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Relevance of Microbial Fermentation for Long-Term Health Effects of High Protein Diets

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Abstract

Proteins are important macronutrients with several beneficial health effects. Today, protein-rich diets are gaining popularity, especially in the context of achieving or preserving a healthy weight. However, epidemiological studies associate long-term consumption of protein-rich diets with adverse health outcomes and increased mortality. These adverse effects, at least partially, are mediated by the activity of microbial products obtained by protein fermentation. Undigested food components reach the colon, where the gut microbiota transforms food residues into various metabolites. Given that side chain groups of amino acids are chemically heterogeneous, undigested proteins provide a mix of substrates for microbial fermentation. By using different amino acids, the gut microbiota can produce toxic, genotoxic, and carcinogenic compounds, but also metabolites that impair normal insulin signaling and cardiovascular function. Biological activity of microbial metabolites can contribute to the development of cardiovascular diseases and cancer, which are associated with high-protein diets. In principle, microbiota metabolic products are beneficial for humans and complementary to human metabolism. However, when diet composition is out of balance (e.g. when proteins are present in an excessive amount), microbiota activity shifts towards production of hazardous metabolites. Therefore, the gut microbiota and its activity must be taken into consideration when designing nutritional strategies to promote health.

Key words: gut microbiota, high-protein diets, cancer, cardiometabolic risk, fermentation

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Introduction

Proteins are important macronutrients with a range of well-recognized health benefits. To start with, protein-rich diets stimulate the production of muscle mass and boost strength (1). Therefore, proteins are excessively consumed by athletes and individuals who are actively training. Moreover, in various weight-loss programs, proteins are the dominant diet component because they contribute to weight loss by multiple mechanisms. First of all, high protein intake prevents muscle loss during weight loss (2), while extracting energy from protein is associated with higher energy consumption, i.e., thermogenesis (3). Furthermore, protein in the diet can influence appetite and increase satiety (3), and this phenomenon can be explained by down-regulating the level of hunger hormones, as shown for ghrelin (4). Therefore, it is not surprising that numerous weight-loss regimes are based on high protein intake, including Atkins, Dukan, Protein Power, Stillman, and Zone, to name a few. The popularity of high protein diets and protein supplements is further supported by the fact that, in addition to the nutritional value, proteins and peptides might have beneficial biological functions such as antioxidant, immuno-modulatory, antihypertensive, etc. (5). In line with the scientifically proven benefits of protein consumption, it is not surprising that there is a high demand for protein ingredients and that global protein market is rising, while alternative sources of protein are excessively searched for (6).

In nutrition, balance is important. Eating a variety of foods in a well-balanced diet is essential for maintaining health. It is very well established that excessive intake of important nutrients such as carbohydrates, fats, salt (and other minerals), and vitamins can compromise health. While a similar principle should also apply to the amount of proteins in the diet, this is not the case in reality. This could possibly be explained by the fact that high protein diets do not provoke immediate and measurable negative responses in the human body. For instance, it is easy to evaluate the effect of carbohydrate-rich foods on postprandial glucose levels (7), while protein-rich diets do not provoke similar, immediate undesired metabolic responses. Nevertheless, prospective studies provide evidence that there are some health risks related to high protein intake. In contrast to proteins, carbohydrates in the diet are generally perceived as “problematic”. However, it has been shown that both low and high carbohydrate intake pose similar health risks (8). In particular, if a low carbohydrate dietary pattern is associated with a high intake of animal-derived protein and fat, the risk of mortality increases (8). Long-term negative consequences of high protein intake include increased risk for the development of bone disorders, coronary artery disease, and various cancers, while the function of the liver and kidneys is compromised (9). Mechanisms behind these negative effects, which lead to an evident increased mortality, are not fully elucidated. It is important to note that one cannot fully understand the effect of any dietary pattern on the human metabolism if analyzing the metabolism of *Homo sapiens* alone. Ingested food interacts with human digestive enzymes and organs of the digestive tract, but it also interacts with trillions of microbial cells that reside in the digestive tract. Humans live in symbiosis with a complex microbial ecosystem that inhabits various niches of the human body, while the densest ecosystem

