞} and C_{max}, while decreasing their coefficient of variation, which indicates that rivaroxaban has higher and more consistent bioavailability and should be taken with food [164].

In other cases, co-administration with food enhances drug exposure. When taken with food, T_{max} delayed by 1.5 h, C_{max} decreased by 30%, and AUC increased by 30% for administered rivastigmine [165]. Hence, it is recommended that rivastigmine be co-administered with meals for an attenuated peak plasma concentration, which is related to potential adverse effects. When administered with a high-fat meal, misoprostol [166] had a marked decrement in its absorption rate, hence, postprandial administration of misoprostol can potentially weaken its side effects while maintaining desirable local effects on the mucosa considering that its actual active moiety, misoprostol acid [167], is associated with unwanted systemic side effects, such as diarrhea. Amiodarone hydrochloride [168], when taken with a high-fat breakfast, exhibited a significantly faster absorption rate, with T_{max} changes from 7.1 to 4.5 h, and an increased extent of absorption, with AUC increasing by a factor of 1.4. Thus, it is advised that amiodarone be consistently taken with meals. Atazanavir sulfate [169] must be taken with food because administration with a high-fat meal increases its AUC by 70% and reduces inter-patient PK variability by 43% when compared with fasting levels. Administering mefloquine [170] in the presence of a high-fat meal led to an elevated rate and extent of absorption. Thus, mefloquine should be administered to patients with malaria with or as shortly as possible after a meal to maximize therapeutic efficacy. The same is recommended for other anti-malaria agents, such as chloroquine [85] and atovaquone [171].

Sometimes, a food effect is needed based on pharmacodynamic considerations: taking the drug with food reduces its unwanted effects. For digoxin [172], a swift absorption rate in a fasting condition may result in nausea; thus, a food effect of delayed absorption can have clinical benefits. A similar case is carvedilol [173]; being taken with food reduced its absorption rate and therefore prevents orthostatic effects. Some drugs, such as aspirin, metformin, and sulpiride, should be taken with food to minimize irritation to the GI tract [174, 175]. These cases illustrate that food effect can potentially be exploited for maximum clinical benefits, and careful consideration should be given when recommending whether medications be taken with or without food.

3.2 Considerations for Clinically Significant Food Effect

Although many drugs have demonstrated a statistically significant food effect, only a few have demonstrated significant clinical relevance (Table 2). This section lists several factors to consider when speculating whether there may be a clinically significant food effect.

3.2.1 Drug Systemic Exposure Concerns

When the average drug concentration is related to therapeutic efficacy, it is often believed that the food effect is not clinically significant if there is no change in the extent of absorption. However, there are exceptions where the

