

The fate of dietary protein in the gastrointestinal tract and implications for colonic disease

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Abstract

Protein is an essential nutrient in the human diet. Global Westernization and modern dietary trends have seen protein become a more substantial contributor to the Western diet, with dietary sources expanding beyond traditional wholefoods to a myriad of processed protein-enriched food products. Although dietary protein is critical for human health, it has also been implicated in colonic health and disease both directly via the microbial fermentation of protein entering the colonic environment and indirectly by affecting the intake of other nutrients in the diet such as fibre. Although protein digestion in the small intestine is highly efficient, there are numerous factors that can influence the capacity for protein digestion and absorption, particularly dietary factors representative of modern-day protein intakes such as high protein diets and food manufacturing. The subsequent fermentation of protein and production of microbial metabolites in the colon is in turn affected by the source of protein entering the colon and the presence of fibre. In this Review, we examine factors that influence human digestion and absorption of protein in the small intestine and protein fermentation in the colon, describing implications for colonic health and disease.

Sections

Introduction

Protein — basic principles

Epidemiological trends

Factors that influence dietary protein fate

Dietary protein intake and colonic health

Future directions and clinical implications

Conclusions

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Key points

- Global Westernization has changed the way protein is consumed in modern-day society with trends focused on high protein diets and processed protein sources.
- Dietary and non-dietary factors including protein source, fibre intake and medications influence capacity for digestion and absorption of protein in the small intestine and subsequent availability for colonic fermentation.
- Metabolites produced during colonic protein fermentation have the potential to exert beneficial and/or detrimental effects on the colonic mucosa.
- Optimization of protein intake requires careful consideration of the effect of protein on colonic health directly via its colonic fermentation and indirectly by its effect on dietary intake of other nutrients.
- Further research is required to personalize protein recommendations based on genetic, environmental and microbial data to optimize health and minimize the risk of colonic disease.

Introduction

Protein is an essential nutrient in the human diet, providing amino acids critical to bodily functions and overall health¹. Humans derive most protein from exogenous dietary sources, traditionally from wholefood protein sources including meat, fish, poultry, dairy and legumes^{2,3}. Processed alternatives to wholefood protein sources such as plant-based milks, meat analogues and protein supplements as well as protein-enriched foods have now become popular, with food industry, health and environmental concerns influencing dietary trends and protein consumption^{4,5}. The expansion of food products alongside the promotion of protein for its nutritional and health benefits has led to considerable modern-day pressure to put the type and amount of protein people are eating at the forefront of consumer food choices.

Dietary protein must be broken down by digestive enzymes into peptides and amino acids, which can be transported across the epithelium of the small intestine to be absorbed into the bloodstream and metabolized by the body¹. However, this process is not 100% efficient. Proteins can escape digestion if there is rapid intestinal transit or if the load consumed exceeds absorptive capacity^{6,7}. Other proteins might be structurally resistant to digestion because of their chemical conformation; such proteins have recently been termed ‘resistant proteins’^{8,9}. Proteins that enter the colon partially digested or undigested are used as substrates for microbial activity in which they are subject to proteolysis^{10,11}. Microorganisms can use the resultant small peptides and amino acids, channelling them into synthesis of new proteins or fermentative pathways to produce energy and various metabolites¹⁰. Metabolites produced during colonic protein fermentation are of interest owing to their potential to exert beneficial and/or detrimental effects on the colonic microenvironment.

Despite considerable focus on dietary protein intake, its relevance to colonic health and disease is often overlooked. When dietary protein intake is altered, it can indirectly affect the dietary intake of other nutrients and directly affect the availability of protein substrate for microbial fermentation in the colon¹². This Review examines the factors

influencing human digestion and absorption of protein in the small intestine, and protein fermentation in the colon, and describes the implications for colonic health and disease.

Protein — basic principles

Proteins are large macromolecules that comprise amino acids, linked by peptide bonds¹³. Protein structures are determined by amino acid composition, molecular forces and post-translational modifications¹⁴ (Supplementary Fig. 1). Proteins may be endogenous (produced by the host) or exogenous (obtained from an external source)¹³. In humans, endogenous proteins are transported into and out of the gastrointestinal tract and include host digestive secretions and enzymes, mucin, plasma proteins, exudate and desquamated epithelial cells^{15,16}. Exogenous proteins can come from microbes that live on or within human tissues, but are primarily obtained through dietary intake of wholefoods and processed food products, and originate from plant and animal protein sources. These proteins can be digested, absorbed and fermented throughout the gastrointestinal tract¹⁴ (Fig. 1, Box 1).

A human’s need for protein is driven by the metabolic demand for amino acids¹, the body’s main source of nitrogen, a critical nutrient for sustaining life¹³. Since the human body cannot store excess nitrogen, it aims to maintain a nitrogen balance through protein turnover, which involves the breakdown (catabolism) and synthesis (anabolism) of amino acids that can be utilized, or degraded and excreted by the body¹. Of the 20 amino acids required by humans, nine are indispensable, meaning they cannot be produced endogenously and must be obtained from exogenous sources¹⁷ (Supplementary Fig. 1). The term ‘conditionally indispensable’ is applied to amino acids that become essential at certain life stages¹³. Although this classification is helpful from a nutritional standpoint, it has been criticized as oversimplified since there are exceptions to this rule at the metabolic level¹³. For example, indispensable amino acids can be synthesized endogenously from urea salvage¹³. Unique amino acid sequences influence the structure and resultant functionality of a protein, which drives the body’s need for an appropriate supply of the 20 amino acids¹⁴ (Box 2).

Epidemiological trends

The soaring protein market

Global trends in dietary protein intake have evolved remarkably since the twentieth century (Fig. 2), driven by numerous factors including socioeconomics, health, food supply and the environment³. In Western countries, despite protein deficiency not being a prevalent issue, protein is gradually becoming a more substantial component of the diet, coinciding with the expansion of higher protein recommendations in the literature and media. Australian Health Survey data for 1995, 2012 and 2023 show that the mean contribution of protein to overall daily energy intake has risen from 16% to 18% to 19%, respectively^{18,19}. Additionally, 71% of US residents were actively trying to consume more protein in 2024, an increase from 59% in 2022 (ref. 20). There is a further rise predicted, with growing global interest in protein, sports and health foods along with a substantial increase in the availability and marketing of ‘high protein’ food products and protein supplements over the past 10 years^{21,22}. For example, 94.5% of non-athlete Australian adults who consume sports foods are choosing protein-based products²³.

Although plant proteins continue to be the primary protein source globally, Westernization has led to a considerable increase in consumption of animal protein worldwide^{2,3,24}. By 2030, it is predicted that calorie consumption from livestock products will be more than 1.5-fold greater than in 1962 (ref. 2). Paradoxically, with a spotlight

