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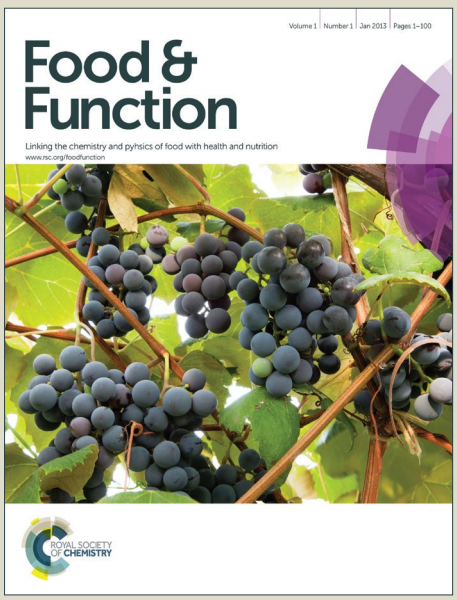

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REVIEW ARTICLE

Interactions between acrylamide, microorganisms, and food components – a review.

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Acrylamide (AA) and its metabolites have been recognised as potential carcinogens, but also they can cause other negative symptoms in human or animal organisms so this chemical compounds still attract a lot of attention. Those substances are usually formed during heating asparagine in the presence of compounds that have α-hydroxycarbonyl groups, α,β,γ,δ-diunsaturated carbonyl groups or α-dicarbonyl groups. Acrolein pathway and enzymatic decarboxylation of asparagine as well as endogenic processes are another alternatives to AA formation. It has been demonstrated that animal model used for examining AA toxicity may not be sufficient to investigate those changes in humans so it is necessary to design an *in vitro* model, which could provide more accurate insight into the direction of those processes in human organisms. Acrylamide can be metabolised through both oxidative and reductive pathway; moreover, there is also a chance that some representatives of intestinal microbiota are able to transform that substance. It was shown that there are various microorganisms, mostly bacteria, that produce amidases – enzymes decomposing AA. Lactic acid bacteria also seem to demonstrate the ability to use acrylamide as a carbon source but it still requires further investigations. Another way to prevent AA toxicity is related to the presence of some food compounds, which might be found in food products, such as certain proteins or polyphenols. There is still a lot of gaps in the current knowledge related to AA toxicity so potential research directions were presented in this review as well.

Introduction

In 1994, acrylamide (AA) was classified as the substance potentially carcinogenic for humans[1], however, studies on rodents confirmed AA-induced carcinogenesis in many organs of those mammals, including lungs, brain, placenta, liver, skin and various glands[2–5]. Due to the fact that acrylamide does not exert mutagenic effect in bacterial cells, it was agreed that its carcinogenic activity is related to glycidamide (GA) – acrylamide metabolite formed in mammalian cells. Mutagenic and genotoxic effects of GA have been already confirmed in various *in vitro* and *in vivo* studies. The research on rodents has shown that as the result of metabolic reactions, acrylamide is transformed to glycidamide, which induces the formation of DNA adducts resulting in mutagenesis and the development of cancers[2,6,7,8]. Up to date, it has not been confirmed in humans that AA is able to bind DNA, however, it was proved to bind calf thymus DNA *via* Michael-type addition[9]. On the other hand, glycidamide binds to both DNA and proteins, such as hemoglobin, causing formation of adducts, which are markers of human exposure to acrylamide[8]. Acrylamide also shows neurotoxic activity resulting in damage of distal axons in central and peripheral nervous systems, which leads to the impairment of learning functions and causes the damage in cerebral cortex, thalamus and hippocampus[2,10]. AA is a chemical compound easily migrating into the environment and it undergoes biodegradation very fast (especially in soil) without transferring into the air so its occurrence in the environment should not present potential threat to human health. The only exception are aquatic environments, where acceptable concentration of AA reaches few ppb, depending on the legislation related to drinking water in different countries, but it never exceeds 5 ppb[11–13].