Table 2 Drugs with clinically significant food effect

Therapeutic class	Drugs	Class	Route	Recommendations regarding food intake	References	Level[b]
Anthelmintic	Albendazole[a]	II	p.o.	Take each dose of albendazole with a meal; otherwise inadequate blood concentrations and reduced effectiveness	[191]	II-1
Antiarrhythmic agent	Amiodarone hydrochloride[a]	II	i.v./p.o.	Amiodarone may be taken with or without food but should be taken the same way each time	[168]	I
	Digoxin	III	i.v./p.o.	Minor but administration of digoxin immediately after food may prevent nausea	[172]	I
Antibiotic	Ampicillin[a]	III	p.o./i.v.	Ampicillin should be administered 1 h before or 2 h after meals	[75]	I
	Cefpodoxime proxetil[a]	II	p.o.	Take cefpodoxime tablets with food to increase absorption by the body	[55]	I
	Erythromycin stearate[a]	IV	p.o./i.v.	Take erythromycin on an empty stomach at least 30 min before or 2 h after a meal	[76]	II-1
	Metronidazole	I	p.o./i.v.	Administer it with food to ensure a local gastric effect	[176]	I
	Norfloxacin[a]	IV	p.o.	Take norfloxacin on an empty stomach at least 1 h before or 2 h after eating a meal or consuming dairy products	[192]	II-1
	Rifampin	II	p.o./i.v.	Give rifampin on an empty stomach whenever possible	[193]	I
	Tetracycline hydrochloride[a]	III	p.o.	Avoid iron supplements, multivitamins, calcium supplements, or any dairy products within 2 h before or after taking it	[47]	II-1
Anticancer agent	Capecitabine[a]	I	p.o.	Capecitabine should be taken with food or within 30 min after eating a meal	[71]	I
	Erlotinib hydrochloride[a]	II	p.o.	Erlotinib should be taken on an empty stomach 1 h before or 2 h after a meal	[194]	I
	Lapatinib ditosylate	II	p.o.	Take lapatinib on an empty stomach 1 h before or 1 h after a meal	[14]	I
	Melphalan	I	p.o./i.v.	To ensure optimum absorption of the drug, melphalan should not be taken with food	[195]	I
	Nelfinavir	II	p.o.	Recommended to be taken with food to ensure enough effective exposure	[196]	I
	Rufinamide[a]	II	p.o.	To ensure maximal oral absorption, rufinamide should be administered with or immediately after a meal	[197]	I
Antifungal agent	Posaconazole[a]	II	p.o./i.v.	Take the tablet with food and the oral suspension during or immediately (within 20 min) after a full meal	[198]	I
	Voriconazole[a]	II	p.o./i.v.	Take voriconazole on an empty stomach 1 h before or 2 h after a meal	[199]	I
Anti-malaria agent	Mefloquine[a]	II	p.o.	Food can enhance the concentrations of mefloquine in your body; take mefloquine immediately after a meal	[170]	I
	Primaquine	I	p.o.	Recommended to be taken with food to enhance bioavailability while minimizing GI disturbances	[200]	I
Antimuscarinic agent	Trospium chloride[a]	III	p.o.	Trospium should be taken on an empty stomach 1 h before or 2 h after a meal	[163]	III
Antiparkinsonian agent	Levodopa[a]	I	p.o.	Taken with high-protein food may cause an increased risk of certain side effects	[30]	I
Antiviral agent	Atazanavir sulfate	II	p.o.	Administration with food can increase bioavailability and reduce interpatient PK variability	[169]	II-1
	Darunavir[a]	II	p.o.	Take darunavir with food; the type of food does not matter	[58]	I
	Didanosine[a]	III	p.o.	Take didanosine on an empty stomach at least 30 min before or 2 h after a meal	[201]	II-1
	Entecavir[a]	III	p.o.	Take entecavir on an empty stomach 2 h before or 2 h after a meal	[202]	I
	Etravirine[a]	II	p.o.	Etravirine should always be administered following a meal. Food enhances etravirine concentrations in your body	[40]	I

