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Food Matrix and Macronutrient Digestion

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Abstract

Food digestion may be regarded as a physiological interface between food and health. During digestion, the food matrix is broken down and the component nutrients and bioactive compounds are absorbed through a synergy of mechanical, chemical, and biochemical processes. The food matrix modulates the extent and kinetics to which nutrients and bioactive compounds make themselves available for absorption, hence regulating their concentration profile in the blood and their utilization in peripheral tissues. In this review, we discuss the structural and compositional aspects of food that modulate macronutrient digestibility in each step of digestion. We also discuss in silico modeling approaches to describe the effect of the food matrix on macronutrient digestion. The detailed knowledge of how the food matrix is digested can provide a mechanistic basis to elucidate the complex effect of food on human health and design food with improved functionality.

INTRODUCTION

Alongside its hedonic and social functions, the primary function of food is to provide nourishment. Decades ago, the prevailing paradigm in nutrition science was that the link between food and health would merely depend on the presence or absence of specific nutrients, i.e., food is a mere sum of nutrients. However, it became obvious that this approach was clearly inappropriate because it neglects the interactions between nutrients and the food matrix. The term food matrix appears in the scientific literature with a variety of meanings and, most often, is poorly, if at all, defined. It generally refers to the idea that the same food component behaves differently when it is in an isolated form compared to when it occurs in foods and behaves differently when it occurs in different foods. Here, we define the food matrix as the whole of the interactions between food components (Capuano et al. 2017). These interactions occur at different length scales and produce distinct microstructures and macrostructures (Aguilera 2019). Digestion can be considered as a physiological interface between foods and their effect on health. During digestion, the food matrix modulates the health effect of nutrients by modulating the availability of those nutrients to the body. We call this modulation the food matrix effect. In this review, we elaborate on this effect with specific emphasis on the digestion of macronutrients, starch, proteins, and lipids in the upper intestinal tract. Finally, we briefly discuss in silico modeling approaches to describe the effect of the food matrix on digestion.

STARCH

In plant tissues, starch is stored in the endosperm of grains and tubers in the form of semicrystalline granules of different sizes and shapes as well as structural organizations (**Figure 1*a***). In processed foods, starch is mostly present as granules dispersed in a biopolymer matrix, e.g., in bread, pasta or other bakery products, and extruded products. In a few cases, starch is dispersed in solution, e.g., in soups and sauces.

The rate and the extent of starch digestion may have remarkable consequences on health. The rate of starch digestion affects the postprandial rise in blood glucose and the consequent insulinemic response. Postprandial blood glucose has been implicated in the etiology of chronic metabolic diseases such as obesity, type 2 diabetes mellitus, and cardiovascular disease (Blaak et al. 2012). The tendency of food (or meals) to increase postprandial glycemia can be expressed in terms of the glycemic index (GI) (Ludwig 2002). The extent of starch digestion has an impact on the overall caloric content of food, the amount of glucose available, and the amount of starch that enters the colon. This last fraction, known as resistant starch (RS), has a beneficial effect on health through gut microbiota fermentation producing short-chain fatty acids (FAs) (Bindels et al. 2017, Johnston et al. 2009, Maki et al. 2012, Robertson et al. 2005).

Starch digestion starts in the mouth by means of salivary α-amylase and is completed in the duodenum by means of pancreatic α-amylase. Amylases produce maltose, isomaltose, maltotriose, and maltodextrins, which are hydrolyzed into glucose by brush-border maltase-glucoamylase and sucrase-isomaltase. Despite the short duration of the oral phase and inactivation of salivary amylase at pH < 4, acidification in the stomach may still be sufficiently slow to allow salivary amylase to significantly contribute to starch digestion. A recent in vitro study in bread reports that salivary amylase is responsible for up to 80% of bread starch digestion in the first 30 min of gastric digestion (Freitas & Le Feunteun 2019). The presence of proteins in a food or a meal is known to buffer the gastric pH, thus potentially prolonging the activity of salivary amylase. Furthermore, the actual pH experienced by salivary amylase within bolus particles may be higher than the pH measured in the liquid fraction of the stomach, which may further protect salivary amylase.

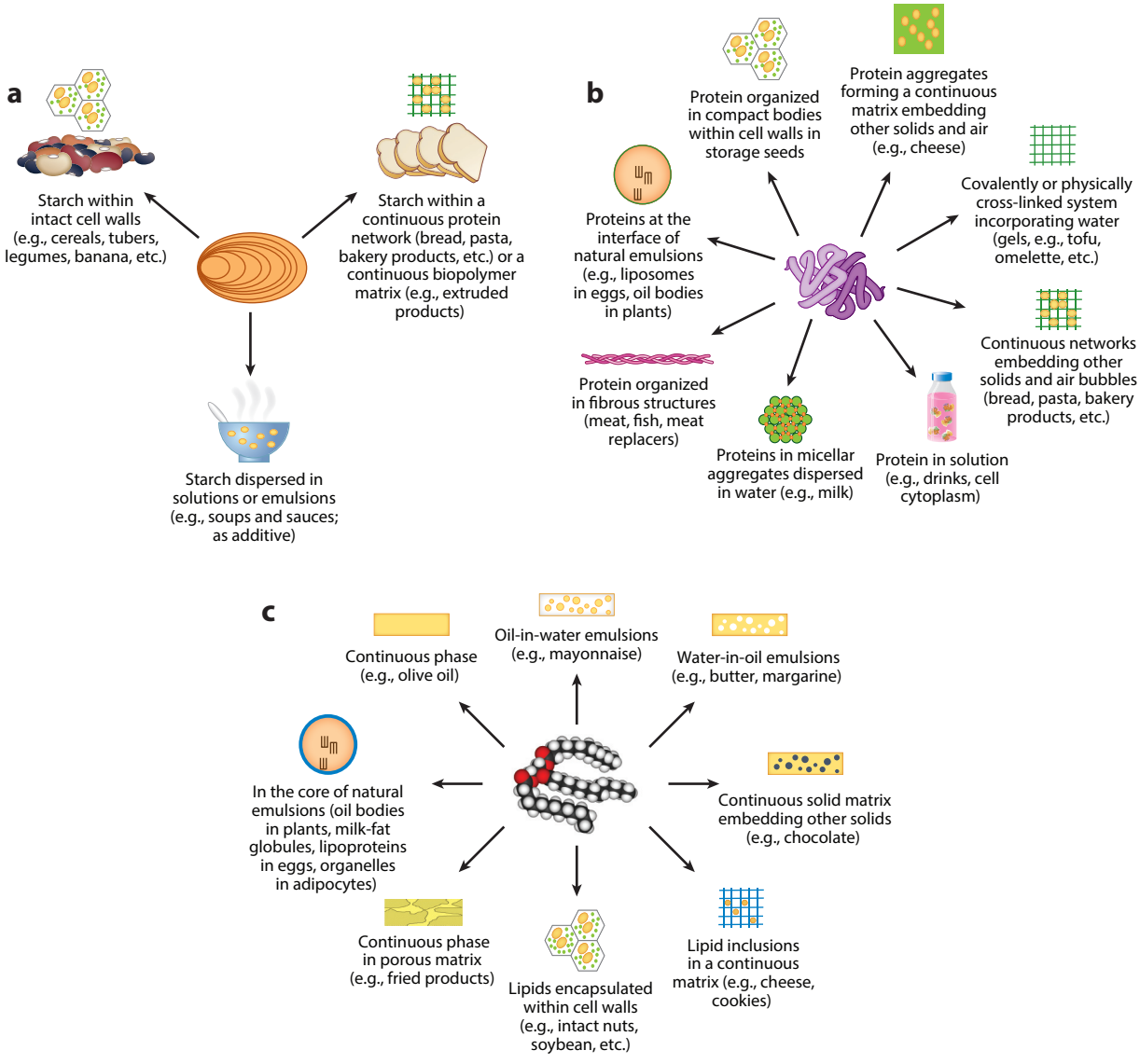

Figure 1

Overview of the supramolecular structures in which macronutrients occur or that macronutrients contribute to produce in native and processed food: (*a*) starch, (*b*) proteins, and (*c*) lipids.

Granule size, shape, porosity, type and degree of crystallinity, amylose:amylopectin ratio, distribution of amylose and amylopectin molecular weights, and degree of amylopectin branching all affect the digestibility of native starch (Dhital et al. 2017). Type of crystallinity of starch refers to the features of its X-ray diffraction pattern. Typically, the digestibility of raw starch granules is very low, and these granules are known as RS type 2. However, the digestibility is higher for A-type crystalline starch (cereals) compared to B-type crystalline starch (potato), which is partly related to the presence in A-type starch of pores and channels that substantially increase the total granule surface. Analogously, digestibility of native starch decreases with granule size (Dhital et al. 2010).