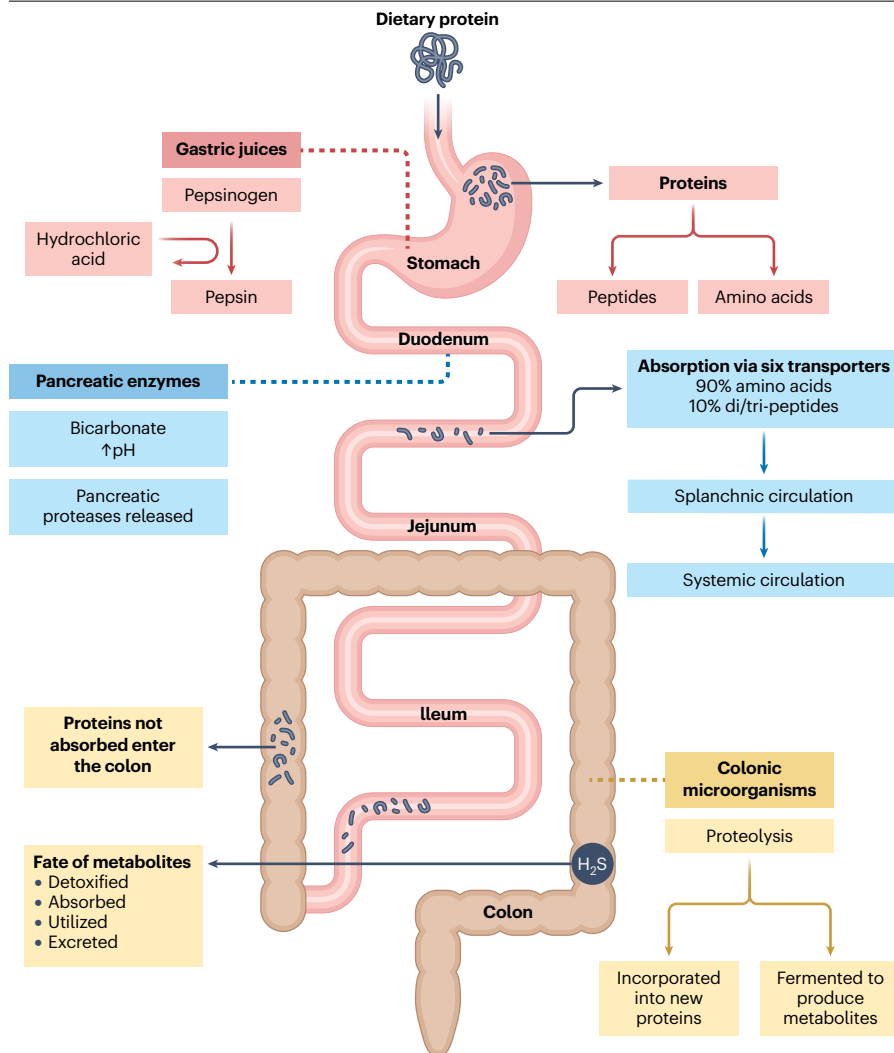


Fig. 1 | The fate of dietary protein in the human gastrointestinal tract. The gastric phase of protein digestion is characterized by the breakdown of proteins into smaller subunits. Upon reaching the small intestine, pancreatic enzymes break proteins down into small peptides or amino acids that are suitable for uptake into the circulation by specific transporters. Proteins that escape or resist digestion in the small intestine are delivered to the colon. Microorganisms can break proteins down into smaller units that can be utilized for protein synthesis or fermented to produce a vast array of metabolites^{12,152}.

on environmental sustainability and chronic disease burden, there is growing worldwide interest in plant-based protein alternatives^{5,22}. Data from the UK National Diet and Nutrition Survey show that consumption of plant-based alternatives increased from 6.7% in 2008–2011 to 13% in 2017–2019 (ref. 25). These trends suggest that globally, both animal and plant protein consumption will concurrently increase, with disparity across different nations anticipated based on supply, demand and socioeconomic factors.

Dietary protein intake and colonic disease

The global burden of colonic disease is growing (Fig. 2), with environmental and microbial-driven factors implicated in the pathogenesis of conditions such as colorectal cancer and inflammatory bowel disease^{26,27}. Adoption of a Western dietary pattern that is higher in animal protein, fats and sugars and lower in dietary fibre, alongside global industrialization, coincides with rising prevalence²⁴.

Undigested dietary substrates that reach the colon can modulate microbial activity, mechanistically altering the colonic microenvironment with an ensuing influence on colonic health¹². The concept of colonic protein fermentation was first described in the late 1970s and

attention has since been drawn to resultant metabolites with both protective and toxic effects depending on their concentrations²⁸ (Table 1). Red and processed meat are implicated in the risk of ulcerative colitis and colorectal cancer^{29,30}. The purported drivers of colonic inflammation and carcinogenesis include toxic levels of metabolites such as hydrogen sulfide, nitric oxide and ammonia, which can negatively affect the colonic mucosa^{10,31}. Indirectly, high intake of animal protein often coincides with reduced fibre consumption, a dietary component known to be protective for colonic health^{24,32}. This finding fits the Western dietary pattern observed in Australia, with 2023 data highlighting an increase in consumption of meat products, high intake of discretionary processed foods and subsequent inadequate intake of dietary fibre¹⁹.

Although associations between animal protein consumption and colonic disease risk are recognized, the influence of the recent increases in the consumption of protein, protein supplements and meat analogues remains poorly understood¹². For example, if a 150 g serving of meat (providing 30 g of protein) is consumed at a meal and is accompanied by consumption of a protein shake providing an additional 30 g of protein, it is uncertain whether doubling the amount of

Box 1 | Anatomical overview of protein digestion, absorption and fermentation

Ingestion of protein triggers release of hormones including gastrin, cholecystokinin and secretin, stimulating release of gastric secretions¹⁵³ (Fig. 1). Pepsin is activated from pepsinogen in an autocatalytic process within a specific pH range, influenced by secretion of hydrochloric acid¹⁵³.

In response to chyme, containing peptides, amino acids and gastric secretions entering the duodenum, the pancreas releases bicarbonate, increasing luminal pH and proteases, which are subsequently activated^{15,66}. Proteases act at specific peptide linkage sites within the lumen and brush border of mucosal cells across the small intestine, rendering peptides suitable for absorption^{15,16}. Small peptides and amino acids are transported across the enterocyte apical membrane of the small intestine via sodium-dependent or hydrogen-dependent transporters, or via independent mechanisms^{15,16,153}. Small peptides can be further hydrolysed by cytoplasmic proteases within the enterocytes¹⁵. A proportion of amino acids are retained for use by enterocytes within the intestine, but the majority flow through the portal vein for transport to the liver before release into the systemic circulation for uptake by peripheral tissues^{66,154}. The liver has a key

role in protein metabolism and processes amino acids that are in excess of body requirements¹³. Deamination (removal of the nitrogen-containing amino group) results in production of ammonia, which is toxic to human cells and is converted to urea with most (>90%) delivered to the kidneys for excretion¹⁵⁵.

Approximately 6–18 g protein per day reaches the colon in adults, with variation in quantity largely influenced by the proportion of protein that escapes or resists digestion in the small intestine¹². The process of proteolysis by bacterial proteases and peptidases results in production of smaller peptides and amino acids¹⁴³. These substrates could be used for protein synthesis and incorporated into structural and microbial proteins, or fermented by gut microorganisms¹². Protein fermentation is more prominent in the distal colon and is associated with a higher pH and the production of various metabolites such as branched-chain fatty acids (BCFAs), hydrogen sulfide, ammonia and phenols^{150,152}. Metabolites produced through protein fermentation can be detoxified by colonocytes, absorbed by colonocytes and transported into the circulation, utilized by microorganisms or excreted in faeces¹².

protein consumed will increase absorption in the small intestine or increase the load of protein substrate delivered to the colon. Notably, resistant proteins and phytochemicals naturally found in plant proteins

might provide colonic and general health benefits^{8,33}; however, it is unclear whether these benefits are lost when modern-day manufactured protein products, such as meat analogues, are consumed. Dietary proteins cannot be viewed in isolation; concurrent dietary fibre intake, protein source, quantity consumed and degree of manufacturing must be evaluated collectively for a nuanced interpretation of risk and health benefit. Given evolving Western dietary patterns, understanding how modern protein consumption affects colonic health is imperative^{2,24}.

Box 2 | Why do we need protein and how much should we be consuming?

Dietary protein provides amino acids that are required primarily for growth, development and protein synthesis¹⁵⁶. Protein synthesis is defined as an anabolic process whereby amino acids are used as the building blocks for new proteins¹⁷. Amino acids can have key regulatory roles in metabolic pathways including gene expression, synthesis and secretion of hormones, nutrient metabolism, oxidative defence, reproductive cell development and immune function¹⁵⁶. Amino acids can also be used as an energy source through ATP synthesis by intestinal tissues and peripheral tissues if required¹.