It seems that the presence of acrylamide in food products, which are consumed frequently in high quantities with daily diet, is more serious problem[2,14]. This phenomenon is related to the goods

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that are subjected to the thermal processing (temperature above 120°C) such as frying, roasting or baking, which include breakfast cereals, cereal products[15,16], roasted coffee beans[17], chips, crisps[5,18,19] and other. It is worth highlighting that among food products, not French fries but coffee delivers the most (36%) of total AA dose ingested with food[20]. The comparison and compilation of various food products containing acrylamide has been already presented in several review papers[2,10,16] so this issue will not be addressed in details in the current review.

There are various methods to reduce AA content in food products: (a) application of cultivars of fruits and vegetables, which are low in AA precursors – mainly asparagine and glucose; (b) removal of AA precursors before further processing, *e.g.*, through asparagine degradation by asparaginase[21]; (c) optimisation of technological processing aiming to reduce AA formation[16]; (d) addition of food ingredients that prevent AA formation; (e) AA removal/binding after its synthesis by chromatography, evaporation, polymerisation or by reacting with other food compounds; (f) reduction of *in vivo* toxicity[22]. Application of legume proteins for the production of potato fries[23], soaking potatoes in citric acid solution, blanching and decreasing frying temperature from 190 to 150°C[19,24] and adding sodium or magnesium ions[25] might be mentioned as examples of those methods.

The main goal of this review was to present a detailed insight into interactions between acrylamide and microorganisms, especially those related to food and human organism. The following aspects were discussed: pathways of acrylamide formation, AA metabolism, enzymatic transformations of AA carried out by microorganisms, and description of protective mechanisms of selected food compounds against acrylamide formation and/or toxicity.

Acrylamide formation

The most probable pathways of acrylamide formation in food are presented in Figure 1. Asparagine is sought to be the most important AA precursor. That amino acid gives trace quantities of acrylamide during thermal processing, however, this phenomenon might be accelerated in the presence of carbonyl groups. The classical pathway (A) occurs during heating asparagine in the presence of compounds that have α-hydroxycarbonyl groups (*e.g.*, reducing sugars), which leads to the formation of Schiff bases in Maillard reaction. Schiff base might undergo the transformation into Amadori compounds, which eventually provide the colour and flavour of food products, but it also might be decarboxylated to azomethine ylide. Acrylamide is formed directly from azomethine ylide or through β-elimination of decarboxylated Amadori compound (obtained also by tautomerisation of azomethine ylide) or through the hydrolysis of ylide followed by the deamination of 3-aminopropionamide (3-APA), which is sought to be the key, direct AA precursor[26,27].

Except for compounds with carbonyl α-OH groups, other reactive carbonyls might also participate in AA formation. It seems that the alternative pathway (B in Fig. 1) is activated when α,β,γ,δ-diunsaturated carbonyl groups or α-dicarbonyl groups are available. Even though compounds containing α-dicarbonyl or α,β,γ,δ-diunsaturated carbonyl groups are abundant, that pathway favours such sugar fragments as glyoxal, hydroxyethanal, glyceraldehyde or specific lipid oxidized products (2,4-decadienal). Asparagine and reactive carbonyl groups form adequate Schiff base, which undergoes decarboxylation to azomethine ylide leading indirectly or directly to AA formation.

Nevertheless, asparagine might also react with food compounds such as 5-hydroxymethylfurfural (5-HMF). 5-HMF is formed in Maillard reaction during thermal processing of raw materials or food rich in carbohydrates and/or amino acids[28]. It was demonstrated that HMF containing α,β,γ,δ-diunsaturated carbonyl groups might accelerate asparagine transformation to AA during thermal processing through an alternative pathway[29].

Acrylamide might be also generated at high temperatures during deep-frying of products rich in asparagine despite the absence of reducing sugars - it is so called acrolein pathway (C in Fig. 1). Acrolein and acrylic acid (oxidized acrolein) are formed through the degradation of fats followed by glycerol dehydration and they give acrylamide in the reaction with ammonia (coming from the degradation of asparagine and other amino acids). Those processes occur very intensely in fish fats, then plant fats and the slowest rate of that reaction takes place in the lard[30].