is present in the colon (10). This complex ecosystem is collectively termed microbiota, while gut microbiota refers to the ecosystem residing in the digestive tract. The gut microbiota ferments undigested food components and contributes to health and disease. It is generally perceived that fermentation of carbohydrates yields beneficial metabolites, while fermentation of proteins produces hazardous metabolites (11). Therefore, the gut microbiota and products of microbial protein fermentation might provide a missing explanation for at least part of the evident negative health effects of long-term high protein intake. In this review, various products of protein fermentation pathways are reported and scientific evidence that microbial fermentation can contribute to several pathologies associated with high-protein diets is provided. This data clearly shows that, in human nutrition, the activity of the gut microbiota should be taken into account in order to comprehensively predict the impact of any nutrient on human health.

Gut microbiota as a "black box"

The gut microbiota is a complex microbial ecosystem that inhabits the digestive tract of humans. Members of the human gut microbiota live in a symbiotic relationship with its host. Various microbial species from all three domains of life inhabit the human intestine. The dominant fraction of the gut microbiota are bacteria, which can be contaminated by bacterial viruses – bacteriophages, but archaea and eukarya (mostly fungi) are also part of the ecosystem (12). Currently, ~ 2,000 species of gut microbiota have been identified. Most gut inhabitants can be classified within only three bacterial phyla: Bacillota (previously Firmicutes), Bacteroidota (previously Bacteroidetes), and Actinomycetota (previously Actinobacteria) (13). Many of these bacteria, such as bifidobacteria, or members of the Lachospiraceae family, are highly specialized for living in the digestive tract and cannot be found in other ecosystems.

The gut microbiota has been studied for over a century, but its composition and function are still not completely known. This is because of its great variation between individuals, while ethnicity and geographic origin also play a role in shaping this ecosystem (14). A unique combination of several hundreds of microbial species inhabits each individual, while there are thousands of possible inhabitants of the human gut. There is still a huge knowledge gap about gut microbiota composition and function, because gut microbes are not easy to cultivate. Actually, in recent years, the application of various molecular methods has enabled studying gut microbiota without cultivation, and the application of molecular methods has shown that ~80% of intestinal microbes are uncultured species with unknown function (15). Gut microbes are highly adjusted to the conditions of the human gastrointestinal tract, which are difficult to replicate in the laboratory. Particularly problematic is the fact that the majority of intestinal microbes are strict anaerobes, meaning that they cannot survive exposure to oxygen. In a recent attempt to enlighten "the taxonomy darkness" of the human gut microbiota, three novel bacterial families, 28 novel genera, and 102 novel species were described (16). Many of these species are prevalent and dominant members of the microbiota, while their identity and function were completely unknown until three years ago. Given that there are still many

microbes of unknown identity and function, the gut microbiota can be perceived as a “black box”. This means that even if it is known that one metabolite enters the colon and another metabolite exits it, it is often unknown which microbes of the ecosystem are responsible for the apparent metabolic transformation. An incomplete description of the ecosystem is not the only reason why the microbiota can be treated as a “black box”. In ecosystems, one function is rarely performed by one organism independently of others. In reality, cross-feeding occurs as the metabolic activity of one microorganism relies on the activity or metabolic products of another microorganism. This can be illustrated through an example of lactate. It is very well established that lactic acid bacteria are part of the human gut microbiota, although lactate cannot be detected in human feces. The generated lactate is utilized by other microbes, primarily for the synthesis of propionate and butyrate (17). Finally, the same metabolic transformations can be performed by unrelated microorganisms, due to a phenomenon of functional redundancy, which is common in complex ecosystems (18).