Table 2 continued

Therapeutic class	Drugs	Class	Route	Recommendations regarding food intake	References	Level[b]
Bisphosphonates	Risedronate[a]	III	p.o.	Take risedronate at least 30 min before eating with a full glass (6–8 ounces) of plain water	[60]	I
Calcimimetic agent	Cinacalcet[a]	II	p.o.	Cinacalcet should be taken just after eating food. Do not take it on an empty stomach	[56]	I
Cholinesterase inhibitor	Rivastigmine	I	p.o./TD	Rivastigmine should be administered after meals owing to lowered peak drug concentrations and potential adverse events by food	[165]	III
	Tacrine	I	p.o.	Decreased systemic exposure and attenuated side effects by food should be weighed on whether to take it with food	[203]	I
Hypoglycemic agent	Glipizide	II	p.o.	Administration 0.5 h before a meal yields more optimal insulin release and better glucose disposition	[204]	II-1
	Metformin	III	p.o.	Recommended to be taken with meals to reduce GI side effects	[175]	I
Immunosuppressant	Cyclosporine (Sandimmune®)[a]	II	p.o./i.v.	Take cyclosporine on a consistent schedule with regard to time of day and relation to meals	[205]	I
	Everolimus[a]	I	p.o.	Consistent administration with regard to meals with a full glass of water is recommended	[206]	I
	Sirolimus[a]	I	p.o.	Take sirolimus at least 1 h before eating or take it each time with food to avoid changes in sirolimus concentrations	[184]	I
	Tacrolimus[a]	II	p.o.	Tacrolimus should be taken on a consistent schedule before or after eating at the same times each day	[16]	I
NSAID	Tenoxicam	I	p.o./i.v.	Concurrent food may contribute to the control of GI symptoms	[207]	I
Platelet aggregation inhibitor	Ticlopidine[a]	I	p.o.	Food can enhance the concentrations of ticlopidine in the body. Take with food to lessen stomach upset	[208]	I
Prostaglandin	Misoprostol	I	p.o.	Administration with food could decrease systemic side effects incidence by reducing C_{max} of misoprostol acid	[166]	I
Proton pump inhibitors	Lansoprazole	II	p.o./i.v.	Must be taken on an empty stomach to avoid significantly decreased bioavailability	[209]	I
Renin inhibitor	Aliskiren[a]	I	p.o.	Consistent administration with regard to meals is recommended	[210]	I
Retinoid	Acitretin[a]	II	p.o./top.	Take acitretin with food	[25]	I
Tuberculosis cure	Isoniazid[a]	I	i.m./p.o.	Take isoniazid on an empty stomach at least 1 h before or 2 h after a meal	[211]	I
Vasodilator	Cilostazol[a]	II	p.o.	Take cilostazol on an empty stomach 1 h before or 2 h after a meal	[212]	I

C_{max} maximum blood/plasma/serum/urine concentration, *GI* gastrointestinal, *i.v.* intravenous, *NSAID* non-steroidal anti-inflammatory drug, *PK* pharmacokinetic, *p.o.* oral, *TD* transdermal, *top.* topical

[a] Including information cited from http://www.drugs.com/

[b] Level of evidence (Wikipedia): I: obtained from at least one properly designed randomized controlled trial; II-1: obtained from well-designed controlled trials without randomization; II-2: obtained from well-designed cohort or case–control analytic studies, preferably from more than one center or research group; II-3: obtained from multiple time series designs with or without the intervention; III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

altered absorption rate alone, either delayed absorption, such as in hydrocortisone [162] and misoprostol [166], or accelerated absorption, such as in carvedilol [173], may have significant clinical consequences. Likewise, it may be strongly recommended that a drug be taken with food, despite the meal decreasing the AUC, such as in levodopa [30], which is recommended to be taken with low-protein food because it can reduce competition for levodopa across the blood–brain barrier. Sometimes, a reduced absorption extent may be beneficial for local action. For example, bismuth biskalcitrate, metronidazole, and tetracycline had an almost 90% eradication rate of *Helicobacter pylori* when administered with food [176]. Finally, the statistical significance of a food effect does not always imply a practical or clinical difference. Tolterodine [160] is an example, as its postprandial active metabolite exposure

remained unchanged even though the parent form had a significantly increased AUC after food intake with oral clearance increased as well.

3.2.2 Drugs with Narrow Therapeutic Windows

The therapeutic window of a drug refers to the concentration range of its active form in a bodily system that yields safe and effective therapy. When the therapeutic window is narrow, it is especially susceptible to a clinically significant food effect. Theophylline, which is a bronchodilator for patients who have chronic obstructive lung disease, has a rather narrow therapeutic range [177]. When administered as a solution of choline theophyllinate with concomitant food intake, absorption was significantly slowed, with a lower peak concentration and a prolonged plateau, which might lead to prolonged therapeutic action with fewer side effects. Thus, it is advised that the drug be taken with or shortly after a meal. Digoxin, a cardiac glycoside, also has a narrow therapeutic window that ranges between 0.5 and 1.0 ng/mL for patients who have heart failure [178, 179]. The absorption rate of digoxin, as indicated by C_{max}, decreased in the case of prior food ingestion and this effect was amplified when food was consumed immediately after digoxin tablets compared with food consumed 1.5 h before drug administration [172]. The total amount absorbed did not change in the postprandial state, which is associated with the cardiac effects of digoxin. Nevertheless, it is probable that rapid absorption of single-dose digoxin and, consequently, a higher peak plasma concentration is related to the nausea that is experienced by some patients. Hence, for these patients, it may be important to administer digoxin immediately after food.