Another possibility for forming 3-APA – acrylamide precursor, is enzymatic decarboxylation of asparagine (pathway D in Fig. 1)[2,16] or heating products containing asparagine in the presence of pyruvic acid and at low water content[31]. AA is also formed during thermal decomposition of gluten[32] or other

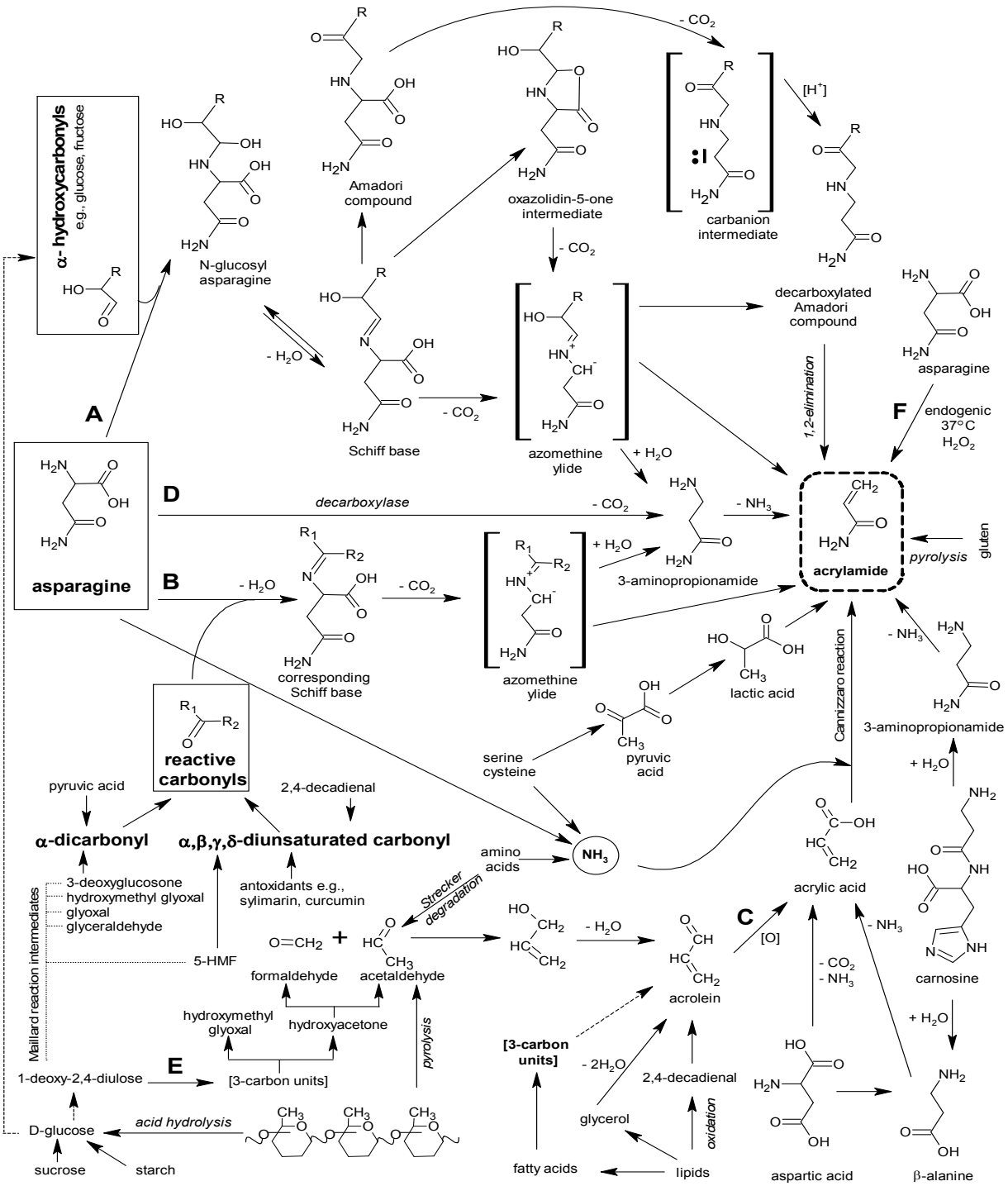

Fig. 1. Scheme presenting possible pathways of acrylamide formation[21,26,27,32–39]