In terms of protein fermentation, the gut microbiota is certainly a “black box”. Proteins are the most complex biological molecules. The degradation of proteins is not straightforward, since specific peptidases can degrade only peptide bonds formed by specific amino acids. Moreover, functional groups of various amino acids are chemically different (can be basic, acidic, aromatic, aliphatic, etc.), and therefore metabolic transformation of different amino acids yields substantially different metabolic products. Since complex chemical structures of proteins are transformed by the incompletely described, yet complex gut microbiota, it is difficult to identify the key microbial players responsible for specific metabolic transformations. Only as an exception, specific microbial metabolizers of amino acids have been identified. For example, recently, a bacterial species *Hominibacterium faecale*, specialized for L-arginine degradation, was isolated from human feces. When growing on L-arginine, this bacterium produces ammonia, but also CO_2, butyrate, and other metabolites. However, although this transformation is described in detail, transformation into denoted metabolites is not the only fate of L-arginine in the human digestive tract. Previous research has shown that L-arginine can be transformed by unidentified gut microbes into nitric oxide and polyamines (19). Therefore, when discussing protein metabolism by the gut microbiota further in the text, the focus will be on the observed metabolites, their metabolic function and health effects, rather than the identity of gut microbes that perform the indicated metabolic transformations.

Carcinogenic products of protein fermentation

High intake of protein is a risk factor for several conditions, including cancer development (9). Among various protein sources, red meat is the one most frequently associated with cancer risks. According to the International Agency for Research on Cancer, of the World Health Organization, red meat is classified as carcinogen group 2a based on the substantial positive association between the consumption of red meat and colorectal, pancreatic and prostate cancer. (19). Carcinogen group 2a means that, based

on scientific data, the identified carcinogen probably causes cancer (21). Since 2015, processed meat has been recognized as carcinogen group 1, indicating that there is sufficient evidence to conclude that processed meat is carcinogenic to humans (18, 19). This recognition is based on the prospective studies that analyzed the possible association between dietary habits and the incidence of cancers. It was determined that daily intake of only 50 g of processed meat increases the risk of colorectal cancer by 18% (22). Additionally, a positive association with the consumption of processed meat was found for stomach cancer. In processed meat, the addition of nitrates or nitrites as preserving agents provides substrates for the synthesis of highly carcinogenic N-nitroso compounds, which are one of the drivers of the carcinogenic effect of processed meat. The effect of carcinogens from processed meat is evident outside the intestinal tract, as shown in a recent retrospective study on over 100,000 individuals. This study showed that high consumers of nitrate food additives had a 24% higher risk for the development of breast cancer, while high consumers of nitrite food additives had a 58% higher prostate cancer risk (23).

N-nitroso compounds are compounds generated through the reaction of secondary amines and nitrites. These compounds can be produced when food containing both amines and nitrites is heated, and therefore many food products contain certain quantities of N-nitroso compounds (24). Even if free of these carcinogens, processed meat products provide substrates for their endogenous synthesis in humans. The reaction of nitrosation can be catalyzed by acidic conditions of the stomach and by the enzymatic activity of some intestinal microbes. The analysis of fecal N-nitroso compounds content showed that both meat treated with nitrite and fresh red meat significantly enhance endogenous nitrosation, although metabolic products of processed meat are more toxic and induce higher oxidative DNA damage (25). It is relevant to mention that high-protein weight-loss diets promote the synthesis of N-nitroso compounds in subjects following these diets (26). Experiments on animal models show significantly lower endogenous synthesis of N-nitroso compounds in germ-free animals, which indicates that the synthesis of these compounds occurs predominantly due to the activity of gut microbes (27). *In vitro* experiments with intestinal bacteria showed that many aerobic bacteria can catalyze the synthesis of N-nitroso compounds, while among the tested anaerobic bacteria only the proteolytic bacterium *Peptoniphilus asaccharolyticus* could produce these carcinogens (28).