Dietary protein requirements are determined by metabolic demand and the rate of utilization¹³. These demands can fluctuate, such as during growth and development, pregnancy and lactation, and illness¹³. According to expert consensus from the WHO, the Food and Agricultural Organization and the United Nations University, a protein intake of 0.83 g/kg per day meets the needs of 97.5% of the healthy adult population¹³. Much higher intakes have been recommended in relation to physical activity and the ageing body and for individuals aiming to achieve and maintain a desired body composition and ratio of muscle to fat mass^{1,4,157}, as follows:

- 1.0–1.2 g/kg per day for people >65 years or age¹⁵⁷
- 1.2–1.5 g/kg per day for people with active disease (for example, inflammatory bowel disease or cancer)^{136,158}
- 1.4–2.0 g/kg per day to promote muscle protein synthesis and for physical training adaptations⁴
- 2 g/kg per day proposed as safe for long-term consumption¹
- 3.5 g/kg per day proposed as a safe tolerable upper limit¹

Factors that influence dietary protein fate

The complexities of human digestion become evident when we consider how dietary intake, food systems and changes to our health intersect. To interpret how different factors influence the processes of protein digestion and fermentation, an understanding of the key metrics used is imperative (Fig. 3 and Box 3, Supplementary Table 1 & 2).

Protein quantity

The quantity of protein consumed influences the proportion delivered to the colon since the efficiency of digestion and subsequent absorption of protein reduces with increasing load (Table 2). Thus, studies of ileostomates have shown that ileal nitrogen excretion correlates with dietary protein intake⁶. However, the utilization of nitrogenous materials by colonic microorganisms is not a simple linear relationship³⁴. Modest increases in protein load through supplementation (2.5–20 g protein per day), equating to less than the amount of protein provided by a standard scoop of protein powder, are not associated with increased concentrations of faecal metabolites such as BCFAs and ammonia^{35,36}. However, larger doses of protein supplementation (58 g protein per day), equating to almost three times a standard scoop of protein powder, are associated with increased concentrations of ammonia in faeces and *p*-cresol in urine, correlating with faecal production^{12,37}. Likewise, high meat intakes (136–212 g protein per day) are associated with increased concentrations of faecal metabolites; ammonia, *N*-nitroso compounds (NOCs) and sulfides compared with those associated with low meat intakes (51–68 g protein per day)^{7,38–40}. By contrast, when

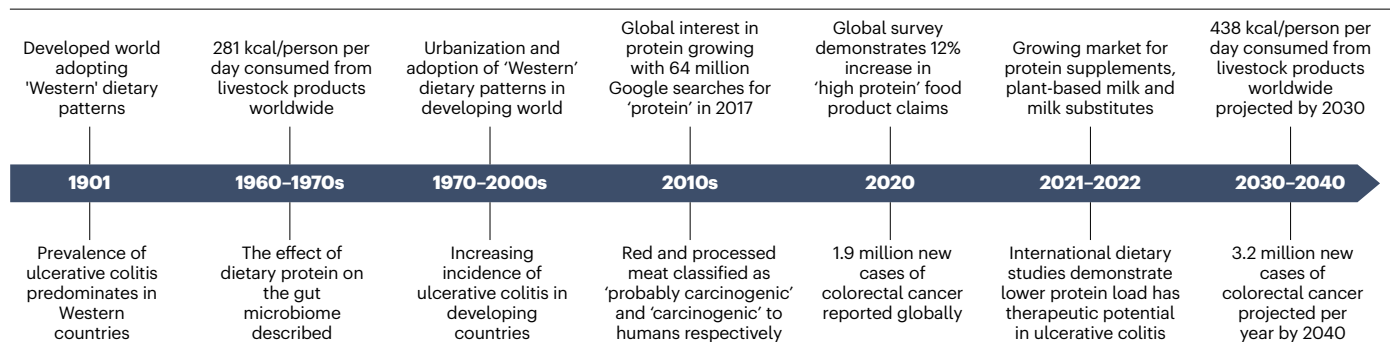


Fig. 2 | Trends in dietary protein intake and colonic disease since inception of Westernized dietary patterns. Westernization across both developed and developing nations since 1901 has led to a considerable increase in consumption of animal protein and demand for processed protein sources worldwide^{2,3,24}.

Westernized dietary patterns are implicated in the concurrent rising prevalence of colonic diseases worldwide. Colonic microbial fermentation of dietary substrates that reach the colonic environment is proposed to underpin this association.

protein intake was near doubled (from 74 to 135 g per day) in 28 older men, markers of protein fermentation (faecal volatile organic compounds, α -diversity and β -diversity of the faecal microbiota) were not altered⁴¹. Fibre intake was high in this cohort (>50 g per day)⁴¹, which might have had a confounding effect on protein fermentation, as discussed below⁴².

Plant and animal proteins

Molecular, structural and physiochemical differences exist between animal-derived and plant-derived proteins, influencing digestibility in the small intestine and fermentability in the colon¹⁴ (Supplementary Table 3). Many plant proteins have compact structures with intrinsically disordered and aggregated peptide bonds, tightly linked β -sheets and stable disulfide bonds, rendering them less accessible to digestive enzymes with poor aqueous solubility^{14,43}. Plant proteins also often contain natural compounds that stabilize and protect their structure, commonly referred to as anti-nutrients (for example, lectins and phytates, sometimes referred to as non-nutritive compounds)^{33,43,44}. These concepts support the finding that the true ileal digestibility scores observed for wholefood plant proteins (60–84%) are lower than for wholefood animal proteins (>90%)^{6,45–49} (Supplementary Table 4).

Increased delivery of plant-based nitrogenous material to the colon does not necessarily equate with greater protein fermentation (Table 2). In fact, animal protein-based diets (for example, Western and carnivore diets) are associated with greater concentrations of metabolites such as BCFA or hydrogen sulfide in the faeces and *p*-cresol in the urine than plant protein-based diets (for example, vegetarian and vegan diets)^{11,50–52}. The effects of plant protein-based compared with animal protein-based diets on the α -diversity or β -diversity of the faecal microbiota, however, are more variable^{11,50,51}. The absence of greater protein fermentation with plant-based diets could be explained by the structural complexity of plant proteins, reducing access to peptide bonds by colonic microbes, and the presence of fibre that may be preferentially fermented⁴².

Fibre

Dietary fibre can inhibit protein digestion and absorption through mechanisms that depend on their physiochemical properties and how they are consumed⁵³ (Table 2). For example, resistant starch and rye products are associated with reductions in true and apparent ileal digestibility scores, respectively^{6,54}. In the colon, whether fermentation

is directed towards predominantly carbohydrate or protein substrates is determined by substrate availability and the preference of bacteria in general to generate energy from carbohydrates^{55–57} (Fig. 4). Studies in vitro in faecal slurries have shown that the inhibitory effect of carbohydrate substrates on the rate of protein fermentation is dependent upon fermentability of the former⁵⁸. This finding is reflected in vivo by the finding that addition of poorly fermentable non-starch polysaccharide alone (12–30 g per day) to 'normal' and 'high' protein diets did not change faecal ammonia concentrations in humans^{39,40,59}. In multiple studies in humans, the addition of fermentable fibre (resistant starch and fructo-oligosaccharides) to the diet has been shown to potentially suppress faecal markers of protein fermentation^{58,60,61}, but in a crossover study in eight men resistant starch in the diet did not alter faecal concentrations of NOCs and ammonia³⁸. The variability of the results is likely to be related to the region of the colon where predominant protein fermentation was occurring. Delivery of fermentable fibres to the distal colon is needed to divert bacterial fermentation away from protein to carbohydrate^{12,42,62}. This aspect has been demonstrated in rats, pigs and humans in whom concomitant ingestion of non-fermentable fibre (for example, wheat bran or sugarcane bagasse) and fermentable fibre (for example, resistant starch) pushes carbohydrate fermentation distally with concomitant reduction in protein fermentation^{59,62–64}.