3.2.3 Inter- and Intra-Individual Variability

Variability is a vital feature for developing safe and efficacious dosing [180]. Food effect may reduce or exacerbate the variability in drug absorption. When a drug has high variability, especially with a relatively low therapeutic index, there is a higher risk of both sub-therapeutic and/or toxic exposure [180]. Several drugs, in addition to rivaroxaban, had altered variability with food intake. Mebendazole [181], an anti-helmintic agent effective against a broad range of human GI helminth pathogens, has substantial intra- and inter-individual variation in its plasma concentrations, yet the concomitant intake of food lessened the variation. However, tretinoin is an oxidative product in the physiological pathway of retinol metabolism [182]. In one study, the oral absorption of all-*trans* retinoid acid was highly variable among patients, which indicates the need for PK drug monitoring [183]. When taken with food, it has enlarged intra- and inter-individual variation despite improved oral absorption efficiency.

Intriguingly, for some drugs that have large inter-individual variability, the variation from food intake may be trivial, as with sirolimus [184] and oxybutynin [185]. There was a 35% increase in the AUC of sirolimus after a high-fat meal, which is comparatively small relative to its inter-individual variability in clearance. Similarly, there was a 20% increase in the AUC of the oxybutynin active metabolite, *N*-desethyloxybutynin, which is of limited clinical significance because it is within the normal range of inter-individual variability. In this case, one may conclude that variability in the drug absorption and disposition is much larger than the variation that is caused by food, and therefore, the food effect appears insignificant. Overall, it is advised that these drugs be taken consistently, either with or without food, in individual patients to minimize unnecessary fluctuations.

3.2.4 Indications and Expected Effects of Drugs

For drugs aimed at causing a rapid onset of effects for treating acute diseases, delayed absorption by food intake can be clinically undesirable because the drugs should exert pharmacological effects as soon as possible after administration. Ketoprofen [186], a non-steroidal anti-inflammatory drug, is usually given in multiple doses and with food to counter its undesirable GI side effects. Therefore, its decreased C_{max} and prolonged T_{max} from food is generally considered of no clinical importance because the AUC of ketoprofen can remain constant. However, if a rapid onset of analgesia is desired, co-administration with a gastroprotective agent may be an alternative to food. In addition, glibornuride [187], a sulfonylurea, should also be taken before meals to exert a timely hypoglycemic effect.

In addition, because food intake sometimes results in unpredictable effects on systemic exposure, consistent administration with meals is recommended to ensure compliance. For example, absorbing hydrocortisone [162] was delayed in a non-fasting situation. C_{max} significantly decreased and T_{max} significantly increased when hydrocortisone was ingested after food. Thus, it is important to note that compliance with oral hydrocortisone therapy should include taking this drug routinely on an empty stomach. Occasionally, a drug is not used alone but in combination with other agents. Leucovorin [86] is usually co-administered with UFT, which is a mixture of tegafur, a pro-drug of 5-fluorouacil, and uracil, and was developed for the first-line oral treatment of metastatic colorectal cancer. When this combination of drugs was taken immediately after a high-fat meal, the AUC of leucovorin and its active metabolite increased but the AUC for uracil and

5-fluorouacil decreased by 37–76%. Given the efficacy of 5-fluorouacil vs. the increased absorption extent of leucovorin, it is recommended that this combination should not be simultaneously taken with food.