Ileostomy: an ileostomy is a surgical opening that diverts the ileum out onto the surface of the skin

In human diets, starch is almost uniquely consumed as gelatinized starch (with the exception of, e.g., banana starch). Gelatinization is the irreversible physical change that occurs when starch is heated in enough water. During gelatinization starch absorbs water and swells, disassembling and losing crystallinity and birefringence (Wang et al. 2016, 2019). Starch is much more susceptible to amylases when gelatinized compared to the native semicrystalline state. The presence of ungelatinized starch in food can thus reduce its digestibility. Full gelatinization requires temperatures higher than the starch gelatinization temperature (which differs among starch botanical sources). This means that the temperature gradient within a food determines the amount and distribution of gelatinized starch, and this gradient depends on the thermal properties of the food matrix. For example, during the boiling of potato, a gelatinization gradient can be observed across the tuber that reflects the temperature gradient developing within the potato tissue during boiling (Verlinden et al. 1995). Full gelatinization also requires the presence of an adequate amount of water. The amount of RS is higher and the digestibility of starch is lower when starch is cooked in <40% water (w/w on starch) than when cooked in 100% water (Mishra et al. 2012). In bread, the crust shows a higher percentage of ungelatinized starch compared to the crumb because the rapid water evaporation and low moisture content limit complete gelatinization (Primo-Martin et al. 2007). In chickpea particles, the degree of starch gelatinization (DG%; the fraction of residual gelatinization enthalpy compared to the theoretical maximum enthalpy) after boiling decreases with particle size because the intact cell walls restrict heat and water transfer to the core of bigger particles and cause spatial restrictions in the starch granule swelling (Edwards et al. 2015b). Local availability of moisture may also be limited by the presence in the food matrix of hydrocolloids such as dietary fiber (DF) and sugars.

Even though the rate and the extent of starch digestion increase after gelatinization, this is not directly proportional to DG%. In a recent study in potato and lotus seed starch, the correlation between the first-order rate constant for in vitro starch hydrolysis and maximum digestibility with DG% was not linear (Wang et al. 2019). Digestibility rapidly increased with DG% and then reached a plateau. After gelatinization, starch digestibility is independent of granule size or porosity, and chemical properties such as the molecular weight distribution of amylose and amylopectin and the number and length of amylose and amylopectin branches seem to play the most important role (Syahariza et al. 2013, Yu et al. 2018). Retrogradation of starch also results in the formation of starch fractions resistant to digestion, which are known as RS type 3. Starch retrogradation is the process by which disordered and disaggregated amylose and amylopectin chains (produced by gelatinization) partially reassociate to form more ordered assemblies (Wang et al. 2015). This typically happens during storage of previously cooked starchy foods. For instance, in ileostomy subjects who consumed freshly cooked potatoes, only 3% of starch was resistant to digestion, whereas 12% of starch was recovered in the ileostomy effluent upon consumption of cooked and cooled potatoes (Englyst & Cummings 1987). At present, the effect of the food matrix on starch retrogradation is poorly understood. Although the effect of water content has been described (Zeleznak & Hoseney 1986), the effect of food components (e.g., DF, monosaccharides, salts, amino acids, etc.) on starch retrogradation is compound specific and likely depends on competition for water (Wang et al. 2015).

The most important structural feature of plant tissues (fruits and vegetables, nuts, grains, and legumes) is the interconnected, continuous network of cell walls that surround and protect plant cells. Cell walls are constituted of polysaccharides that cannot be hydrolyzed by human digestive enzymes. These polysaccharides represent the most abundant source of DF in our diet. When cellular integrity is retained, macronutrients are encapsulated within cell walls, which shields them from digestive enzymes and bile acids and reduces their digestibility (Capuano 2016, Capuano et al. 2018a, Grundy et al. 2016b). Unless a solution of continuity is present in the cell wall (e.g.,

in damaged or broken cells), enzymes can access the intracellular space only through the natural pores in the cell wall. The result of this structural feature is that the digestibility of macronutrients in plant foods is inversely proportional to the degree of structural integrity of the plant material, i.e., the fraction of intact cells. It has been repeatedly demonstrated that the relatively low GI of legumes depends on the presence of a thick and resistant cell wall limiting the contact of starch granules with amylase (Berg et al. 2012, Dhital et al. 2016, Pallares et al. 2018, Rovalino-Córdova et al. 2018). The effect has been also demonstrated in cereals in vitro (Bhattarai et al. 2018, Mandalari et al. 2018). Edwards and coworkers showed that preserving the integrity of wheat endosperm reduces the GI of wheat-based porridge in ileostomy patients (Edwards et al. 2015a). Encapsulation by intact cells within plant tissues can also generate RS, which is known as RS type 1.

Additionally, the presence of an intact cell wall contributes to keeping a relatively tightly packed intracellular matrix in place. The intracellular matrix represents an additional barrier to diffusion of digestive enzymes and further contributes to limiting starch digestion as described for maize and sorghum (Ezeogu et al. 2008, Wong et al. 2009) and, more recently, kidney beans (Rovalino-Córdova et al. 2019). Furthermore, binding of amylase to cell wall polysaccharides has been reported, and this may have a substantial effect on starch digestibility (Dhital et al. 2016). Cell walls and intracellular proteins are not the only structural components that can act as a barrier for amylase. In both bread and pasta, starch granules are embedded in a gluten network. Pasta has a more compact structure with the gluten network tightly embedding the starch granules, which would limit the contact with amylase. This is apparently one of the reasons for the relatively lower GI of pasta compared to bread. It has been suggested that a limited gelatinization of the starch granules located in the inner core of spaghetti may also contribute to the relatively low GI of pasta (Zou et al. 2015).

Extrusion is a thermomechanical cooking method that combines heat transfer and shear to produce a variety of food products (puffed snacks, breakfast cereals, pet foods, meat analogs, etc.) from raw materials. Extrusion cooking almost invariably results in substantial changes in starch granule morphology as a consequence of melting and disintegration of the granules and reassociation of the glucan molecules in which the original granular nature is replaced by a honeycomb-like structure (Pérez & Bertoft 2010) that can retain a substantial degree of crystallinity (Shrestha et al. 2010). Extrusion increases starch digestibility compared to that of raw materials as a result of debranching and reduction of the molecular weight of the amylose and amylopectin molecules (Liu et al. 2010) and the formation of a porous, open structure surrounding the starch granules.

The digestibility of starch can also be modulated by the presence of certain food components in the same starchy food or in other foods within the meal. Polyphenols are known to interact with proteins via nonspecific, noncovalent interactions (Jakobek 2015, Le Bourvellec & Renard 2012). When this interaction involves digestive enzymes, enzymes may be partially inhibited (McDougall & Stewart 2005). It has been suggested that polyphenols may be used to modulate carbohydrate digestion and reduce the GI of food or meals. However, at the moment, there are few examples of human intervention studies in which the intake of polyphenols in realistic concentrations could favorably modulate postprandial glycemia (Castro-Acosta et al. 2017, Smith et al. 2019, Törrönen et al. 2010). Moreover, the efficacy of polyphenols seems to depend on the interactions of polyphenols with other food components. For instance, the efficacy of berry polyphenols in reducing in vitro starch digestibility in bread is higher when polyphenols are codigested with bread rather than incorporated into bread (Kan et al. 2020). The direct interaction of polyphenols with the starch granule may also produce complexes that are more resistant to digestion (Amoako & Awika 2019).

Another food component that can modulate starch digestion is DF. The inclusion of soluble DF in food or meals has been frequently reported to reduce the postprandial blood glucose level. Although several mechanisms have been proposed (recently reviewed in Goff et al. 2018),

the increase in digesta viscosity is the most cited and investigated. Incorporation of soluble, high molecular weight, poorly branched, rod-like indigestible polysaccharides in a food or meal would increase the viscosity of digesta almost dose-dependently. The resulting delay of diffusive or convective transport of starch, amylase, and starch hydrolysis products to, and through, the mucous layer would determine the observed effect on postprandial glycemia. When considering the effect of soluble, viscous DF on digesta processes, the effect of the food matrix must be taken into account. Upon ingestion of plant tissues containing soluble DF-like β-glucan, the viscosity of the digesta depends on the amount of DF that solubilizes from the cell walls into the digestive fluids. The amount of DF that solubilizes can vary upon food processing because of changes in DF structure or in the architecture of the cell wall. For instance, the amount of oat β-glucan that solubilized into digestive fluids ranged from 15% to 40% depending on whether the oat was provided as flakes or flour or whether the oat β-glucan was previously extracted (Grundy et al. 2017). Further differences were observed between raw and cooked oat-based foods. Thus, providing the same amount of β-glucan but in different oat matrices would produce distinctive effects on glucose metabolism.

PROTEINS

Proteins are present in food in a variety of forms and structures and often represent the very structural backbone of food (**Figure 1*b***). In natural foods, proteins exist as storage organelles in cells (protein bodies in plants); as soluble proteins in the cell cytoplasm; as fibers in meat and fish; in the form of colloidal water-soluble particles such as micelles in milk; and associated with lipids as protein–lipid complexes (i.e., liposomes in eggs). In processed foods, proteins can also take on the form of gels (omelet, tofu, etc.), fibrous structures (meat replacers), and 3D networks (gluten in bread); they can also be solubilized in water (high-protein drinks) and be present as surfactants at the interface of emulsions.

The extent of protein digestion determines its biological value. The Digestible Indispensable Amino Acid Score (DIAAS), recently proposed by FAO as the standard ranking method for protein quality (FAO 2011), is based on the bioavailability of essential amino acids and is determined at ileum level. The extent of protein digestion also determines the amount of protein that escapes digestion in the small intestine and enters the colon, where they can be fermented by the gut microbiota with supposedly detrimental effects for gut health (Blachier et al. 2007, Windey et al. 2012). The kinetics of protein digestion is also emerging as an important determinant for health; for example, a fast protein (digested and absorbed faster) is more beneficial than a slow one in elderly subjects because fast proteins limit body protein loss (Dangin et al. 2002). The dynamics of protein digestion are also important in relation to the generation of bioactive peptides and to protein allergenicity.