The gut microbiota compositions of colorectal cancer patients and healthy controls are different, and an increased number of several proteolytic bacteria (including *Porphyromonas, Parvimonas,* and *Peptostreptococcus*), alongside with an increase of *Fusobacterium nucleatum,* was detected in patients (29). *F. nucleatum* is the strongest microbial marker of colorectal cancer, which exacerbates cancer progression by the induction of specific immune responses (30). *F. nucleatum* contribution to carcinogenesis appears to be independent of protein fermentation, clearly showing that protein consumption is not the only driver of these undesired processes. However, in search of carcinogenesis drivers, it is relevant to keep in mind that, in patients with colorectal cancer, the most evident and strongly significant shift of microbiota metabolic potential

is the increase of genes involved in amino acid degradation (29). In addition, there is sufficient evidence that several metabolic products of amino acid fermentation are genotoxic or carcinogenic, and examples of such metabolites are presented in Figure 1. Here it should be noted that, in addition to the production of genotoxic substances, the microbiota can contribute to their degradation (31). While this subject is out of the scope of this review, there is considerable evidence that the ability of the microbiota to degrade various genotoxic substances is an important feature that facilitates longevity (32).

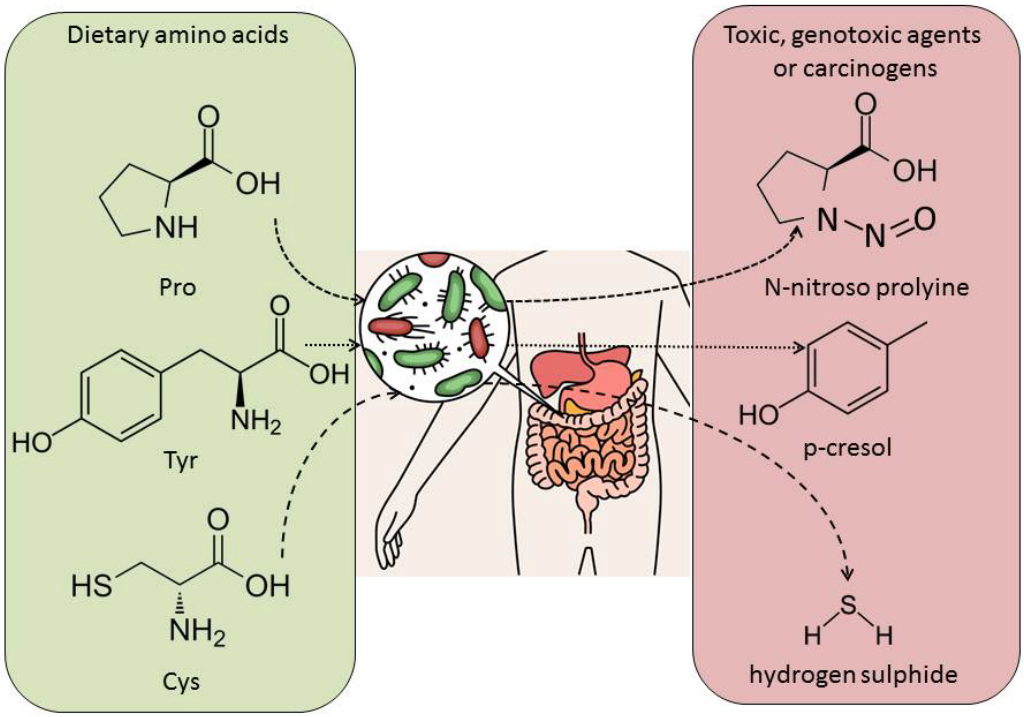

Figure 1. **Schematic representation of examples of gut microbiota mediated transformation of dietary amino acids into genotoxic and carcinogenic substances. Figure is constructed by using freely available vectors on vecteezy.com.**

Slika 1. **Šematski prikaz primera tranformacija amino kiselina iz hrane pod dejstvom crevne mikrobiote u supstance koje ispoljavaju toksično i kancerogeno dejstvo na čoveka. Slika je sačinjena uz korišćenje javno dosutupnih vektora sa vecteezy.com.**