Food manufacturing

Food processing techniques can alter protein digestibility, although their effects on colonic fermentation is less well understood^{65,66} (Table 2). Industrial methods, including physical, chemical and structural modifications, are applied to enhance safety, palatability, convenience, nutrition and shelf-life of foods. Physical methods, such as heating, pressurizing or milling, are commonly applied to modify food properties or improve safety and shelf-life (for example, long-life milk)⁶⁵. Heat can improve, hinder or have no effect on protein digestibility^{49,67–70}. The response, is likely to depend upon the temperature which proteins are exposed to, how long they are exposed to heat, their moisture content, pressure, the stability of the proteins subjected to heating and the testing environment (for example, feeding studies compared with in vitro studies)⁶⁶. Techniques such as fractionation and filtration can concentrate or isolate a protein to improve its functionality and increase protein content (for example, protein powders)⁴⁴. This approach can improve digestibility, as seen with isolated plant proteins

Table 1 | Effect of metabolites produced during protein fermentation on the colonic mucosa and colonic homeostasis

Metabolites	Mechanism of action in the colon	
	Beneficial to colonic homeostasis	Detrimental to colonic homeostasis
Short-chain fatty acids	Widely accepted as beneficial, can maintain intestinal barrier function, exert anti-inflammatory effects, promote mucus production and provide a source of energy to colonocytes (butyrate in particular) in humans ^{32,56}	Butyrate can be toxic to cells in vitro; however, data do not support detrimental effects in the functioning human colonic mucosa; susceptible cells include stem cells, which are protected, and cancer cells, for which toxicity could be of benefit in inducing cell death ^{96,98}
Branched-chain fatty acids	Iso-butyrate can provide a source of energy to colonocytes in rats ¹⁴⁰	Insufficient evidence to support any direct negative effect on the colonic epithelium in human cell line models ⁹⁴
Indoles or skatole	Metabolites and derivatives can increase expression of tight junction-associated molecules, improve trans-epithelial resistance and maintain intestinal barrier function in humans and preclinical models ⁹⁴	High concentrations of indoles and derivatives in a susceptible environment can be pro-inflammatory and disrupt epithelial autophagy in animal studies ¹⁴¹
Phenols (phenol/p-cresol)	Phenols largely associated with negative effects on colonic homeostasis in vitro ¹⁴²	Reduce trans-epithelial resistance, increase paracellular permeability, decrease ATP cell content, reduce colonocyte viability and can be genotoxic to colonocytes inducing DNA damage in preclinical models ^{26,94,142}
Nitric oxide	Endogenous nitric oxide is an important signalling molecule in humans involved in mucus production and motility ⁹⁴	Increased concentrations are associated with an increase in paracellular permeability, decrease in ATP cell content and impairment to hydrogen sulfide detoxification in humans and preclinical models ^{94,119}
Ammonia	Stimulates colonic epithelial cell proliferation (can be detrimental if uncontrollably upregulated), at low concentrations might not affect cell viability and can be detoxified in preclinical models ^{143,144}	Higher concentrations can lead to loss of mucus, damage the integrity of the mucous layer, reduce butyrate uptake by colonocytes, increase paracellular permeability and contribute to DNA damage in preclinical models ¹⁴³
Amines	Various amines can be present in the human colon and their direct effect on the epithelial lining is largely unknown ^{94,143}	Amines can undergo nitrosation to form N-nitroso compounds, which cause DNA damage and increase oxidative stress in human ex vivo models ⁹⁴
Hydrogen sulfide	Can be used as an inorganic energy source by colonocytes, maintains mucous integrity and can be protective against pathogenic species in humans ^{101,143}	High concentrations can exceed capacity for detoxification and can increase mucous barrier permeability, reduce colonocyte capacity for butyrate oxidation, inhibit cellular respiration and contribute to DNA damage in human ex vivo models ^{91,94,124}

(for example, pea protein isolate) that can achieve digestibility scores (>86%) similar to animal proteins (>90%) probably due, at least in part, to removal of anti-nutrients and fibre^{44,45,47} (Supplementary Table 4).

Chemical methods including enzymatic hydrolysis under acidic or basic conditions, often at high temperatures, disrupt peptide bonds and produce small peptides and amino acids (in order, for example, to improve digestibility or reduce allergenicity)^{65,70}. Not unexpectedly, the incremental improvement in digestibility in hydrolysed proteins varies according to the digestibility of the native protein. For example, in human studies micellar casein aggregates in the stomach and has a slow rate of digestion⁷¹, which can be improved by hydrolysis or acidification^{72–75}. By contrast, whey protein is quickly emptied into the small intestine and is highly digestible in its native form, and as such, is not substantially influenced by hydrolysis^{66,74}.

Structural changes can arise from non-enzymatic chemical reactions such as the Maillard reaction, whereby amino acids react with reducing sugar molecules to produce products such as glycated proteins⁷⁶. These are commonly found in processed and cooked foods, favoured for their organoleptic properties (for example, golden-brown colour and rich, roasted flavours)⁷⁶. These structural changes reduce protein digestibility scores when compared with unprocessed diets in studies in humans and animals^{76–78}. Maillard reaction products that reach the colon can be metabolized by gut microorganisms⁷⁹, with reduction in β -diversity and increased abundance of sulfate-reducing bacteria seen in studies in animals and in in vitro studies using human faeces^{77,80}. Further reactions yield stable and irreversible advanced glycation end products (AGEs), which can bind to receptors for AGEs (RAGEs) that are expressed on intestinal epithelial cells and can trigger

inflammatory reactions in murine models^{81,82}. RAGE expression is elevated in inflamed intestine, perpetuating oxidative damage and inflammatory cytokine production^{81,82}.

Medications and supplements

Medications and supplements that alter the gastrointestinal environment influence protein digestibility (Table 2). Some medications can impede protein digestibility, such as proton pump inhibitors, commonly used to manage gastro-oesophageal reflux disease and gastric or duodenal ulcers⁸³. Proton pump inhibitors reduce acid secretion in the stomach, which increases gastric pH to a therapeutic target of >3–4 (refs. 83,84). At these pH values, the enzymatic activity of pepsin is reduced⁸⁵. In a quantitative study in 16 healthy humans, protein breakdown and subsequent absorption was diminished and colonic protein fermentation increased with omeprazole therapy compared with placebo⁸⁵. By contrast, plant proteases such as bromelain, papain and actinidin from fruits including pineapple, papaya and Hayward green kiwifruit, respectively, have been shown in studies in humans and animals and in in vitro studies to aid protein digestion through assisting enzymatic activity and functioning at a higher pH than pepsin^{86–90}.

Probiotics have also been postulated to have direct and indirect effects on protein digestion⁹¹. In three small studies in humans, supplementation with lactic acid-producing probiotics was associated with an increase in the postprandial maximum concentration of indispensable amino acids for both animal and plant proteins when compared with placebo^{91–93}. However, postprandial levels of indispensable branched chain and total amino acids were variable and the benefit to protein digestion remains uncertain^{91–93}.

Dietary protein intake and colonic health

Historically, the clinical relevance of maintaining optimal protein intake relates to protein synthesis and maintenance of nutritional status¹³ (Box 2). However, two domains of relevance to colonic health should be considered when protein intake is changed quantitatively and/or qualitatively. Specifically, the effects of protein that escaped or resisted small intestinal digestion largely via its colonic fermentation, and the effects of the displacement or optimization of other macronutrients and dietary components, as a consequence of increasing protein intake^{10,12}.