Protein digestion starts in the stomach, where the low pH (typically <2 in the fasted state) and acid-stable pepsin are responsible for the partial hydrolysis of proteins. Hydrolysis is completed in the small intestine by means of trypsin, chymotrypsin, and carboxypeptidases A and B, which produce a mix of free amino acids, dipeptides, and tripeptides. Peptides are further hydrolyzed into free amino acids by membrane-bound peptidases. Ultimately, amino acids and intact di- and tripeptides are then absorbed by highly specialized transporters in the intestinal epithelium.

The extent of structuring of the protein determines how easily the protein is digested. The digestion mostly depends on how the proteases in the gastric and intestinal environments are able to reach the protein and how the enzyme is able to carry out the hydrolysis of the peptide bonds. In general, soluble proteins are easily accessible for the enzyme. However, the acid environment in the stomach can cause aggregate and clot formation. This has been shown for unheated skim

milk (Van Aken et al. 2011, Ye et al. 2016). When brought into contact with gastric juice, a firm and dense clot is formed with a porous network structure. This cloth is marginally permeable to gastric juice, which means that it is more difficult for the enzyme to reach the core of the cloth. This led to reduced digestibility.

If proteins are present in a structured matrix or a clot-like structure is formed in the gastric environment, gastric juice needs to penetrate this structured matrix to digest the protein. This means the diffusion of enzymes, H^+, and other ions needs to be considered. Also, water uptake or release might be taken into account. Diffusion coefficients of pepsin in various protein structures have been measured by using fluorescence correlation spectroscopy (Luo et al. 2017, Luo et al. 2019) or fluorescence recovery after photobleaching (Thevenot et al. 2017). A reduction of a factor of 2–10 has been measured for the diffusion coefficient of pepsin in a structured matrix as compared to water. It shows that diffusion of pepsin is one of the reasons for the reduced digestion rate in a structured food matrix.

Besides being able to reach the substrate, the enzyme also needs to be in its active conformation. The activity of pepsin appears to be highest around $pH = 2$ (Kondjoyan et al. 2015). At $pH > 3$, pepsin activity is very low. After ingesting a meal, it is known that the pH in the stomach increases. Malagelada et al. (1979) showed that the pH in the fasted state is in the range of 1.3–2.5. After ingesting a meal, the pH rises to 4.5–5.8 (Malagelada et al. 1979). Bornhorst et al. (2014) investigated the mixing behavior and pH profile in pig stomach after ingesting brown and white rice and raw and roasted almonds. From this study, it is very clear that it takes time before the gastric content is completely mixed. This study also showed that the pH distribution in the stomach varies with time and is dependent on the type of meal (Bornhorst et al. 2014). The pH distribution in the stomach is dependent on the buffering capacity of food. The protein content and initial pH of the food are the most important factors for the buffering capacity in the gastric environment (Mennah-Govela et al. 2019). Food with a higher buffering capacity requires more gastric juice to reduce the pH in the stomach. As long as the (local) pH is above 3, pepsin shows very low activity and proteins are not hydrolyzed.

A very instructive example of the role in the food matrix of pepsin and H^+ penetration in protein digestion in the stomach is Nyemb et al.'s (2016) study on egg-white gel. The egg-white gels were prepared via heat treatment at different pHs and ionic strengths, which resulted in different gel structures with a similar protein composition. The peptide profile during in vitro gastric and intestinal digestion showed clear differences, which means that the different structures induced different proteolysis kinetics and provoked the release of specific peptides. In vivo, even a single specific peptide could be significant in terms of bioactivity or allergenicity. In another study using liquid milk and a variety of gelled structures obtained thereof (rennet gel, acid gel, and stirred gel) in growing pigs, it was also shown that gelling decreased the appearance of leucine in plasma and that the formation of stiffer gels prolongs the residence time of chime in the stomach with delayed gastric emptying (Barbé et al. 2013) (see the sidebar titled Gastric pH and Protein Digestion).

Protein gels are not the only example of supramolecular assemblies formed by proteins. Protein bodies represent one of the most common ways for the deposition of storage proteins in grains. An interesting study on a mutant line of sorghum suggests that structural features like total surface area of the protein body and its level of packing may play a role in plant protein digestibility (Oria et al. 2000). Proteins can form supramolecular assemblies as a consequence of thermal treatment. Thermal treatment at temperatures above the denaturation temperatures increases the exposure of peptide bonds otherwise hidden in the core of globular proteins because of the polypeptide unfolding. Whether this results in an increased or decreased digestibility depends on the aggregation/cross-linking of the unfolded proteins (Bax et al. 2012). The formation of

GASTRIC pH AND PROTEIN DIGESTION

Along with mixing and food composition, the pH of the gastric juice plays a role in protein digestion. The pH of the gastric juice of adults in the fasted state is typically less than 2 and can be as low as 1. However, in the elderly and infants, gastric juices have a reduced acid content and therefore a higher pH. Additionally, lower levels of pepsin are present. At lower acid concentrations, it takes longer to reduce the pH to a level at which pepsin can be active. Together with a lower pepsin concentration, this is an explanation for the reduced digestibility and higher protein requirements for the elderly. For infants, it has been shown that different peptides are formed during digestion (Dupont et al. 2010). This indicates a different, pH-dependent pathway of protein degradation. Dupont et al. (2010) suggested this as an explanation for cow milk and hen's egg allergies as diseases of infancy. They disappear when growing up, as the pH of the gastric juice is reduced.

aggregates may hide peptide bonds from proteases compared to denatured but isolated molecules. The effect of cooking on the digestibility of meat proteins is a good example of such complex relationships. Meat proteins are digested very efficiently, with true ileal digestibility often around 95% (Gilani et al. 2005). A recent study in human volunteers using isotopically labeled meat showed that the digestibility of beef cooked rare (55°C for 5 minutes) was higher (95%) than that of well-cooked beef (90%, cooked at 95°C for 30 minutes) (Oberli et al. 2015). This was confirmed by a study on in vitro digestion of raw and cooked beef (Kaur et al. 2014). Another study in pigs that were fed beef reported no differences in the true ileal digestibility but reported differences in the rate of leucine appearance in the blood in the following order: moderate cooking > mild cooking > severe cooking, which is what would be anticipated with the simultaneous effects of denaturation and aggregation explained above (Bax et al. 2013). Meat analogs are a class of food products that imitate the sensory attributes of meat products but are produced from protein from more sustainable sources, e.g., plant protein isolates, that are subjected to extrusion or shear-cell technology. These processes impart deformation at high temperature, which produces denaturation and aggregation of the proteins to produce a fibrous structure. The effect on protein digestibility is highly variable and depends on the process-induced level of denaturation and aggregation produced by the conditions applied (Duque-Estrada et al. 2019).

The aggregation level is enhanced by the presence of reducing sugars that triggers a Maillard reaction and ultimately the formation of melanoidins, the bioavailability of which is considered very poor (Faist & Erbersdobler 2001). In general, protein digestibility is reduced in products that underwent severe thermal treatments such as spray drying, in-batch sterilization, and dry cooking. In bread, the digestibility of proteins in the crust is reduced by the relatively high temperature reached in the crust during baking compared to the crumb (Pasini et al. 2001). A human intervention study showed that the amount of excreted N was higher after consumption of ultra-high-temperature processed milk compared to microfiltered or pasteurized milk (Lacroix et al. 2008). Similarly, protein digestibility in liquid-concentrate infant formulas (subjected to more severe heating) was lower compared to that of powdered infant formulas (Gilani et al. 2012).

As already described for starch, in intact plant food cellular integrity regulates the amount of protein digested in the gastrointestinal tract. This may be one of the reasons for the lower digestibility reported for plant proteins compared to animal proteins (Gilani et al. 2005). Several studies suggest that the extent of cell rupture is positively correlated to protein digestibility in legumes and cereals (Bhattarai et al. 2017, Mandalari et al. 2018, Melito & Tovar 1995, Rovalino-Córdova et al. 2019, Zahir et al. 2018). The extent of cell rupture is proportional to the level of disintegration of the plant matrix but also depends on whether this disintegration occurs before

True ileal digestibility: measure of the bioavailability of dietary amino acids at the ileum level corrected for the contribution of endogenous amino acids

Maillard reaction: nonenzymatic reaction occurring in foods between reducing sugars and amino groups (mostly proteins and amino acids)

or after a thermal treatment because thermal solubilization of pectin in the cell wall may produce cell separation rather than cell rupture (Waldron et al. 1997, Zahir et al. 2018). A recent study in rats showed that the digestibility of sunflower protein isolate is almost as high as that of goat whey proteins (Tessier et al. 2020).

Protein digestibility from plant sources is also reduced by the presence of food compounds that are historically indicated as antinutritional factors (Gilani et al. 2005). These include DF, polyphenols, proteases inhibitors, and phytates. The inclusion of DF in the diet increases the amount of fecal nitrogen (Bach Knudsen 2001). The role of DF in impairing protein digestibility is similar to that described for starch (increasing viscosity and reducing the mixing regimes in the gastrointestinal tract; increasing the transit time), but complicating factors are the presence of antinutritional copassengers like tannins and phytases often associated with less purified DF ingredients. The inhibitory effect of polyphenols, with special emphasis on tannins, stems from the interaction of the phenolics with either proteases or dietary proteins. Finally, protease inhibitors (e.g., trypsin inhibitors) and lectins impair protein digestibility by interacting with proteases and limiting their efficiency. Thermal treatments are usually sufficient to remove most of the heat-labile antinutritional factors like trypsin inhibitors (Gilani et al. 2005). Animal food may contain protease inhibitors like those found in eggs, where the presence of ovomucin is likely responsible for the very low protein digestibility in raw eggs compared to cooked eggs (Evenepoel et al. 1998). Fermentation and germination are useful methods to reduce the phytate content in food by the action of microbial or endogenous phytases.