4 Biopharmaceutics Drug Disposition Classification System (BDDCS) and Food Effect

4.1 BDDCS

The BDDCS was developed by Wu and Benet [188]. Unlike the previous Biopharmaceutics Classification System (BCS) [189], the BDDCS replaces the permeability criteria with the metabolism extent. Similar to BCS, in BDDCS, a drug is considered 'highly soluble' when the highest dose strength is soluble in 250 mL or less of aqueous media over a pH range of 1–7.5 at 37 °C [188]. In addition, the definition of 'extensive metabolism' reflects more than 70% metabolism extent of an oral dose in vivo in humans, while 'poor metabolism' is defined as when more than 50% of the dose is excreted unchanged. Because a drug must permeate inside a cell to be metabolized, there is a correlation between the metabolism extent and human intestinal permeability [5], which indicates that BDDCS Class I and Class II drugs usually have high permeability, while Class III and Class IV drugs have low permeability.

4.2 BDDCS and Food Effect

Previous research found that BDDCS can predict food effect [27]. In this review, we examined food effect studies (ESM) of high-fat food and standard meals. The indicators for the absorption rate are T_{max} and C_{max}, while AUC and bioavailability are measures of the extent of absorption (Fig. 1). For example, if T_{max} is increased and C_{max} is decreased, there is a delayed absorption rate; however, a similar magnitude of change on both C_{max} and AUC with an unaffected T_{max} only indicates that there is an altered extent of absorption. When a change on C_{max} is far more or less than that on AUC (beyond the range of 0.8–1.25), the absorption rate is viewed as altered [190].

Our search resulted in food effect studies for 229 drugs that have classified food effects. Tables 3 and 4 summarize the results, which include 75 Class I, 86 Class II, 56 Class III, and 12 Class IV drugs (Fig. 2). Moreover, the association between BDDCS classes and food effect categories was analyzed with chi-square tests. For both absorption rate and absorption extent, BDDCS classification is significantly associated with their changes in them ($p = 1.194 \times 10^{-2}$ and $p = 2.231 \times 10^{-5}$, respectively).

The BDDCS Class I drugs that are soluble and non-polar can easily move across the intestinal barrier regardless of being substrates for influx or efflux transporters in the gut. Research has shown that an intake of fatty meals does not have a significant effect on bioavailability for Class I drugs because their absorption occurs through passive diffusion and there should be no transporter–drug interactions [27]. However, an intake of high-fat meals can delay stomach emptying and will usually cause an increase in peak time. The absorption of Class I drugs is the least to be affected by high-fat meals.

The BDDCS Class II drugs that have a significant food effect are more likely to have an increased absorption extent with high-fat meals. Food effect studies from the literature appear to provide two mechanistic explanations. First, co-administered fat can enhance solubilization for poorly soluble Class II drugs; second, fat may also reduce access to drug-metabolizing enzymes owing to limited drug cycling by inhibition efflux transporters [27], which results in decreased intestinal metabolism and higher bioavailability. As a result of high permeability, they can easily access the intestinal membranes without the assistance of uptake transporters. Nevertheless, their concentration is limited by their low solubility, which suggests that they have a low concentration gradient across intestinal epithelial cells. Enhanced solubilization increases luminal concentration and therefore facilitates absorption. However, cellular drug concentrations may not be high enough to saturate efflux transporters such as P-gp, or intestinal enzymes such as CYP3A4. As a result, functional changes, including induction or inhibition in efflux transporters and intestinal enzymes, can significantly affect Class II drugs absorption. High-fat meals will increase the bioavailability of Class II drugs, which may be due to the inhibition of efflux transporters and the related interplay between transporters and enzymes [27]. However, as with all other drugs, when there is delayed gastric emptying, there may be a prolonged time to peak.