Hydrogen sulfide (H_2S) is genotoxic product of gut microbiota fermentation (33). The microbiota can produce H_2S through several pathways, including the reduction of sulfate (present in mucus) by sulfate-reducing bacteria, but also by the transformation of sulphur-containing amino acids and taurocholic acid (primary bile acid) (11). This metabolite has been studied in relation to several intestinal pathologies since it is toxic and genotoxic, and can promote the proliferation of cancer cells (34). Although in many scientific publications sulfate reduction was depicted as the most relevant source of H_2S,

proteins in the diet are the main drivers of sulfide synthesis. In a controlled feeding study on humans, it was shown that fecal concentration of H_2S is directly correlated to the amount of meat in the diet (35). Metagenomic analysis shows that microbial sulfur metabolism is significantly elevated in colorectal cancer (36), while another recent study showed that orally and nasally exhaled H_2S can be used for a non-invasive diagnosis of this pathology (37), which is indicative of the pivotal relationship between this metabolite and pathology. H_2S is a signaling molecule, which is produced in small amounts by human cells. It appears that H_2S is increased in cancer cells due to up-regulation of the H_2S-producing enzyme in cancer cells (38). This phenomenon is (most likely) independent of gut microbiota activity, but it is indicative of complex interactions between various tissues, microbes and molecules in health and pathological conditions.

To finalize the list of carcinogenic compounds that can be produced by gut bacteria by using protein-rich substrates, a genotoxic metabolite of tyrosine – *p*-cresol should be mentioned (39). *p*-cresol is increased in the urine of patients diagnosed with leukemia, lung, colorectal, breast, and bladder cancers (40). This genotoxic substance (41) can be produced from tyrosine by phylogenetically diverse gut microorganisms, while the most effective production is observed for enterobacteria and *Fusobacterium, Clostridium,* and *Olsenella* species (42). It is estimated that in the intestine *p*-cresol can reach a physiologically relevant level concentration to exhibit genotoxicity (39), while further metabolic transformations of p-cresol to p-cresol sulfate in human tissues contribute to systemic negative effects (43). Interestingly, p-cresol sulfate is one of the most relevant uremic toxins, which contributes to worsening outcomes in chronic kidney disease patients (44), another disease associated with high protein diets. Although large cohort studies showing the association of *p*-cresol with any dietary pattern are lacking, a pilot study on vegetarians and omnivores showed that vegetarians produce significantly lower amounts of this harmful substance (45).

Protein fermentation and metabolic and cardiovascular risk

Cardiovascular diseases are the leading cause of mortality globally. The most relevant risk factors for the development of cardiovascular diseases are physical inactivity, dyslipidemia, hyperglycemia, high blood pressure, obesity, older age, thrombosis/smoking, kidney dysfunction, and familial hypercholesterolemia (46). To tackle some of these parameters such as obesity, dyslipidemia, or hyperglycemia, some patients are advised to switch their diet towards weight-loss protein-rich diets. This dietary advice might have short-term benefits, but in the long term high-protein diets actually contribute to the progression of coronary artery disease (9).

There are several microbial metabolites that pose a risk for cardiovascular diseases (Figure 2). Concerning cardiovascular disease, microbial transformation of phenylalanine appears to be highly relevant. In a comprehensive analysis of serum metabolites of almost 15,000 individuals, higher phenylalanine was the strongest predictor of cardiovascular events, which increased the risk by 18% (47). This amino acid can be transformed by intestinal microbes into several harmful metabolites. Phenylacetyl glutamine is a

metabolite that interacts with adrenergic receptors, which are essential for cardiovascular health (48). This metabolite promotes platelet aggregation and thrombosis, and increases the risk for the development of adverse cardiovascular phenotypes (49). In a comprehensive search for microbial metabolites in blood associated with incidents of major adverse cardiovascular events (myocardial infarction, stroke, or death), two microbiota-derived phenylalanine metabolites were identified as key molecules (phenylacetyl glutamine and phenylacetyl glycine) (50). In the same study, p-cresol, p-cresol sulfate and p-cresol glucuronide (metabolites of histidine) were also denoted as relevant for cardiovascular adverse events. In another independent study, increased levels of total p-cresol-sulfate were identified as one of the major markers for coronary artery disease in patients with diabetic nephropathy (51).