LIPIDS

Food lipids are constituted mostly of triglycerides (TAGs) (90–95%) and, in smaller amounts, phospholipids, cholesterol, esters, and lipophilic vitamins. For this reason, we focus hereafter only on TAG digestion. In natural foods, lipids are present as globules or droplets of variable sizes dispersed in the cellular or extracellular aqueous environment and stabilized by (typically) multiple layers of emulsifying compounds (**Figure 1*c***): In milk and dairy products, lipids are present as globules surrounded by a milk-fat globule membrane made up of phospholipids and proteins; in seeds, lipids are mostly stored as oil bodies surrounded by polar lipids and proteins (caleosins and oleosins); in eggs, lipids are part of liposomes, constituted by a lipid core surrounded by polar lipids and proteins; in adipocytes, lipids are stored in globules surrounded by a phospholipid double layer in subcellular organelles; and in processed foods, lipids occur in different forms: oil-in-water emulsions (mayonnaise, sauces, and spreads) and water-in-oil emulsions (butter and margarine); lipid continuous phase (edible oils), lipid continuous phase embedding solid particles (chocolate), and filled-in microscopic-sized capillaries (fried products); and lipid droplets embedded in a 3D network of proteins (bakery products, cheese).

The rate and extent of lipid digestion have consequences for health. The amount of lipid digested contributes to the total metabolizable energy of food as well as to the level of circulating essential FAs. The rate of lipid digestion determines the postprandial plasma TAG level, which has been identified as a risk factor for the development of cardiovascular diseases and type 2 diabetes (Carstensen et al. 2004, Pirillo et al. 2014). Finally, the rate at which the products of lipid hydrolysis appear in the lumen of the gastrointestinal tract contributes to the regulation of satiety through complex neurohormonal mechanisms (Maljaars et al. 2008a,b).

Lipid digestion starts in the stomach by means of acid-stable gastric lipases. In humans, this lipase is responsible for the digestion of up to 30% of the dietary TAGs. The human gastric lipase is capable of releasing FAs from position 3 of the glycerol backbone only. The bulk of the digestion occurs in the duodenum by means of pancreatic lipase, which requires colipase and

calcium ions to work and hydrolyzes FAs esterified in the sn-l,3 positions of TAGs. The products of lipid digestion, i.e., FAs and monoglycerides, are then incorporated into mixed micelles (formation of which is facilitated by bile acids) and absorbed by the small intestinal epithelium by passive diffusion or carrier-mediated transport. Apart from the biochemical details, colloidal aspects are of paramount importance in lipid digestion. Irrespective of whether lipids are ingested in an emulsified or nonemulsified form, by the effect of oral and gastric mixing, passage through the pylorus, and the presence of dietary and endogenous surfactants (bile acids and phospholipids in the bile), lipids occur in an emulsified form in the gastrointestinal tract. Because lipases act at the interface between lipid droplets and the aqueous environment of the gastrointestinal tract, the dynamics of lipid digestion are determined by the competition between lipases and surfactants for access to the available emulsion interface. The nature of the surfactants determines emulsion stability and therefore the extent of available surface. There is substantial evidence that the rate of lipid hydrolysis in the stomach and small intestine is proportional to the overall surface offered to pancreatic lipase, i.e., to the size of the lipid droplets (Armand et al. 1999). This also explains why pre-emulsified fats are digested faster than bulk, nonemulsified fats of the same composition (bigger lipid droplets are produced in the latter case) (Vors et al. 2013).

During passage through the stomach, emulsions can be destabilized depending on the type of surfactants present. Protein surfactants can be partially removed by pepsin, whereas negatively charged surfactants can be neutralized, thus favoring flocculation and, if the surfactant layer is relatively thin, partial or complete coalescence of the emulsion under the physiological mixing regimes occurring in the stomach. Therefore, emulsions with exactly the same composition and droplet-size distribution but stabilized by different surfactants may be digested at different rates (Golding et al. 2011). A complete coalescence and breakage of the emulsion may determine the layering of the fat on top of the gastric content. When this happens, the stomach empties the relatively fat-depleted solution more quickly than emulsions with fat droplets that are uniformly distributed and are stable in the stomach (Marciani et al. 2008).

Digestion of lipids is typically extremely efficient, with >95% of the lipids digested and absorbed after ingestion of typical diets (Merrill & Watt 1973). A notable exception is represented by lipids in oilseeds like nuts and soybeans. Here, a substantial amount of lipids may escape digestion because of the barrier effect exerted by intact cell walls. A human study reported that the metabolizable energy obtained from almonds is almost 30% lower than achievable from the application of the Atwater factors for energy calculation (Novotny et al. 2012). Similar levels of discrepancy have been found for walnuts (Baer et al. 2014), but for cashew nuts (Baer & Novotny 2019) and pistachios (Baer et al. 2012), the discrepancy was lower. The fraction of lipids escaping digestion is proportional to the total area of ruptured cells exposed on the surface of nut particles and is less dependent on the permeability of cell walls to pancreatic lipases (Grassby et al. 2014, Grundy et al. 2016a). Heat treatments, e.g., boiling or roasting, can increase lipid digestibility in nuts (Capuano & Pellegrini 2019, Groopman et al. 2015), which may be related to an increase of cell wall permeability to lipase or destabilization of the oil bodies' surface (Capuano et al. 2018b). This effect may occur in other plant-based, lipid-rich foods (soybeans, avocado, algae). Studies on microalgae clearly showed that the integrity of cell walls may largely limit the utilization of lipids (and other nutrients) from algae-based ingredients (Cavonius et al. 2016). This barrier effect to lipases exerted by indigestible polysaccharides can also be exploited for the formulation of engineered matrices such as lipid-rich emulsion-filled alginate or carrageenan beads (Corstens et al. 2018).

Another structural factor to consider is the TAG chemical structure, i.e., the FA composition. The rate of FA incorporation in mixed micelles is higher for short- and medium-chain FAs compared to long-chain FAs (Giang et al. 2016). In the case of long-chain FAs, this may be caused by

a higher steric hindrance, slower incorporation in mixed micelles, or more extensive precipitation of the FAs in the lumen as insoluble soaps (see below). Given the stereospecificity of pancreatic lipase, it is not surprising that the distribution of FAs on the glycerol backbone may determine the rate at which FAs are released in the intestinal lumen. Stereospecificity is also relevant because the nature of free FAs and monoglycerides produced by pancreatic lipase in the lumen of the gastrointestinal tract determines (at least partially) the TAG composition in the blood (Christensen & Høy 1996).

In several foods, lipids are present as liquid or solid inclusions in a continuous solid matrix (e.g., bread or cheese), but the rate of lipid digestion is not dependent on the rate of disintegration of the surrounding matrix. Differences in the kinetics of appearance of TAGs in the blood after cheese consumption are likely related to a different rate of gastric emptying or differences in the fat globule size (which depends on cheese-specific manufacturing) rather than a difference in the rate of disintegration of the casein matrix (Drouin-Chartier et al. 2017). A recent intervention study measured the postprandial lipemia to test foods with the same lipid content and composition but different structures, e.g., a solid, semisolid, and liquid food. The solid food produced a lower increase in serum TAGs than the liquid food and produced higher fullness, likely because of delayed gastric emptying and bigger globule size in the solid food (Dias et al. 2019).

The physical state of fat may also affect the rate of lipid digestion. Early studies reported that fully hydrogenated (more solid) soybean oil was poorly digested in rats compared to more liquid soybean oil (Kamei et al. 1995, Kaplan & Greenwood 1998). However, it is not clear to what extent the FA composition of the oils rather than the fat physical state is responsible for the differences observed. When solid and liquid emulsions of the same composition were compared, emulsions prepared from solid fat were digested more slowly (Bonnaire et al. 2008). A promising strategy to modulate the kinetics of lipid digestion seems to be oleogelation, i.e., adding an oleogelator (e.g., waxes) to bulk oils or emulsions to form a 3D network that immobilizes liquid oils to create a viscoelastic material called oleogel. Oleogelation of emulsified lipids has proven effective in reducing duodenal lipolysis in vitro and attenuating the postprandial TAGs in vivo after consumption of a carbohydrate breakfast and coconut oil meal (Tan et al. 2017).

The amount of calcium ions available in the lumen of the small intestine is known to play an important role in lipid digestion. Adequate amounts of calcium ions are essential to sustain lipid digestion by stimulating the hydrolytic activity of pancreatic lipase and removing FAs from the droplet surface (Cervantes-Paz et al. 2017). However, it has been proposed that an excess of calcium ions can increase fecal fat excretion by precipitating FAs in the lumen of the gastrointestinal tract as insoluble soaps (Christensen et al. 2009, Lorenzen & Astrup 2011). In one randomized crossover study with healthy subjects, fecal fat excretion and total fecal energy excretion were higher in high-calcium, dairy-containing diets compared to a low-calcium dairy-free isocaloric diet (Soerensen et al. 2014). Another feeding study in growing pigs has shown that the amount of fat excreted in the feces is higher when dairy fat is provided in the meal as cheese rather than as butter or a cheese–butter mix (Thorning et al. 2016). One explanation is that the cheese meal contains more calcium, resulting in more fat lost in the feces as insoluble calcium soaps. It is worth noticing that the solubility of FA soaps in the small intestine decreases with the FA saturation level and chain length, i.e., long and saturated FAs are more easily lost as insoluble soaps (Graham & Sackman 1983). Given the stereospecificity of pancreatic lipase, the distribution of FAs on the glycerol backbone may determine the amount of fat lost as insoluble soaps. Infant formulas formulated with vegetable oils have palmitic acid mostly esterified in position 1 and 3 of the glycerol backbone, which results in a substantially higher loss of palmitic acid as insoluble soaps compared to human milk, where palmitic acid is esterified in position 2 and thus available for absorption in the form of 2-monoglyceride. This has prompted the design of a new formula

produced by interesterification of TAGs with palmitic acid mostly in position 2 of the glycerol backbone (Carnielli et al. 1996, Wilcox et al. 2014).