The BDDCS Class III drugs are more likely to have a decreased AUC when taken with high-fat meals because fat might inhibit intestinal uptake transporters that mediate the absorption of these poorly permeable drugs. Owing to their high solubility, a sufficient amount of drugs would be available in the intestinal tract; however, influx transporters will be needed to overcome the poor permeability characteristics of these drugs. Because their absorption is limited by influx transporters, the cellular drug concentration may not be sufficient for saturating efflux transporters and thus the effects of efflux transporters cannot be neglected. Class III drugs should have a lower extent of availability with high-fat meals owing to the inhibition of intestinal influx transporters, such as OATPs. It is further suggested that the high-fat food effect on Class III drugs should be balanced by effects on both the influx and the counteracting efflux transporters, which can explain the increase or no

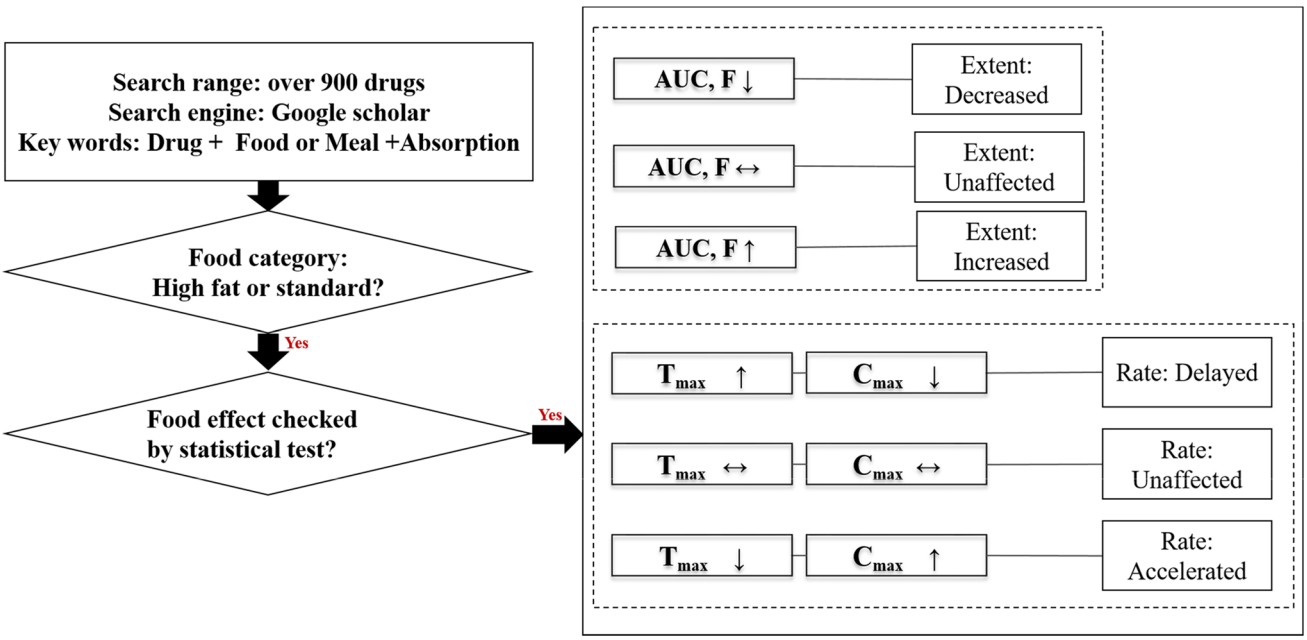

Fig. 1 Decision tree to classify food effect categories. *AUC* area under the concentration–time curve, C_{max} maximum blood/plasma/serum/urine concentration, *F* oral bioavailability, T_{max} time to reach C_{max}

Table 3 Effect of high-fat food/standard meals on the absorption rate

BDDCS class	Delayed absorption	Unaffected absorption	Accelerated absorption
I	33	39	3
II	36	31	19
III	29	21	6
IV	8	3	1

Chi-square test is used to test the association between BDDCS class and food effect; p value $= 1.194 \times 10^{-2}$

BDDCS Biopharmaceutics Drug Disposition Classification System

Table 4 Effect of high-fat food/standard meals on the absorption extent

BDDCS class	Decreased absorption	Unaffected absorption	Increased absorption
I	13	49	13
II	10	42	34
III	17	33	6
IV	6	6	0

Chi-square test is used to test the association between BDDCS class and food effect; p value $= 2.231 \times 10^{-5}$

BDDCS Biopharmaceutics Drug Disposition Classification System

change in the AUC after an intake of high-fat meals. For Class III drugs, the peak time is also expected to be delayed.