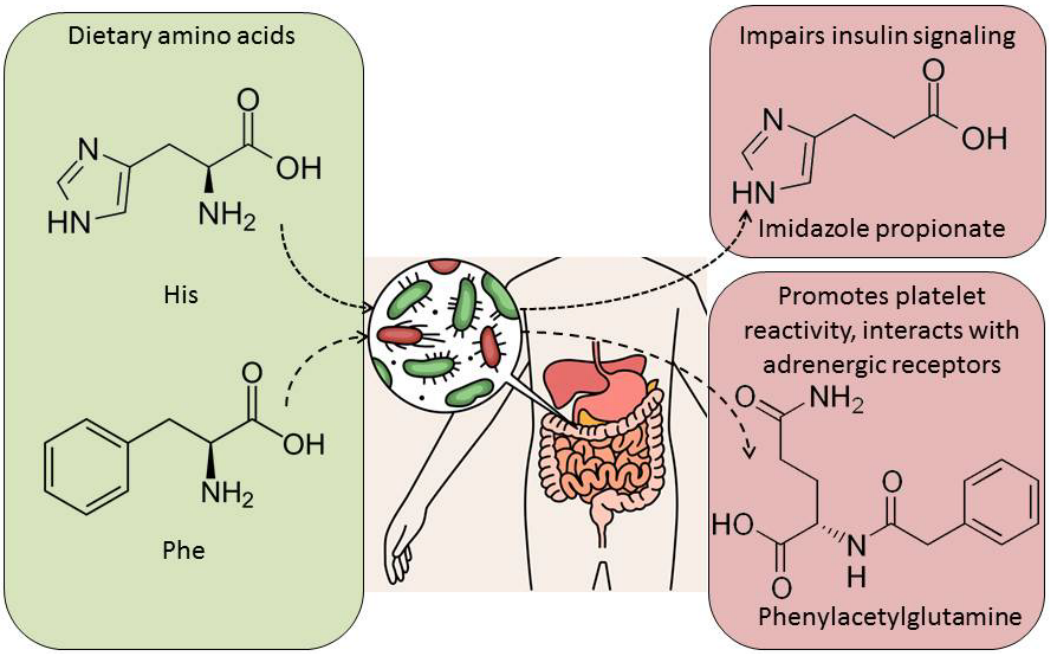

Figure 2. **Schematic representation of examples of gut microbiota mediated transformation of dietary amino acids into metabolites that impact metabolic and cardiovascular health. Figure is constructed by using freely available vectors on vecteezy.com.**

Slika 2. **Šematski prikaz primera transformacija amino kiselina iz hrane pod dejstvom crevne mikrobiote u supstance koje utiču kardiovaskularno i metaboličko zdravlje čoveka. Slika je sačinjena uz korišćenje javno dosutupnih vektora sa vecteezy.com.**

As previously mentioned, L-arginine can be transformed by gut microbes into nitric oxide (NO) and polyamines (19), and this could also be relevant for systemic health. NO is a remarkably simple molecule which regulates crucial features of neuronal communication, blood vessel modulation and immune response (52). Three enzyme

systems regulate endogenous production of NO in various tissues, while the physiological effects of NO are critically depend on its concentration (53). Therefore, microbial synthesis of NO could impact various physiological processes, and it has already been acknowledged that microbial production of NO might be of critical importance for cardiovascular health (54). Studies have shown that the application of antiseptic mouthwash or overuse of antibiotics, which impacts oral and gut microbiota, causes blood pressure to increase. While this notation needs further investigation, it has already been noted that the modulation of oral microbiota in hypertension management is a new paradigm in cardiovascular medicine (54).