Analogously to what was discussed for starch and protein, the presence of DF in food and diets can modulate lipid digestion, typically reducing lipid digestibility (Dikeman & Fahey Jr. 2006). Besides the well-known effect of viscosity, DF can also act in several, interconnected ways: by interfering with the emulsification of dietary lipids; promoting emulsion instability (such as the depletion flocculation mechanism); binding calcium ions; entrapping or binding bile acids; and directly inhibiting pancreatic lipase (Cervantes-Paz et al. 2017, Espinal-Ruiz et al. 2014, Minekus et al. 2005, Pasquier et al. 1996).

IN SILICO MODELING

Most information discussed in this review was derived from in vivo and in vitro studies (see the sidebar titled In Vitro Models of Digestion). In vivo measurements give a global indication of food digestibility in its full biological context, whereas in vitro experiments simplify the physiology of the human gastrointestinal tract but provide more insight into the different chemical and physical mechanisms. In silico digestion, i.e., the mathematical modeling (or in silico modeling) of the digestive processes, can connect these two domains and provide information that is difficult or even impossible to obtain via in vivo or in vitro studies only.

Various modeling approaches have been described in the literature. In early work, modeling was used to describe the dry matter loss or wet mass retention during in vitro digestion of food products via empirical relations (Kong & Singh 2008). In later studies, the focus shifted to the hydrolysis kinetics of the main macronutrients via kinetic models based on studies on enzyme kinetics for proteins (Kondjoyan et al. 2015, Luo et al. 2018, Tonda et al. 2017), starch (Li et al. 2019, Nguyen & Sopade 2018), and lipids (Verkempinck et al. 2019). These types of models predict the concentration and degree of hydrolysis of the macronutrients in one or more compartments of the digestive system.

Other models are made to predict the transport of the food through the digestive system. This includes gastric emptying and description of peristaltic movement through the stomach and intestinal tract. Often an engineering approach is used by assuming the digestive tract as a series of bioreactors that can be described by mass balances. These mass balances are written as a set of

IN VITRO MODELS OF DIGESTION

In vitro digestion models aim to simulate the digestive processes in test tubes. Food is prepared in a standardized way and sequentially subjected to oral, gastric, and small intestinal digestion. In static models, only the chemical and biochemical processes (e.g., pH, enzymes, bile salts, etc.) are simulated at specified conditions; in dynamic models, some of the physiological or mechanical aspects of digestion (e.g., dynamic change in pH, enzymes secretion or dynamic gastric emptying) are also simulated. Absorption is often reproduced with passive diffusion of the nutrients through membranes or the postexposure of digested samples to appropriate cell lines. Digestibility or bioaccessibility is measured by the accumulation of a proper biomarker in the tubes. In vitro digestion models can be adapted to specific physiological conditions by modifying chemical (e.g., pH) and biochemical parameters (activity of enzymes), but they cannot account for hormonal and neural regulation of the digestive processes, e.g., regulation of gastric emptying, propulsion, and absorption. These models are very useful, cheap, and versatile tools for screening samples/treatments and providing a more mechanistic understanding of the changes occurring during digestion. Their use for accurate prediction of digestion extent or kinetics must be interpreted with care.

differential equations (Barbé et al. 2012; Moxon et al. 2016, 2017; Taghipoor et al. 2012, 2014). Another example is a mechanistic model for digestion of starch within intact cells (Rovalino-Córdova et al. 2021). The model is constituted of a set of differential equations that describe the diffusion of α-amylase from the intestinal lumen to the intracellular environment and the diffusion of starch hydrolysis products from the cells to the lumen. Also, computational fluid dynamics modeling has been used, e.g., for calculating the mixing behavior in the gastric environment as a function of the viscosity of the food (Ferrua & Singh 2010, Ferrua et al. 2011) and flow behavior, including peristaltic contractions in the small intestine (Love et al. 2013). In recent years, models that take into account the food matrix have been described in which the reaction and diffusion are included in the model (Sicard et al. 2018). Physical chemistry approaches appear to be promising for describing the digestion of complex food matrices, as shown by Novev et al. (2020), who studied polymer aggregate digestion via coarse-grained mesoscale simulations (Novev et al. 2020). Van der Sman et al. (2020) also used a physical chemistry approach to model the swelling of protein gels by using the Flory-Rehner theory (van der Sman et al. 2020). This has been combined with the Gibbs-Donnan theory to include the distribution of ions between the gastric juice and the protein matrix. The resulting model provided insight into the charge of proteins at different pH conditions, the swelling kinetics of the protein matrix, and ion transport between the matrix and the gastric juice. Along these lines, in silico models can be further improved to gain a better understanding of the phenomena that are essential in the digestion of the food matrix.

CONCLUSIONS AND FUTURE PERSPECTIVES

The link between food and digestion has gained much interest recently, and it has become clear that incorporating concepts of food science and technology would benefit our understanding of the relationship between our diets and health. This has produced a paradigm shift that considers the food matrix as a key element in understanding the effect of food and diet on health. In this review, the structural and compositional properties of the food matrix that have an effect on macronutrient digestion in the upper intestinal tract were discussed. The intriguing question of how these same properties affect macronutrient utilization by the gut microbiota is still largely unexplored (see the sidebar titled Food Matrix and the Gut Microbiota).

The efforts in understanding the role of food matrix on digestion are also reflected in the research on in silico modeling of digestion in foods. Although laudable, those efforts have focused

FOOD MATRIX AND THE GUT MICROBIOTA

It is currently common to refer to humans as superorganisms, where the human part is complemented by a complex symbiotic microbiota. A bidirectional link exists between diet and the gut microbiota. On one hand, the gut microbiota acts as an additional digestive organ that metabolizes the remnants of small intestine digestion and produces a range of metabolites that can impact health well beyond the gut. On the other hand, our diet modulates the microbiota composition and metabolic activity. Whereas the effects of specific compounds on microbiota metabolism have been revealed, the effect of the food matrix is still largely unknown and may contribute to the modulation of the gut microbiota community and metabolism. The effect exerted by the food matrix in the upper intestinal tract determines the composition of what enters the colon. Microstructural elements of food may also be important for the modulation of gut microbiota metabolism. These would include, e.g., the presence of a natural barrier for nutrients in intact plant tissue, the supramolecular organization of polysaccharides in cell walls or starch granules, the complexation of polyphenols with proteins and dietary fiber, and the supramolecular organization of dietary proteins.

mostly on isolated ingredients, the biochemical events, and the accurate description of the mixing and transport phenomena in the upper intestine. This is clearly the first, necessary step, but the inclusion of an additional layer of complexity, represented by the food matrix, needs to be included if we want to use such mechanistic models for the design of new foods. The recently developed physical chemistry models are a promising step in this direction.

The next step is represented by the incorporation of the interaction between foods within a meal because if it is true that we ingest foods and not nutrients, it is also true that we mostly ingest meals and not isolated foods. At the moment, a comprehensive understanding of how a certain meal is translated into the structural and rheological properties of the resulting bolus, chime, or digesta is still lacking.

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LITERATURE CITED

Aguilera JM. 2019. The food matrix: implications in processing, nutrition and health. *Crit. Rev. Food Sci. Nutr.* 59:3612–29

Amoako DB, Awika JM. 2019. Resistant starch formation through intrahelical V-complexes between polymeric proanthocyanidins and amylose. *Food Chem.* 285:326–33

Armand M, Pasquier B, André M, Borel P, Senft M, et al. 1999. Digestion and absorption of 2 fat emulsions with different droplet sizes in the human digestive tract. *Am. J. Clin. Nutr.* 70:1096–106

Bach Knudsen KE. 2001. The nutritional significance of "dietary fibre" analysis. *Anim. Feed Sci. Technol.* 90:3–20

Baer DJ, Gebauer SK, Novotny JA. 2012. Measured energy value of pistachios in the human diet. *Br. J. Nutr.* 107:120–25

Baer D, Gebauer S, Novotny J. 2014. Atwater factors overestimate the calorie content of walnuts. *FASEB J.* 28(S1):371.1

Baer DJ, Novotny JA. 2019. Metabolizable energy from cashew nuts is less than that predicted by Atwater factors. *Nutrients* 11:33

Barbé F, Le Feunteun S, Laroche B, Dupont D. 2012. Mathematical modelling of milk proteins digestion dynamics. *IFAC Proc. Volumes* 45:1437–41

Barbé F, Ménard O, Le Gouar Y, Buffière C, Famelart M-H, et al. 2013. The heat treatment and the gelation are strong determinants of the kinetics of milk proteins digestion and of the peripheral availability of amino acids. *Food Chem.* 136:1203–12

Bax M-L, Aubry L, Ferreira C, Daudin J-D, Gatellier P, et al. 2012. Cooking temperature is a key determinant of in vitro meat protein digestion rate: investigation of underlying mechanisms. *J. Agric. Food Chem.* 60:2569–76