Metabolites of protein fermentation

Eight main groups of microbial metabolites produced during colonic protein fermentation have been linked to modulation of mucosal barrier function, mucus production, cellular toxicity and microbial community structure^{10,94} (Table 1). Key uncertainties in defining actual beneficial or detrimental effects on the colonic mucosa include: the luminal concentrations at which metabolites exert beneficial and/or detrimental effects; regional variations in metabolite concentration and the effect across the colon and crypt surface axis; translation of in vitro findings to human biology; and the influence of protein type and quantity, especially in the context of other nutrients concomitantly consumed^{94,95}. Nonetheless, the mechanistic action of metabolites, and the substrates from which they are produced (Fig. 3), provide clues to their role in colonic health.

Short-chain fatty acids (SCFAs), such as butyrate, exemplify these uncertainties. Butyrate can be toxic to cells in vitro at concentrations found in the colonic lumen^{96,97}. However, cells that might be more susceptible to toxicity (for example, stem cells at the crypt base) are protected in the functioning colonic mucosa^{96,98}. In fact, SCFAs are widely recognized to support colonic homeostasis by, for example, mucus production and providing structural integrity to the intestinal epithelium, amongst other functions³² (Table 1). Protein-derived carbon skeletons could contribute to SCFA production after deamination, but their quantitative contribution to the SCFA pool is small, as shown in batch cultures with protein as the sole dietary substrate^{56,99}. Instead, protein might support SCFA production indirectly as nitrogen released from proteolysis can be used for proliferation of microorganisms, enhancing SCFA production from available substrates⁹.

Metabolites that degrade mucus, damage epithelial cells and impair barrier resistance can be considered detrimental to intestinal barrier function¹⁰⁰ (Table 1). However, metabolites such as hydrogen sulfide and nitric oxide, often discussed in relation to their toxic properties, can have beneficial effects at low concentrations in humans^{94,101}. The difficulty in quantifying luminal and mucosal concentrations to define the level at which detrimental effects might occur limits definitive conclusions regarding their role in disease pathogenesis and therapy. Although the colonic mucosa is resilient, metabolites that confer sustained detrimental effects could contribute

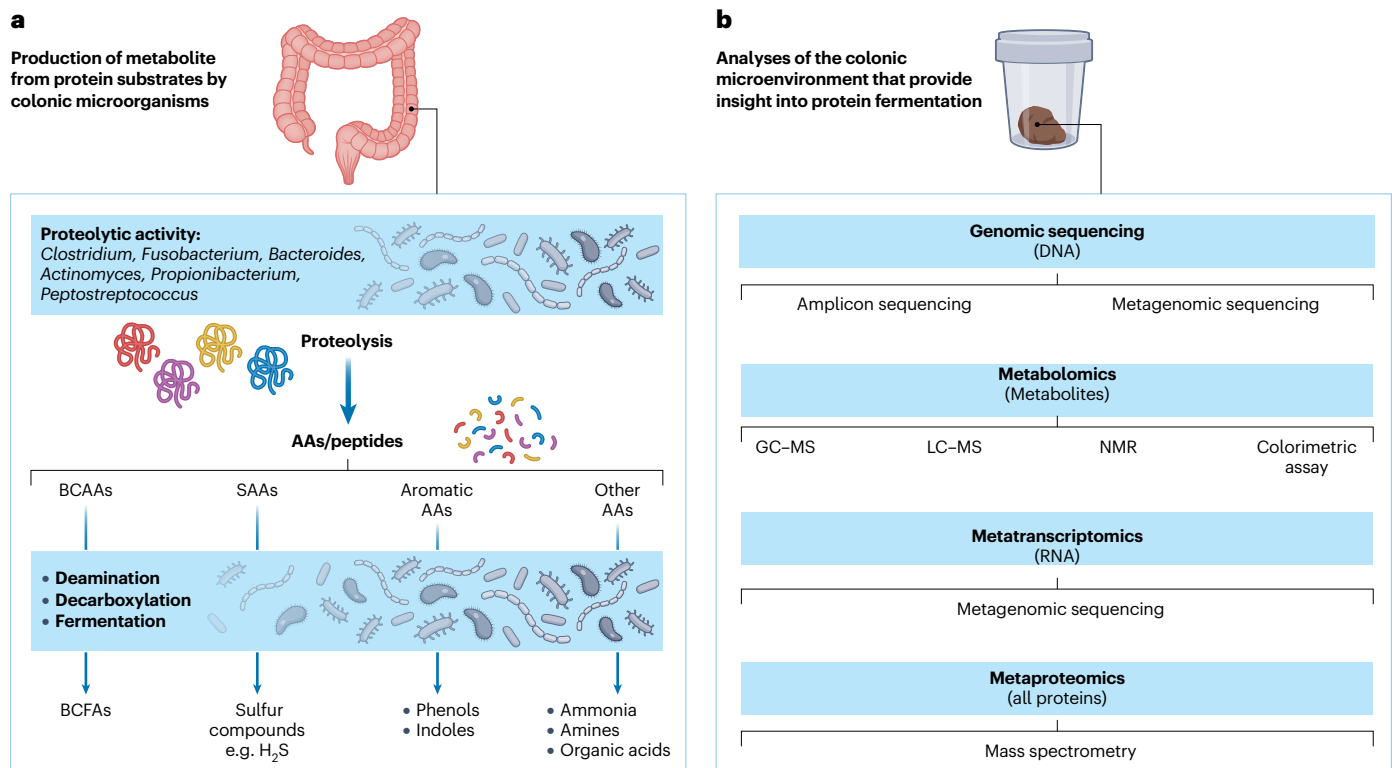


Fig. 3 | Production of metabolites from protein substrates by colonic microorganisms and their subsequent analysis in biological samples.

a, Colonic microorganisms will ferment available amino acids and peptides if they are not required to synthesize proteins, resulting in the production of various metabolites^{10,12,150}. Branched-chain fatty acids (BCFAs), indoles and phenols are of particular interest due to their specificity to protein fermentation and other gaseous metabolites including hydrogen sulfide (H₂S), ammonia and nitric

oxide are of interest due to their association with colonic disease^{12,152}. **b**, Various techniques can be used to gain insight into colonic microbial processes and will yield different types of data for interpretation. AAs, amino acids; BCAAs, branched-chain amino acids; GC-MS, gas chromatography-mass spectrometry; LC-MS, liquid chromatography-mass spectrometry; NMR, nuclear magnetic resonance; SAAs, sulfur amino acids.

Box 3 | Key metrics of protein digestion, quality and fermentation

Digestibility metrics provide valuable data regarding how well a protein can be digested, either by the end of the small intestine (referred to as 'ileal digestibility') or the end of the entire gastrointestinal tract (referred to as 'faecal digestibility')¹⁵⁹ (Supplementary Table 1). 'True ileal digestibility' — the proportion of a dietary protein that has been digested and absorbed up to the end of the terminal ileum — is the favoured measure because endogenous losses and colonic microbial activity do not interfere with the scores^{154,159}. Standard techniques to measure digestibility are invasive, but advances in indirect techniques that use stable isotopes to measure the appearance of amino acids in plasma show promise for future human protein digestibility studies¹⁶⁰. Methods that measure plasma amino acid appearance can also determine amino acid kinetics, providing insights into the rate of absorption⁷¹.

Quality scores provide insights into how well a protein meets the body's demand for nitrogen and amino acids¹³ (Supplementary Table 1). The digestible indispensable amino acid score is currently considered the gold standard measure of protein quality, as it accounts for the ileal digestibility of individual amino acids¹⁶¹. Scores that measure nitrogen utilization are reported in the literature and remain of value, but are intensive and lack consideration of individual amino acids¹³.