One of the most intriguing molecules produced during protein fermentation in terms of metabolic health is imidazole propionate. In 1972, it was already established that individuals with type 2 diabetes, in contrast to healthy controls, have detectable amounts of this metabolite in their urine (55). The origin of imidazole propionate was unknown until 2018, when it was revealed that it is a microbial metabolite, produced by a phylogenetically distant gut bacteria, by deamination and reduction of histidine. It appears that in individuals who consume large quantities of animal protein in their diet, urocanate (deaminated histidine) is used by gut bacteria as the terminal electron acceptor in the process of anaerobic respiration (56). The synthetized imidazole propionate acts as an insulin antagonist as it impairs insulin signaling (56). A high intake of protein is not the only driver of imidazole propionate synthesis, as this metabolite is produced only in individuals with specific microbiota composition (57). Based on this finding, it could be speculated that high protein intake is important for the etiology of insulin resistance, while foods with a high glycemic index provoke and reveal symptoms of the existing pathology. There is an increasing trend in the serum concentration of imidazole propionate from healthy via prediabetic to diabetic individuals, and this suggests that the presence of this metabolite is a disruptive factor of metabolic homeostasis (57). The pivotal role of imidazole propionate in metabolic health is further supported by the finding that suggests that the plasma concentration of oimidazole propionate is positively correlated with blood pressure in a cohort of overweight and obese humans (58), and that a higher concentration of this metabolite is associated with heart failure and mortality (59).

Conclusion

The gut microbiota is an ecosystem of tremendous importance for human wellbeing. Although the microbiota is very complex and still insufficiently described, it is evident that its activity systemically impacts health. In recent years, in line with different technological developments, it has been possible to identify several microbial metabolites that are essential for preserving health, on the one hand, and metabolites that are implicated in various diseases, on the other hand. In general, carbohydrate fermentation is thought to result in the synthesis of beneficial metabolites, while protein fermentation can yield a very heterogenic group of metabolites. There is scientific evidence for several hazardous metabolites from microbial fermentation that could be related to pathologies associated with high protein intake. By using different amino acids

as substrates, gut microbiota produces carcinogenic and genotoxic substances, including N-nitroso amines, hydrogen sulfide, and p-cresol. Furthermore, several microbial products, including imidazole propionate, p-cresol sulfate, nitric oxide and phenylacetyl glutamine, are implicated in the development of metabolic disorders and strongly associated with adverse cardiovascular events. Therefore, it can be concluded that microbial transformation of (excessive) protein in the diet is one of the drivers of the adverse health effects observed in individuals consuming such diets.

It should be noted that only selected microbial metabolites were reported in this review, while in the complex interaction between food, microbiota and health there are other types of interactions. For instance, in addition to the production of genotoxic substances, the microbiota can contribute to the degradation of xenobiotics, such as heterocyclic amines (31). There is considerable evidence that the ability of microbiota to degrade various xenobiotic substances is an important feature that facilitates longevity (32). Furthermore, the dominant product of protein fermentation, branch chained fatty acids, were not even mentioned. Branch chained fatty acids are produced by the fermentation of valine, isoleucine, leucine, glycine, and alanine, and these microbial metabolites are associated with energy extraction and no adverse health effects (60, 61). Furthermore, tryptophan degradation leads to the synthesis of various indole-containing molecules. Importantly, these molecules can activate aryl hydrocarbon receptors present on the gut epithelium relevant for immunological homeostasis (62). In patients with advanced atherosclerosis, it was found that tryptophan and several microbial tryptophan metabolites, including indole, indole-3-propionic acid, and indole-3-aldehyde, were depleted in advanced atherosclerosis (63). However, another microbial metabolite of tryptophan, indoxyl sulphate, acts as a cardiotoxin and uremic toxin. This illustrates that different microbial metabolites derived from protein fermentation, and even single amino acids, can have opposite effects on the course of pathological processes.