Bax M-L, Buffière C, Hafnaoui N, Gaudichon C, Savary-Auzeloux I, et al. 2013. Effects of meat cooking, and of ingested amount, on protein digestion speed and entry of residual proteins into the colon: a study in minipigs. *PLOS ONE* 8(4):e61252

Berg T, Singh J, Hardacre A, Boland MJ. 2012. The role of cotyledon cell structure during in vitro digestion of starch in navy beans. *Carbohydr. Polym.* 87:1678–88

Bhattarai RR, Dhital S, Mense A, Gidley MJ, Shi Y-C. 2018. Intact cellular structure in cereal endosperm limits starch digestion in vitro. *Food Hydrocoll.* 2:139–48

Bhattarai RR, Dhital S, Wu P, Chen XD, Gidley MJ. 2017. Digestion of isolated legume cells in a stomach-duodenum model: three mechanisms limit starch and protein hydrolysis. *Food Funct.* 8:2573–82

Bindels LB, Munoz RRS, Gomes-Neto JC, Mutemberezi V, Martínez I, et al. 2017. Resistant starch can improve insulin sensitivity independently of the gut microbiota. *Microbiome* 5:12

Blaak E, Antoine JM, Benton D, Björck I, Bozzetto L, et al. 2012. Impact of postprandial glycaemia on health and prevention of disease. *Obes. Rev.* 13:923–84

Blachier F, Mariotti F, Huneau J-F, Tomé D. 2007. Effects of amino acid–derived luminal metabolites on the colonic epithelium and physiopathological consequences. *Amino Acids* 33:547–62

Bonnaire L, Sandra S, Helgason T, Decker EA, Weiss J, McClements DJ. 2008. Influence of lipid physical state on the in vitro digestibility of emulsified lipids. *J. Agric. Food Chem.* 56:3791–97

Bornhorst GM, Rutherfurd SM, Roman MJ, Burri BJ, Moughan PJ, Singh RP. 2014. Gastric pH distribution and mixing of soft and rigid food particles in the stomach using a dual-marker technique. *Food Biophys.* 9:292–300

Capuano E. 2016. The behaviour of dietary fibre in the gastrointestinal tract determines its physiological effect. *Crit. Rev. Food Sci. Nutr.* 57(16):3543–64

Capuano E, Oliviero T, Fogliano V, Pellegrini N. 2018a. Role of the food matrix and digestion on calculation of the actual energy content of food. *Nutr. Rev.* 76:274–89

Capuano E, Oliviero T, van Boekel MAJS. 2017. Modeling food matrix effects on chemical reactivity: challenges and perspectives. *Crit. Rev. Food Sci. Nutr.* 58(16):2814–28

Capuano E, Pellegrini N. 2019. An integrated look at the effect of structure on nutrient bioavailability in plant foods. *J. Sci. Food Agric.* 99:493–98

Capuano E, Pellegrini N, Ntone E, Nikiforidis CV. 2018b. In vitro lipid digestion in raw and roasted hazelnut particles and oil bodies. *Food Funct.* 9:2508–16

Carnielli VP, Luijendijk IH, Van Goudoever JB, Sulkers EJ, Boerlage AA, et al. 1996. Structural position and amount of palmitic acid in infant formulas: effects on fat, fatty acid, and mineral balance. *J. Pediatr. Gastroenterol. Nutr.* 23:553–60

Carstensen M, Thomsen C, Gotzsche O, Holst JJ, Schrezenmeir J, Hermansen K. 2004. Differential postprandial lipoprotein responses in type 2 diabetic men with and without clinical evidence of a former myocardial infarction. *Rev. Diabet. Stud.* 1(4):175–84

Castro-Acosta ML, Stone SG, Mok JE, Mhajan RK, Fu C-I, et al. 2017. Apple and blackcurrant polyphenol-rich drinks decrease postprandial glucose, insulin and incretin response to a high-carbohydrate meal in healthy men and women. *J. Nutr. Biochem.* 49:53–62

Cavonius LR, Albers E, Undeland I. 2016. In vitro bioaccessibility of proteins and lipids of pH-shift processed Nannochloropsis oculata microalga. *Food Funct.* 7(4):2016–24

Cervantes-Paz B, de Jesús Ornelas-Paz J, Ruiz-Cruz S, Rios-Velasco C, Ibarra-Junquera V, et al. 2017. Effects of pectin on lipid digestion and possible implications for carotenoid bioavailability during pre-absorptive stages: a review. *Food Res. Int.* 99:917–27

Christensen MS, Høy C-E. 1996. Effects of dietary triacylglycerol structure on triacylglycerols of resultant chylomicrons from fish oil- and seal oil-fed rats. *Lipids* 31:341–44

Christensen R, Lorenzen JK, Svith CR, Bartels EM, Melanson EL, et al. 2009. Effect of calcium from dairy and dietary supplements on faecal fat excretion: a meta-analysis of randomized controlled trials. *Obes. Rev.* 10:475–86

Corstens MN, Berton-Carabin CC, Schroën K, Viau M, Meynier A. 2018. Emulsion encapsulation in calcium-alginate beads delays lipolysis during dynamic in vitro digestion. *J. Funct. Foods* 46:394–402

Dangin M, Boirie Y, Guillet C, Beaufrère B. 2002. Influence of the protein digestion rate on protein turnover in young and elderly subjects. *J. Nutr.* 132:3228S–33

Dhital S, Bhattarai RR, Gorham J, Gidley MJ. 2016. Intactness of cell wall structure controls the in vitro digestion of starch in legumes. *Food Funct.* 7:1367–79

Dhital S, Shrestha AK, Gidley MJ. 2010. Relationship between granule size and in vitro digestibility of maize and potato starches. *Carbohydr. Polym.* 82:480–88

Dhital S, Warren FJ, Butterworth PJ, Ellis PR, Gidley MJ. 2017. Mechanisms of starch digestion by α-amylase—structural basis for kinetic properties. *Crit. Rev. Food Sci. Nutr.* 57:875–92

Dias CB, Zhu X, Thompson AK, Singh H, Garg ML. 2019. Effect of the food form and structure on lipid digestion and postprandial lipaemic response. *Food Funct.* 10:112–24

Dikeman CL, Fahey GC Jr. 2006. Viscosity as related to dietary fiber: a review. *Crit. Rev. Food Sci. Nutr.* 46:649–63

Drouin-Chartier J-P, Tremblay AJ, Maltais-Giguère J, Charest A, Guinot L, et al. 2017. Differential impact of the cheese matrix on the postprandial lipid response: a randomized, crossover, controlled trial. *Am. J. Clin. Nutr.* 106:1358–65

Dupont D, Mandalari G, Molle D, Jardin J, Léonil J, et al. 2010. Comparative resistance of food proteins to adult and infant in vitro digestion models. *Mol. Nutr. Food Res.* 54:767–80

Duque-Estrada P, Berton-Carabin CC, Nieuwkoop M, Dekkers BL, Janssen AE, Van Der Goot AJ. 2019. Protein oxidation and in vitro gastric digestion of processed soy-based matrices. *J. Agric. Food Chem.* 67:9591–600

Edwards CH, Grundy MM, Grassby T, Vasilopoulou D, Frost GS, et al. 2015a. Manipulation of starch bioaccessibility in wheat endosperm to regulate starch digestion, postprandial glycemia, insulinemia, and gut hormone responses: a randomized controlled trial in healthy ileostomy participants. *Am. J. Clin. Nutr.* 102:791–800

Edwards CH, Warren FJ, Campbell GM, Gaisford S, Royall PG, et al. 2015b. A study of starch gelatinisation behaviour in hydrothermally-processed plant food tissues and implications for in vitro digestibility. *Food Funct.* 6:3634–41

Englyst HN, Cummings JH. 1987. Digestion of polysaccharides of potato in the small intestine of man. *Am. J. Clin. Nutr.* 45:423–31

Espinal-Ruiz M, Parada-Alfonso F, Restrepo-Sánchez L-P, Narváez-Cuenca C-E, McClements DJ. 2014. Impact of dietary fibers [methyl cellulose, chitosan, and pectin] on digestion of lipids under simulated gastrointestinal conditions. *Food Funct.* 5:3083–95

Evenepoel P, Geypens B, Luypaerts A, Hiele M, Ghoos Y, Rutgeerts P. 1998. Digestibility of cooked and raw egg protein in humans as assessed by stable isotope techniques. *J. Nutr.* 128:1716–22

Ezeogu LI, Duodu KG, Emmambux MN, Taylor JR. 2008. Influence of cooking conditions on the protein matrix of sorghum and maize endosperm flours. *Cereal Chem.* 85:397–402

Faist V, Erbersdobler HF. 2001. Metabolic transit and in vivo effects of melanoidins and precursor compounds deriving from the Maillard reaction. *Ann. Nutr. Metab.* 45:1–12

FAO. 2011. *Dietary protein quality evaluation in human nutrition*. Rep. Expert Consult., FAO, Rome

Ferrua MJ, Kong F, Singh RP. 2011. Computational modeling of gastric digestion and the role of food material properties. *Trends Food Sci. Technol.* 22:480–91

Ferrua MJ, Singh RP. 2010. Modeling the fluid dynamics in a human stomach to gain insight of food digestion. *J. Food Sci.* 75:R151–62

Freitas D, Le Feunteun S. 2019. Inhibitory effect of black tea, lemon juice, and other beverages on salivary and pancreatic amylases: what impact on bread starch digestion? A dynamic in vitro study. *Food Chem.* 297:124885