The BDDCS Class IV drugs have unfortunate properties in both solubility and permeability, and few marketed drugs fall into this class. Thus, the number of food effect studies with BDDCS Class IV drugs is limited [5]. By improving absorption characteristics through formulation methods, such as enhanced solubility or enhanced permeability, they can act like Class II or Class III drugs. For Class IV drugs, food effect on the absorption extent is either negative or unaffected. The absorption rate is also

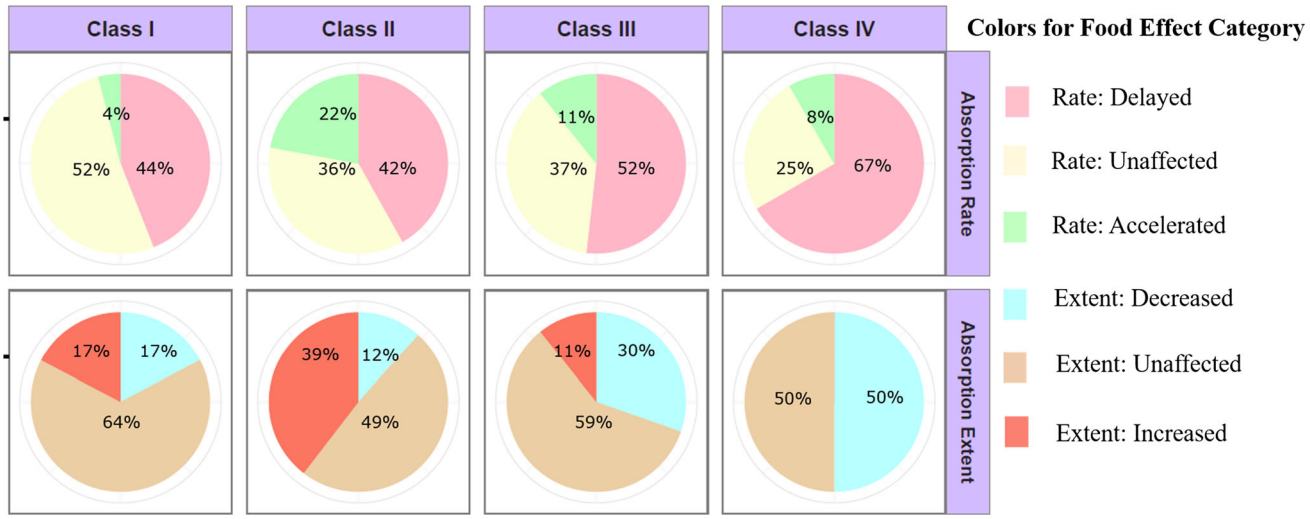

Fig. 2 Food effect for Biopharmaceutics Drug Disposition Classification System, Class I–IV drugs

prolonged in most cases. Because of the unique properties of individual drugs and the small sample size, predicting food effect is not feasible based on the current dataset.

5 Conclusion

Food effect is a common phenomenon for orally administered drugs, which can pose a challenge for therapeutic efficacy. The nature of different meal types adds to the complexity of food effect. Food effect has many underlying physiological mechanisms and other contributing factors, such as the specific PK properties of each unique drug and dosage regimens. Importantly, multiple mechanisms may be present at the same time and may counteract or potentiate each other. Therefore, it is important to consider these different aspects together when anticipating the potential effects from food. In this review, food effect is analyzed with consideration on study schemes and clinically relevant food–drug interactions are highlighted for 273 drugs. In addition, we examined the BDDCS as a predictor of food effect, which is statistically associated with high-fat food or standard meals effects on both the absorption rate and absorption extent. A thorough understanding of potential food effect, either absent or present, on the rate and/or extent of absorption, combined with a careful consideration of the clinical context, is needed when deciding whether a food effect is expected to be clinically significant, and whether it brings promise or peril to medication therapy.

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Compliance with Ethical Standards

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