Furthermore, it is important to mention that, in general, high-protein dietary patterns are typically based on a high intake of animal protein. Health risks associated with plant- or animal-derived proteins are not the same (64). In principle, the health effects of plant-based diets are beneficial, and this can be explained by the direct biological activity of various phytochemicals on the human metabolism, but also by the beneficial effect of fibers and polyphenols on gut microbiota activity (65, 66). In contrast to plant-based foods, animal-based foods contain other nutrients that can be metabolized into hazardous metabolites by gut microbiota. In this respect, microbial metabolism of choline is particularly problematic and is of critical importance for colorectal cancer (67) and cardiovascular disease development (68). In the anthropocentric approach to human nutrition, choline is consumed as a supplement because it is not synthesized in sufficient amounts in the human body, while it is required for the maintenance of the structural integrity of cell membranes and supporting neural signaling. Interestingly, choline in the form of supplements elevates hazardous microbial metabolites in the blood significantly more than choline from eggs (69). It has been known for a long time that nutrients' bioavailability and health impact depend on the food matrix in which they are consumed,

while in the future we must learn to acknowledge that nutrients' bioavailability and health impact also largely depend on their interaction with the gut microbiota. When diet composition is out of balance, nutrient supply to the gut microbiota changes, and this has an effect on both the composition and function of the microbiota. In weight-loss protein-rich diets, proteins are present in an excessive amount, and this overrepresentation of protein in the absence of resistant carbohydrates shifts microbiota activity towards production of hazardous metabolites. The production of hazardous microbial metabolites poses risks for adverse health effects, but only in the long term. Although the health effects of gut microbiota metabolites are not acute, the gut microbiota and its activity should be taken into consideration when designing nutritional strategies to promote health.

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Declaration of Competing Interest

The author declares to have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Author contributions

MRS contributed to the manuscript by taking the following roles: Conceptualization; Writing - original draft, review & editing.

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Značaj mikrobne fermentacije za dugoročne zdravstvene efekte ishrane bogate proteinima

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Kratak sadržaj

Proteini su značajni makronutrijenti sa nizom dokazanih pozitivnih efekata na zdravlje. Danas je ishrana bogata proteinima široko primenjivana, naročito u cilju dostizanja i održavanje zdrave telesne mase. Iako se povezuje sa pozitivnim zdravstvenim efektima, dugoročna ishrana bazirana na visokom sadržaju proteina je zapravo povezana sa više oboljenja i sa kraćim životnim vekom. Negativni zdravstveni efekti proteinskih dijeta su, makar delimično, posredovani aktivnošću mikrobnih metabolita dobijenih fermentacijom proteina. Naime, sve nesvarene komponente hrane se u debelom crevu fermentišu od strane crevne mikrobiote. S obzirom na to da su bočni ostaci aminokiselina hemijski raznovrsni, nesvareni proteini obezbeđuju složenu smešu supstrata za mikrobnu fermentaciju. Korišćenjem različitih aminokiselina, mikrobiota može da proizvede toksična, genotoksična i kancerogena jedinjenja, ali i metabolite koji ometaju signalizaciju insulina ili kompromituju kardiovaskularno zdravlje. Postoje naučni dokazi da mikrobni metaboliti više aminokiselina mogu doprineti razvoju kardiovaskularnih bolesti i raka, tj. bolesti koje su povezane sa ishranom bogatom proteinima. Iako su metabolički proizvodi mikrobiote u principu korisni i komplementarni ljudskom metabolizmu, kada je sastav ishrane neuravnotežen (npr. kada su proteini prisutni u prevelikoj količini) aktivnost mikrobiote se menja i dolazi do proizvodnje štetnih produkata. Imajući navedeno u vidu, neophodno je da se pri osmišljavanju zdrave ishrane u obzir uzme i aktivnost crevne mikrobiote.

Ključne reči: crevna mikrobiota, ishrana bogata proteinima, rak, kardiometabolički rizik, fermentacija