Giang TM, Gaucel S, Brestaz P, Anton M, Meynier A, et al. 2016. Dynamic modeling of in vitro lipid digestion: individual fatty acid release and bioaccessibility kinetics. *Food Chem.* 194:1180–88

Gilani GS, Cockell KA, Sepehr E. 2005. Effects of antinutritional factors on protein digestibility and amino acid availability in foods. *J. AOAC Int.* 88:967–87

Gilani GS, Xiao CW, Cockell KA. 2012. Impact of antinutritional factors in food proteins on the digestibility of protein and the bioavailability of amino acids and on protein quality. *Br. J. Nutr.* 108:S315–32

Goff HD, Repin N, Fabek H, El Khoury D, Gidley MJ. 2018. Dietary fibre for glycaemia control: towards a mechanistic understanding. *Bioact. Carbohydr. Diet. Fibre* 14:39–53

Golding M, Wooster TJ, Day L, Xu M, Lundin L, et al. 2011. Impact of gastric structuring on the lipolysis of emulsified lipids. *Soft Matter* 7:3513–23

Graham DY, Sackman JW. 1983. Solubility of calcium soaps of long-chain fatty acids in simulated intestinal environment. *Dig. Dis. Sci.* 28:733–36

Grassby T, Picout DR, Mandalari G, Faulks RM, Kendall CWC, et al. 2014. Modelling of nutrient bioaccessibility in almond seeds based on the fracture properties of their cell walls. *Food Funct.* 5:3096–106

Groopman EE, Carmody RN, Wrangham RW. 2015. Cooking increases net energy gain from a lipid-rich food. *Am. J. Phys. Anthropol.* 156:11–18

Grundy MML, Carrière F, Mackie AR, Gray DA, Butterworth PJ, Ellis PR. 2016a. The role of plant cell wall encapsulation and porosity in regulating lipolysis during the digestion of almond seeds. *Food Funct.* 7:69–78

Grundy MML, Edwards CH, Mackie AR, Gidley MJ, Butterworth PJ, Ellis PR. 2016b. Re-evaluation of the mechanisms of dietary fibre and implications for macronutrient bioaccessibility, digestion and postprandial metabolism. *Br. J. Nutr.* 116:816–33

Grundy MML, Quint J, Rieder A, Ballance S, Dreiss CA, et al. 2017. The impact of oat structure and β-glucan on in vitro lipid digestion. *J. Funct. Foods* 38:378–88

Jakobek L. 2015. Interactions of polyphenols with carbohydrates, lipids and proteins. *Food Chem.* 175:556–67

Johnston K, Thomas EL, Bell JD, Frost G, Robertson MD. 2009. Resistant starch improves insulin sensitivity in metabolic syndrome. *Diabet. Med.* 27(4):391–97

Kamei M, Ohgaki S, Kanbe T, Niiya I, Mizutani H, et al. 1995. Effects of highly hydrogenated soybean oil and cholesterol on plasma, liver cholesterol, and fecal steroids in rats. *Lipids* 30:533–39

Kan L, Oliviero T, Verkerk R, Fogliano V, Capuano E. 2020. Interaction of bread and berry polyphenols affects starch digestibility and polyphenols bio-accessibility. *J. Funct. Foods* 68:103924

Kaplan RJ, Greenwood CE. 1998. Poor digestibility of fully hydrogenated soybean oil in rats: a potential benefit of hydrogenated fats and oils. *J. Nutr.* 128:875–80

Kaur L, Maudens E, Haisman DR, Boland MJ, Singh H. 2014. Microstructure and protein digestibility of beef: the effect of cooking conditions as used in stews and curries. *LWT Food Sci. Technol.* 55:612–20

Kondjoyan A, Daudin J-D, Santé-Lhoutellier V. 2015. Modelling of pepsin digestibility of myofibrillar proteins and of variations due to heating. *Food Chem.* 172:265–71

Kong F, Singh R. 2008. A model stomach system to investigate disintegration kinetics of solid foods during gastric digestion. *J. Food Sci.* 73:E202–10

Lacroix M, Bon C, Bos C, Léonil J, Benamouzig R, et al. 2008. Ultra high temperature treatment, but not pasteurization, affects the postprandial kinetics of milk proteins in humans. *J. Nutr.* 138:2342–47

Le Bourvellec C, Renard C. 2012. Interactions between polyphenols and macromolecules: quantification methods and mechanisms. *Crit. Rev. Food Sci. Nutr.* 52:213–48

Li H, Dhital S, Gidley MJ, Gilbert RG. 2019. A more general approach to fitting digestion kinetics of starch in food. *Carbohydr. Polym.* 225:115244

Liu W-C, Halley PJ, Gilbert RG. 2010. Mechanism of degradation of starch, a highly branched polymer, during extrusion. *Macromolecules* 43:2855–64

Lorenzen JK, Astrup A. 2011. Dairy calcium intake modifies responsiveness of fat metabolism and blood lipids to a high-fat diet. *Br. J. Nutr.* 105:1823–31

Love R, Lentle R, Asvarujanon P, Hemar Y, Stafford K. 2013. An expanded finite element model of the intestinal mixing of digesta. *Food Dig.* 4:26–35

Ludwig DS. 2002. The glycemic index: physiological mechanisms relating to obesity, diabetes, and cardiovascular disease. *JAMA* 287:2414–23

Luo Q, Borst JW, Westphal AH, Boom RM, Janssen AE. 2017. Pepsin diffusivity in whey protein gels and its effect on gastric digestion. *Food Hydrocoll.* 66:318–25

Luo Q, Chen D, Boom RM, Janssen AE. 2018. Revisiting the enzymatic kinetics of pepsin using isothermal titration calorimetry. *Food Chem.* 268:94–100

Luo Q, Sewalt E, Borst JW, Westphal AH, Boom RM, Janssen AE. 2019. Analysis and modeling of enhanced green fluorescent protein diffusivity in whey protein gels. *Food Res. Int.* 120:449–55

Maki KC, Pelkman CL, Finocchiaro ET, Kelley KM, Lawless AL, et al. 2012. Resistant starch from high-amylose maize increases insulin sensitivity in overweight and obese men. *J. Nutr.* 142:717–23

Malagelada J-R, Go VL, Summerskill W. 1979. Different gastric, pancreatic, and biliary responses to solid-liquid or homogenized meals. *Dig. Dis. Sci.* 24:101–10

Maljaars P, Peters H, Mela D, Masclee A. 2008a. Ileal brake: a sensible food target for appetite control. A review. *Physiol. Behav.* 95:271–81

Maljaars P, Symersky T, Kee B, Haddeman E, Peters H, Masclee A. 2008b. Effect of ileal fat perfusion on satiety and hormone release in healthy volunteers. *Int. J. Obes.* 32:1633–39

Mandalari G, Merali Z, Ryden P, Chessa S, Bisignano C, et al. 2018. Durum wheat particle size affects starch and protein digestion in vitro. *Eur. J. Nutr.* 57:319–25

Marciani L, Faulks R, Wickham MS, Bush D, Pick B, et al. 2008. Effect of intragastric acid stability of fat emulsions on gastric emptying, plasma lipid profile and postprandial satiety. *Br. J. Nutr.* 101:919–28

McDougall GJ, Stewart D. 2005. The inhibitory effects of berry polyphenols on digestive enzymes. *Biofactors* 23:189–95

Melito C, Tovar J. 1995. Cell-walls limit in-vitro protein digestibility in processed legume seeds. *Food Chem*. 53:305–7

Mennah-Govela YA, Singh RP, Bornhorst GM. 2019. Buffering capacity of protein-based model food systems in the context of gastric digestion. *Food Funct*. 10:6074–87

Merrill A, Watt B. 1973. *Energy value of foods—basis and derivation*. Agric. Handb. 74, US Dept. of Agric., Washington, DC. **https://www.ars.usda.gov/arsuserfiles/80400535/data/classics/usda%20handbook%2074.pdf**

Minekus M, Jelier M, Xiao J-Z, Kondo S, Iwatsuki K, et al. 2005. Effect of partially hydrolyzed guar gum (PHGG) on the bioaccessibility of fat and cholesterol. *Biosci. Biotechnol. Biochem.* 69:932–38

Mishra S, Hardacre A, Monro J. 2012. Food structure and carbohydrate digestibility. In *Carbohydrates: Comprehensive Studies on Glycobiology and Glycotechnology*, ed. C-F Chang, pp. 289–316. London: IntechOpen

Moxon TE, Gouseti O, Bakalis S. 2016. In silico modelling of mass transfer & absorption in the human gut. *J. Food Eng.* 176:110–20

Moxon TE, Nimmegeers P, Telen D, Fryer PJ, Van Impe J, Bakalis S. 2017. Effect of chyme viscosity and nutrient feedback mechanism on gastric emptying. *Chem. Eng. Sci.* 171:318–30

Nguyen GT, Sopade PA. 2018. Modeling starch digestograms: computational characteristics of kinetic models for in vitro starch digestion in food research. *Compr. Rev. Food Sci. Food Saf.* 17:1422–45

Novev JK, Doostmohammadi A, Zöttl A, Yeomans JM. 2020. Mesoscale modelling of polymer aggregate digestion. *Curr. Res. Food Sci.* 3:122–33

Novotny JA, Gebauer SK, Baer DJ. 2012. Discrepancy between the Atwater factor predicted and empirically measured energy values of almonds in human diets. *Am. J. Clin. Nutr.* 96:296–301