Although digestibility and quality metrics are valuable, they do not provide insights into the fate of proteins that escape or

resist digestion in the small intestine (Fig. 3). Of the multiple ways to interrogate the colonic microenvironment using biological samples, metabolomics and genomic sequencing are currently the most popular assessments, encompassing a range of techniques¹³⁸ (Supplementary Table 2). However, analysis of the colonic microenvironment remains limited by the pragmatics of collecting, processing and storing biological samples (such as stool, urine, saliva, plasma and mucosa) to minimize ex vivo production or loss of microbes and gaseous metabolites, and by the availability of reference data and the need for interpretation with bioinformatics¹³⁸. Stool is the most commonly used biological material, as it is easily accessible, facilitating longitudinal analysis, and can be used to yield information on the structure, composition and function of gut microorganisms¹³⁸. However, stool might not capture microorganisms adherent to the mucosa or reflect the microenvironment of the region of interest (for example, excreted stool that has been stored in the distal colon will not be reflective of the environment in the proximal colon)¹³⁸. Mucosal biopsies and gas-sensing capsules might overcome these issues, but remain limited by feasibility, cost, patient acceptability and information yield¹⁶². As techniques become optimized and refined, they are likely to be invaluable in understanding the colonic microenvironment.

to colonic disease, particularly in individuals with susceptible microbial profiles, genetic predispositions or altered immune responses^{28,100}.

Volatile gases and protein fermentation

The major gas produced during protein fermentation is carbon dioxide, but multiple malodorous gases can be released, as reflected in the alternative term for protein fermentation, putrefaction¹⁰². These gases are mostly sulfur compounds (hydrogen sulfide and mercaptans) derived from catabolism of sulfur amino acids (found abundantly in animal protein sources)¹⁰³. Human olfaction can detect very small concentrations creating a social problem if released into the atmosphere in flatus or in the breath following diffusion into the circulation and subsequent release into the lungs^{103,104}. Malodorous colonic flatus is a commonly reported adverse effect of high protein intake, particularly in contexts such as body building or ketogenic diets, whereby protein-to-carbohydrate ratios are unbalanced^{12,102}. Understanding the role of protein fermentation offers therapeutic potential by adjusting the amount and source of protein consumed and utilizing strategies that enhance delivery of fermentable carbohydrates to the distal colon to reduce such fermentation. Formal studies of this clinical problem are scarce, but decreasing protein intake in pigs can reduce the odour of swine manure¹⁰⁵.

Protein fermentation and inflammation

Higher intakes of red and processed meat have been shown to positively correlate with a greater risk of developing ulcerative colitis, but not Crohn's disease, in large prospective studies^{29,106}. In established ulcerative colitis, the highest quartiles of red and processed meat intake are associated with a greater risk of, and reduced time to, disease flare,

compared with the lowest quartiles of intake^{107,108}. If these associations are causal, the underlying mechanism is likely to involve animal protein, and modulation of intake might beneficially affect mucosal inflammation.

The concentration-dependent toxicity of hydrogen sulfide in the colon in association with distal microbial-driven protein fermentation has been hypothesized to be a factor in the pathogenesis of ulcerative colitis¹⁰⁹. This hypothesis was supported by a proof-of-concept study, in which histological remission was achieved in all four patients with ulcerative colitis with reduced dietary intake of sulfur amino acids, predominantly from animal protein¹¹⁰. Subsequent findings have strengthened this concept. First, microbial community structure in the faeces of patients with ulcerative colitis is characterized by reduced bacterial diversity and richness, and an increased abundance of sulfate-reducing bacteria^{111,112}. Moreover, saccharolytic fermentation in vivo in humans is reduced^{113,114}, which matches the reduced capacity for SCFA production in faecal slurries ex vivo¹¹⁵. Rates of hydrogen sulfide production in the presence of available substrates are greater in those with ulcerative colitis compared with healthy individuals^{116,117}. Furthermore, colonocytes from individuals with ulcerative colitis might have reduced capacity for butyrate oxidation¹¹⁸, and production of nitric oxide can additionally affect the integrity of the intestinal epithelial lining by inhibiting detoxification of hydrogen sulfide in vitro¹¹⁹. Finally, colonic epithelial cells isolated from patients with ulcerative colitis show evidence of injured cell membranes¹²⁰. Barrier disruption allows the luminal contents to interact with the mucosal immune system, triggering inflammation and perpetuating mucosal injury^{100,119}. Indeed, international, open-label, single-arm proof-of-concept studies targeting reduced intake and fermentation of animal

Table 2 | Factors influencing protein metabolism within different segments of the human gastrointestinal tract

Segment of the gastrointestinal tract	Physiological process	Factors affecting protein metabolism	Description of factors affecting protein metabolism	Clinical relevance
Stomach	Digestion	Anatomy	Anatomical change from subtotal or total gastrectomy might impair digestion by physically removing a digestive site ¹⁴⁵	Data show that protease activity in the small intestine is upregulated to account for the anatomical change ¹⁵
		pH	Pepsin acts optimally at pH 1.0–2.0; an increase in gastric pH from PPIs could reduce gastric protein breakdown ⁸⁵ Plant proteases can function at a higher pH (>3) and could assist protein breakdown in an acid suppressed environment ^{88,89}	The effect of manipulating pH and protease activity in the gastric environment needs to be explored further in studies in humans to determine the clinical benefit to protein digestibility ⁸⁹
Small intestine	Digestion and absorption	Anatomy	The duodenum, jejunum and ileum are key sites for protein digestion and absorption; anatomical change (for example, intestinal resection or bypass) could hinder protein digestion depending on the amount and/or number of segments removed ¹⁵	Preclinical and case report data suggest that the gastrointestinal tract can adapt to anatomical change through reduced transit time and enhanced absorptive capacity in remaining segments ^{146,147} ; severe resections might hinder adaptation ¹⁴⁸
		Protein quantity	Increasing protein load can lead to a corresponding rise in amino acids that reach the systemic circulation but can also lead to an increase in nitrogen excreted from the small intestine ^{6,149}	Increasing protein intake beyond what the body requires, or has capacity to absorb, could result in increased delivery of nitrogenous material to the colon ⁶ ; this level of intake is difficult to define and is not dependent on protein quantity alone ¹²
		Protein source	Plant proteins have compact structures and typically coexist with fibre and anti-nutrients, which can protect protein structure and inhibit enzymatic access to peptide bonds for digestion ⁴³ ; animal proteins more closely meet the amino acid demand of the human body ¹⁴	Proteins are rarely consumed in isolation; despite lower digestibility scores in wholefood sources, plant proteins still provide adequate nutrition, especially when a variety are consumed ⁴⁴ ; reduced digestibility of plant proteins could increase delivery of nitrogenous material to the colon
		Processing and manufacturing	Physical techniques and chemical reactions can improve digestibility by enhancing enzymatic access to peptide bonds or hinder digestibility by rendering protein structures more aggregated and hydrophobic, reducing enzymatic access to or recognition of peptide bonds ^{44,45,68,70}	Food manufacturing can be advantageous if digestibility of the protein is improved or preserved; dietary proteins can be subject to numerous processing techniques before consumption, which could compound effects on digestibility ⁶⁵
		Probiotics	Certain bacteria (<i>Lactobacillus paracasei</i> and <i>Bacillus coagulans</i>) might improve nutrient absorption by enhancing the ‘health’ of the intestinal environment and releasing enzymes involved in digestion ^{91,92}	The clinical importance of enhanced digestion through probiotic administration is not yet clear, particularly regarding the clinical circumstances to which they could add meaningful value
		Fibre	Viscous fibres can form a gel or matrix, rendering proteins less accessible to proteolytic enzymes; protein digestion in foods containing NSPs might be hindered as proteins within plant cell walls can remain undigested; fibre can stimulate release of endogenous proteins into the intestinal lumen ⁵³	Although fibre can reduce protein digestibility in the small intestine, the effect of fibre could be more clinically relevant in the colon, where different types of fibre have the potential to influence transit, stool composition and fermentation processes ¹²⁸
Colon	Fermentation	Protein quantity	High-protein diets and protein supplements can lead to increased delivery of nitrogenous material to the colon, providing excess dietary substrate for protein fermentation ⁷	The capacity for protein fermentation depends on additional factors beyond protein quantity such as protein source, availability of amino acids and the presence of other dietary substrates ¹⁵⁰
		Protein source	Heterogeneity is observed between protein sources (for example, red versus white meat, animal versus plant protein) probably due to unique amino acid compositions and protein structures ^{126,151}	The protein source affects availability of substrates for protein fermentation, but needs to be considered in combination with the amount of protein consumed and how it is consumed (that is, wholefoods or processed foods) ⁴²
		Processing	Formation of structures and products that can resist digestion in the small intestine (for example, glycosylated proteins) might be degraded by colonic microorganisms due to their affinity for dietary substrates that have variable chemical and structural compositions ^{42,79}	Proteins subject to numerous manufacturing techniques are becoming a more substantial component of modern food; further investigation of their effect on protein fermentation compared with the effect of wholefood protein sources is warranted ^{65,76}
		Fibre	Fermentable fibre can increase capacity for fibre fermentation ^{42,59} ; increased biomass from fibre fermentation might divert nitrogenous material to bacterial synthesis ¹²⁸ Bulking or viscous fibres can hasten colonic transit time and form complexes with proteins, inhibiting microbial access to amino acids for fermentation ¹²⁸	Combining fibre types (for example, fermentable and non-fermentable fibre) might be most beneficial to reduce protein fermentation by pushing fibre fermentation to the distal colon where it can displace the capacity for protein fermentation ^{59,63}