Nyemb K, Guérin-Dubiard C, Pézennec S, Jardin J, Briard-Bion V, et al. 2016. The structural properties of egg white gels impact the extent of in vitro protein digestion and the nature of peptides generated. *Food Hydrocoll.* 54:315–27

Oberli M, Marsset-Baglieri A, Airinei G, Santé-Lhoutellier V, Khodorova N, et al. 2015. High true ileal digestibility but not postprandial utilization of nitrogen from bovine meat protein in humans is moderately decreased by high-temperature, long-duration cooking. *J. Nutr.* 145:2221–28

Oria MP, Hamaker BR, Axtell JD, Huang C-P. 2000. A highly digestible sorghum mutant cultivar exhibits a unique folded structure of endosperm protein bodies. *PNAS* 97:5065–70

Pallares AP, Miranda BA, Truong NQA, Kyomugasho C, Chigwedere CM, et al. 2018. Process-induced cell wall permeability modulates the in vitro starch digestion kinetics of common bean cotyledon cells. *Food Funct*. 9:6544–54

Pasini G, Simonato B, Giannattasio M, Peruffo AD, Curioni A. 2001. Modifications of wheat flour proteins during in vitro digestion of bread dough, crumb, and crust: an electrophoretic and immunological study. *J. Agric. Food Chem.* 49:2254–61

Pasquier B, Armand M, Castelain C, Guillon F, Borel P, et al. 1996. Emulsification and lipolysis of triacylglycerols are altered by viscous soluble dietary fibres in acidic gastric medium in vitro. *Biochem. J.* 314:269–75

Pérez S, Bertoft E. 2010. The molecular structures of starch components and their contribution to the architecture of starch granules: a comprehensive review. *Starch-Stärke* 62:389–420

Pirillo A, Norata GD, Catapano AL. 2014. Postprandial lipemia as a cardiometabolic risk factor. *Curr. Med. Res. Opin.* 30:1489–503

Primo-Martin C, Van Nieuwenhuijzen N, Hamer R, Van Vliet T. 2007. Crystallinity changes in wheat starch during the bread-making process: starch crystallinity in the bread crust. *J. Cereal Sci.* 45:219–26

Robertson MD, Bickerton AS, Dennis AL, Vidal H, Frayn KN. 2005. Insulin-sensitizing effects of dietary resistant starch and effects on skeletal muscle and adipose tissue metabolism. *Am. J. Clin. Nutr.* 82:559–67

Rovalino-Córdova AM, Aguirre Montesdoca V, Capuano E. 2021. A mechanistic model to study the effect of the cell wall on starch digestion in intact cotyledon cells. *Carbohydr. Polym.* 253:117351

Rovalino-Córdova AM, Fogliano V, Capuano E. 2018. A closer look to cell structural barriers affecting starch digestibility in beans. *Carbohydr. Polym.* 181:994–1002

Rovalino-Córdova AM, Fogliano V, Capuano E. 2019. The effect of cell wall encapsulation on macronutrients digestion: a case study in kidney beans. *Food Chem*. 286:557–66
Shrestha AK, Ng CS, Lopez-Rubio A, Blazek J, Gilbert EP, Gidley MJ. 2010. Enzyme resistance and structural organization in extruded high amylose maize starch. *Carbohydr. Polym.* 80:699–710
Sicard J, Mirade P-S, Portanguen S, Clerjon S, Kondjoyan A. 2018. Simulation of the gastric digestion of proteins of meat bolus using a reaction–diffusion model. *Food Funct*. 9:6455–69
Smith TJ, Karl JP, Wilson MA, Whitney CC, Barrett A, et al. 2019. Glycaemic regulation, appetite and ex vivo oxidative stress in young adults following consumption of high-carbohydrate cereal bars fortified with polyphenol-rich berries. *Br. J. Nutr.* 121:1026–38
Soerensen KV, Thorning TK, Astrup A, Kristensen M, Lorenzen JK. 2014. Effect of dairy calcium from cheese and milk on fecal fat excretion, blood lipids, and appetite in young men. *Am. J. Clin. Nutr.* 99:984–91
Syahariza Z, Sar S, Hasjim J, Tizzotti MJ, Gilbert RG. 2013. The importance of amylose and amylopectin fine structures for starch digestibility in cooked rice grains. *Food Chem*. 136:742–49
Taghipoor M, Barles G, Georgelin C, Licois J-R, Lescoat P. 2014. Digestion modeling in the small intestine: impact of dietary fiber. *Math. Biosci.* 258:101–12
Taghipoor M, Lescoat P, Licois J-R, Georgelin C, Barles G. 2012. Mathematical modeling of transport and degradation of feedstuffs in the small intestine. *J. Theor. Biol.* 294:114–21
Tan S-Y, Peh EW-Y, Marangoni AG, Henry CJ. 2017. Effects of liquid oil versus oleogel co-ingested with a carbohydrate-rich meal on human blood triglycerides, glucose, insulin and appetite. *Food Funct*. 8:241–49
Tessier R, Khodorova N, Calvez J, Kapel R, Quinsac A, et al. 2020. 15N and ^{2}H intrinsic labeling demonstrate that real digestibility in rats of proteins and amino acids from sunflower protein isolate is almost as high as that of goat whey. *J. Nutr.* 150:450–57
Thevenot J, Cauty C, Legland D, Dupont D, Floury J. 2017. Pepsin diffusion in dairy gels depends on casein concentration and microstructure. *Food Chem*. 223:54–61
Thorning TK, Raben A, Bendsen NT, Jørgensen HH, Kiilerich P, et al. 2016. Importance of the fat content within the cheese-matrix for blood lipid profile, faecal fat excretion, and gut microbiome in growing pigs. *Int. Dairy J.* 61:67–75
Tonda A, Grosvenor A, Clerens S, Le Feunteun S. 2017. In silico modeling of protein hydrolysis by endoproteases: a case study on pepsin digestion of bovine lactoferrin. *Food Funct*. 8:4404–13
Törrönen R, Sarkkinen E, Tapola N, Hautaniemi E, Kilpi K, Niskanen L. 2010. Berries modify the postprandial plasma glucose response to sucrose in healthy subjects. *Br. J. Nutr.* 103:1094–97
Van Aken GA, Bomhof E, Zoet FD, Verbeek M, Oosterveld A. 2011. Differences in in vitro gastric behaviour between homogenized milk and emulsions stabilised by Tween 80, whey protein, or whey protein and caseinate. *Food Hydrocoll*. 25:781–88
van der Sman R, Houlder S, Cornet S, Janssen A. 2020. Physical chemistry of gastric digestion of proteins gels. *Curr. Res. Food Sci.* 2:45–60
Verkempinck S, Salvia-Trujillo L, Garcia MI, Hendrickx M, Grauwet T. 2019. From single to multiresponse modelling of food digestion kinetics: the case of lipid digestion. *J. Food Eng.* 260:40–49
Verlinden BE, Nicolaï BM, De Baerdemaeker J. 1995. The starch gelatinization in potatoes during cooking in relation to the modelling of texture kinetics. *J. Food Eng.* 24:165–79
Vors C, Pineau G, Gabert L, Drai J, Louche-Pélissier C, et al. 2013. Modulating absorption and postprandial handling of dietary fatty acids by structuring fat in the meal: a randomized crossover clinical trial. *Am. J. Clin. Nutr.* 97:23–36
Waldron KW, Smith AC, Parr AJ, Ng A, Parker ML. 1997. New approaches to understanding and controlling cell separation in relation to fruit and vegetable texture. *Trends Food Sci. Technol.* 8:213–21
Wang S, Li C, Copeland L, Niu Q, Wang S. 2015. Starch retrogradation: a comprehensive review. *Compr. Rev. Food Sci. Food Saf.* 14:568–85
Wang S, Zhang X, Wang S, Copeland L. 2016. Changes of multi-scale structure during mimicked DSC heating reveal the nature of starch gelatinization. *Sci. Rep.* 6:28271
Wang Y, Chao C, Huang H, Wang S, Wang S, et al. 2019. Revisiting mechanisms underlying digestion of starches. *J. Agric. Food Chem.* 67:8212–26
Wilcox MD, Brownlee IA, Richardson JC, Dettmar PW, Pearson JP. 2014. The modulation of pancreatic lipase activity by alginates. *Food Chem*. 146:479–84

Windey K, De Preter V, Verbeke K. 2012. Relevance of protein fermentation to gut health. *Mol. Nutr. Food Res.* 56:184–96

Wong JH, Lau T, Cai N, Singh J, Pedersen JF, et al. 2009. Digestibility of protein and starch from sorghum (Sorghum bicolor) is linked to biochemical and structural features of grain endosperm. *J. Cereal Sci.* 49:73–82

Ye A, Cui J, Dalgleish D, Singh H. 2016. Formation of a structured clot during the gastric digestion of milk: impact on the rate of protein hydrolysis. *Food Hydrocoll.* 52:478–86

Yu W, Tao K, Gilbert RG. 2018. Improved methodology for analyzing relations between starch digestion kinetics and molecular structure. *Food Chem.* 264:284–92

Zahir M, Fogliano V, Capuano E. 2018. Food matrix and processing modulate in vitro protein digestibility in soybeans. *Food Funct.* 9:6326–36

Zeleznak K, Hoseney R. 1986. The role of water in the retrogradation of wheat starch gels and bread crumb. *Cereal Chem.* 63:407–11

Zou W, Sissons M, Gidley MJ, Gilbert RG, Warren FJ. 2015. Combined techniques for characterising pasta structure reveals how the gluten network slows enzymic digestion rate. *Food Chem.* 188:559–68