NSPs, non-starch polysaccharides; PPIs, proton pump inhibitors.

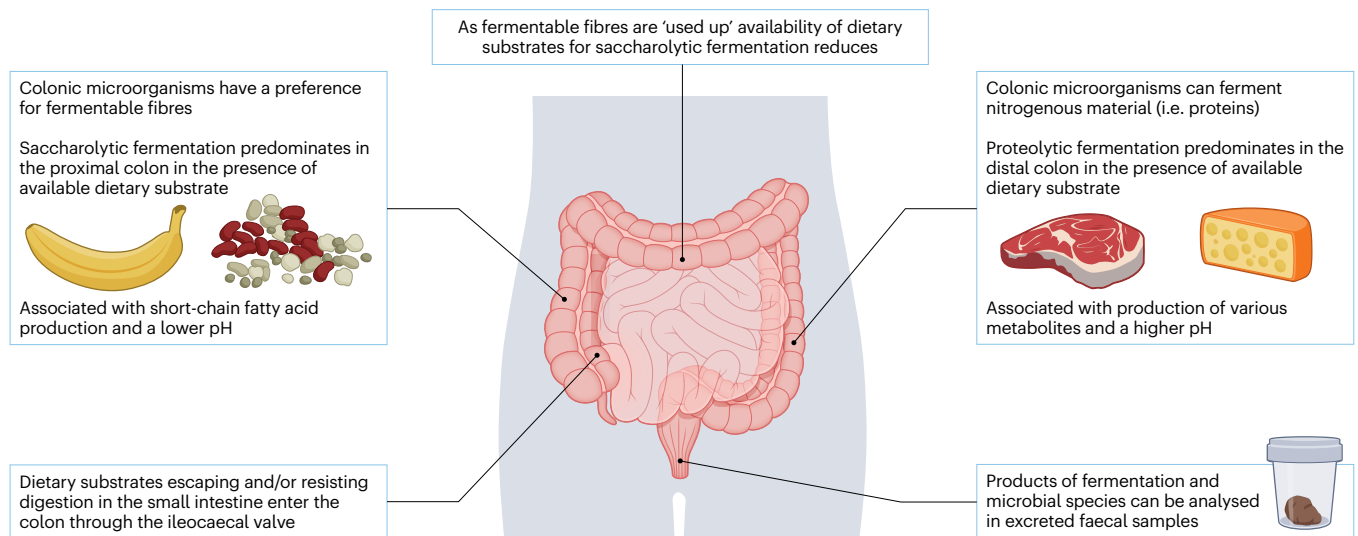


Fig. 4 | Fermentation of dietary substrates across different sections of the colon. Saccharolytic fermentation predominates in the proximal colon with the availability of appropriate substrates^{55,57}. As availability of fermentable fibres

diminishes, protein fermentation increases in the distal colon in the presence of remaining available dietary substrate^{10,55}.

protein have demonstrated clinical, endoscopic and histological responses in mildly to moderately active ulcerative colitis^{121–123}. The performance of randomized controlled trials is warranted to further evaluate these dietary strategies.

Carcinogenic effect of protein fermentation

One proposed mechanism linking Western dietary patterns to colorectal cancer risk involves the fermentation of excess dietary protein entering the colon. Metabolites of protein fermentation, including hydrogen sulfide, ammonia, amines and phenols, can induce colonoocyte DNA damage²⁶ (Table 1). Resultant cellular mutations can disrupt cell cycle regulation leading to uncontrolled cell growth and tumour formation¹²⁴. Additionally, hydrogen sulfide and ammonia can degrade the mucous layer and impair colonoocyte uptake and oxidation of butyrate, resulting in a compromised epithelial barrier and vulnerability to luminal carcinogens^{26,31,124}. Chronic colonic inflammation, partly contributed to by metabolites of protein fermentation, further contributes to tumorigenesis and tumour promotion¹²⁵. Importantly, much of the evidence implicating protein fermentation in carcinogenesis comes from rat and cell-line models. It remains unclear how these mechanisms translate to the human colonic environment.

Associative effects of high protein intake

Collinearity challenges the interpretation of which changes to dietary composition are exerting a given effect. This issue compounds the definition of the exact mechanisms by which Western dietary patterns are associated with the risk of colorectal cancer³⁰. High protein diets could increase the risk of colonic dysfunction and disease by associated effects on dietary intake of other macronutrients and dietary components, which would be another mechanism by which Western dietary patterns are associated with the risk of colorectal cancer. High intakes of red and processed meats contribute carcinogenic compounds such as NOCs, heterocyclic amines and AGEs to the colonic lumen^{5,30,124}.

Red meat contains haem, an iron-containing porphyrin that can be converted to NOCs in the colon¹²⁶, and high-temperature cooking and curing of meats containing amines, nitrates and nitrites can generate NOCs, heterocyclic amines and AGEs^{5,30}. As a result, WHO and in particular the International Agency for Research on Cancer recommend that people of all ages reduce their intake of red, processed and charred meats⁵.

Of particular importance is the effect of high protein diets on reducing carbohydrate intake, particularly dietary fibre intake. Epidemiological data support the view that diets rich in quantity and variety of fibre are associated with reduced risk of colorectal cancer¹²⁷. Fibre is considered protective through multiple mechanisms. First, fibres with viscous and bulking properties can increase stool bulk and hasten colonic transit¹²⁸, which dilutes colonic contents and has been suggested to mechanistically reduce exposure of the colonic mucosa to luminal carcinogens¹²⁹. Second, fermentable fibre contributes to SCFA production and, therefore, maintenance of colonic homeostasis²⁶. Third, a high-fibre diet, in contrast to a Western diet, is associated with better metabolic health in humans, reducing overall chronic disease risk^{125,127}.

Reduced carbohydrate intake with a high protein diet might also affect functional gastrointestinal symptoms; however, studies investigating high protein and supplementation interventions often do not obtain data on bowel habit and functional symptoms^{35,37}. Constipation has been noted in observational data, yet only when coupled with a low intake of carbohydrate¹³⁰. A cohort of 13 patients with diarrhoea-predominant irritable bowel syndrome had improved pain scores, stool frequency and consistency on a high protein, very low carbohydrate diet¹³¹. However, attributing the improvement directly to the high protein intake per se lacks a putative mechanism. By contrast, reduction in carbohydrates will include lower intake of dietary fibre, a well-documented cause of constipation¹²⁸, and of fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAPs) that contribute to gastrointestinal symptoms in such patients¹³².

Therapeutic effects of specific proteins

Certain resistant proteins can exert physiological functions in the colon, exhibiting cardioprotective, anti-inflammatory and anti-carcinogenic effects^{8,43}. For example, resistant protein fractions from soybean and buckwheat exert hypocholesterolaemic effects by increasing faecal steroid excretion in rats⁹. Peptides entering the colon could also exert therapeutic effects by modulating inflammatory pathways, protecting against oxidative stress and inducing apoptosis in cancer cells⁸. This feature has been demonstrated with bioactive components of whey and legume proteins^{9,133}. Although these therapeutic effects are promising, they have yet been shown to confer health benefits *in vivo* in humans.

Specific peptides are also used as drugs to treat a variety of conditions, with unique amino acid sequences providing the ability to mimic the action of natural peptides such as hormones and neurotransmitters¹³⁴. Oral delivery of such drugs is challenged by digestive processes that might reduce the delivery of therapeutic peptides to the site of action. Encapsulation, protease inhibitors and agents that alter pH could be utilized to protect peptide drugs¹³⁴. Investigation of whether resistant proteins could be used to encapsulate therapeutic peptides is warranted. Additionally, some drugs, such as 5-aminosalicylic acid used in the treatment of inflammatory bowel disease, require colonic release via pH-dependent coatings¹³⁵. Altered colonic fermentation, including increased protein fermentation, might influence drug release, as observed with fermentable fibre in ulcerative colitis¹³⁵.

Future directions and clinical implications

Protein remains a critical nutrient for human nutrition and its role in human health, optimizing nutritional status and body composition, should not be overlooked¹. However, this aspect needs to be balanced with the potential for dietary protein to directly and indirectly influence colonic health and disease risk. Several areas in research and clinical practice remain under-developed warranting further attention.

Methods for assessing protein requirements are outdated and imprecise. Historical predictive equations used to inform protein requirements lack consideration of individual factors such as body composition, whereby muscle-to-fat ratio probably influences metabolic demand. Similarly, protein requirements in specific disease states are often extrapolated; for example, in ulcerative colitis the recommendation for 1.2–1.5 g of protein/kg per day in active disease, is based on data from studies in predominantly Crohn's disease populations¹³⁶. Assessment of protein utilization via nitrogen balance studies to inform individual requirements is invasive and lacks utility in the clinical setting¹³. Additionally, current approaches do not consider the importance of protein source. For example, is there a therapeutic target for the intake of sulfur amino acids by an individual with ulcerative colitis?¹²² Or, does someone who eats a plant protein wholefood diet need to aim for the same protein target as someone who eats a diet comprising predominantly processed protein-enriched foods? The way forward is likely to focus on personalized nutrition, in which unique characteristics of individuals are used to inform nutritional approaches¹³⁷. Consideration of genetic makeup and biochemical markers provides insights into how the body responds to nutrients, which can be coupled with evaluating individual body composition, demographics and health history to inform personalized dietary requirements and interventions¹³⁷.

Expansion of processed protein-enriched food products and societal changes to our food supply highlight the need for updated nutritional and food composition data³. Understanding the true composition of the food we eat is fundamental to evaluating its health effects, and the use of current food composition databases to assess

dietary intake lacks consideration of modern-day foods and macronutrient profiles (for example, amino acid composition of proteins) specific to local populations.

Quantifying the amount of dietary protein delivered to the colon is imperative to better understand its effects on colonic health. Dietary assessment alone is insufficient and measuring protein digestibility does not provide consistent results or adequate insights into the fate of undigested protein. Quantifying specific products of protein fermentation such as BCFA or *p*-cresol could ameliorate this problem¹². However, production of such metabolites is only one factor that influences their concentration, and patterns of microbial fermentation can differ markedly across individuals¹³⁸. Formal evaluation of such concepts is warranted. Moreover, female participants are under-represented in older studies and greater female representation should be considered in future research to ensure that potential sex and gender differences are not overlooked.

Finally, the effect of modern-day protein intakes on the colonic microenvironment requires further elucidation. Establishing thresholds at which microbial metabolites confer beneficial or detrimental effects in the colonic lumen could clarify their role in mitigating disease risk. Robust studies with consistent methods for obtaining biological samples, analysing and interpreting metabolomic and metagenomic data are required to enhance the clinical value of such information⁹⁵. Examining microbial composition and function could also help identify specific biomarkers and genomic profiles that can be used to predict individuals or groups who are susceptible to diseases, or likely to respond to therapeutic and dietary interventions, allowing a personalized approach to health recommendations¹³⁹. Advances in genetic testing and bioinformatics have enhanced our ability to interpret such data, although cost and complexity remain barriers. The use of artificial intelligence is being explored to support data management and clinical application with promising results for its application in future research and clinical practice¹³⁷.

Conclusions

Our food supply and consumer dietary preferences have evolved considerably in the past few decades and will continue to do so with societal changes. Dietary protein has become increasingly favoured for its health and nutritional benefits, yet should be recognized for its potential to contribute to colonic dysfunction and disease. There remain many unknowns as to how modern-day protein intakes influence colonic health and disease risk both directly by altering colonic microbial structure and function and indirectly by affecting overall nutritional intake. Additional efforts are needed to strengthen our knowledge in this space, particularly through robust human studies that consider the context of mixed diets, individual factors and variable populations. This research promises to inform personalized dietary, therapeutic and medical recommendations that consider the fate and role of dietary protein in the human body.

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Author contributions

All authors researched data for the article. R.H.D. wrote the original article and created tables and figures. All authors made substantial contributions to discussion of content. All authors reviewed and edited the manuscript before submission.

Competing interests

R.V.B. has received grant, research support or speaker fees (all paid to his employer for research support) from AbbVie, Ferring, Janssen, Shire, Takeda, GSK and Emerge Health; and is a shareholder in Biomebank. P.R.G. is a consultant or advisory board member for Anantara, Atmo Biosciences, Topas and Comvita; has received research grants for investigator-driven studies from Mindset Health, and speaker honoraria from Dr Falk Pharma and Mindset Health Pty.; and is a shareholder in Atmo Biosciences. His salary is derived from sales of a digital application (Monash University FODMAP diet app), patient booklets cookbooks and online courses, all of which relate to the low FODMAP diet therapy. The other authors declare no competing interests.

Additional information

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Review criteria The electronic databases Medline, Embase, Emcare and Cochrane Library were searched up to 18 November 2025 to retrieve articles. A comprehensive search strategy using both keywords and MeSH terms was developed to identify a broad scope of potentially relevant articles (Supplementary Table 5). Search terms and synonyms to signify ‘Protein’, ‘Digestion’, ‘Absorption’ and ‘Fermentation’ were used. No limits were applied to the search strategy. However, a range of synonyms for ‘animals’ and ‘paediatrics’ were used in attempt to refine the search to human adults. Citations from each database were exported into EndNote 20 and then Covidence where duplicates were removed. The resulting 8,331 articles were screened by title and abstract to locate primary studies and reviews detailing digestion, absorption or fermentation of protein in the human gastrointestinal tract. Studies in animals, in vitro or simulated digestion, and studies in infants and children were excluded. Additional papers including animal or in vitro data relevant to the concepts discussed in this paper were subsequently included. Full-text articles were screened to determine relevance for inclusion in this narrative review.

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