dipeptides and oligopeptides, which contain alanine bonded to other amino acids that have hydrogen atoms in β position, such as carnosine[40,41]. Vattem and Shetty (2003)[23] indicated that AA synthesis during frying potato chips might not have oxidative character. *D*-glucose, through a series of enolization and isomerization, can form 1-deoxy-2,4-diulose (pathway E), which after one more keto-enolization forms 1-deoxy-2,5-diulose. This unstable sugar decomposes into two 3-carbon compounds: hydroxyacetone and hydroxymethyl glyoxal. Hydroxyacetone quickly breaks down forming acetaldehyde and formaldehyde that eventually condense into acrolein. Acetaldehyde can be also obtained from the Strecker degradation of free amino acids present in food or during thermal degradation of proteins. Moreover, some amino acids, such as β-alanine, are directly transformed into acrylic acid during thermal decomposition or through the stage of pyruvic and lactic acids – like in case of serine and cysteine[40].

It is worth considering that AA might have an endogenous origin. Tareke et al. (2009)[42] have shown in an *in vitro* study that under conditions of physiological temperature, pH and ionic strength, AA might be formed in the presence of hydrogen peroxide (Fig. 1, pathway F). Except for hydrogen peroxide, also other active oxygen species such as $O^{2-}\bullet$, •OH, and $ONOO^-$ might participate in the generation of endogenous AA, which means that at various pathological states related to the formation of reactive molecules, the enhanced exposition to AA might occur[1].

AA synthesis depends on various physical and chemical parameters. The most important are time and temperature of thermal processing of food products and it is sought that the prerequisite requirement for AA formation is the temperature exceeding 120°C. The higher the temperature of thermal processing and longer the exposure time, the more efficiently Maillard reaction and starch degradation to simple sugars (including *D*-glucose) occur. *D*-glucose can be also produced during acidic hydrolysis of glucans present in food[33]. *D*-glucose is perceived as one of acrylamide precursors because under high temperature, 3-carbon molecules and various Maillard reaction intermediates are generated, both resulting in AA formation[17]. In most of the studies it was proven that extending the exposure time of food compounds to high temperatures causes the increase of AA concentration[17], however, there are some reports state otherwise[20].

It should be highlighted that not only the concentration of AA precursors in food influences the efficiency of acrylamide formation. Food or raw materials with the same chemical composition but different microstructure differ when the acrylamide concentration after heating is considered. Food microstructure is responsible for water (moisture) sorption and, therefore, influences the water content in the food matrix where various reactions occur. It was demonstrated that acrylamide concentration in biscuits prepared by using 20% of water was approximately double than in biscuits prepared with 10% and 15% of water[43]. It was because the low moisture level in food could reduce the solubility of nutrients and limits the mobility of reaction substrates causing the reduction in AA generation. As the asparaginase specifically removes a key precursor for acrylamide formation, the enzyme is used for mitigating AA formation[44]. The asparaginase activity is affected by enzyme dose, reaction time, temperature and pH at which the reaction occurs[45,46], but it also strongly dependents on the contact with the substrate. It means that in products with low moisture level a limited solubility and mobility of substrate and asparaginase resulted in incomplete hydrolysis of asparagine and smaller reduction in AA formation. In contrary, in products with high water content, which favours precursor mobility, the asparaginase capability of AA reduction was enhanced in the final product[43]. Moreover, any technological operation which changes food matrix microstructure and in such way favours the substrate diffusion or its contact with the asparaginase can lead to a greater reduction of acrylamide levels. One of such operation is blanching. This process was proved to enhance the extraction of AA precursors from raw material reducing the AA formation[47]. Blanching produces also microstructural changes in food which facilitate a faster contact between asparagine and asparaginase[46].

Acrylamide metabolism

Acrylamide is rapidly absorbed after oral ingestion and transported throughout the whole organism. Mostly, it is removed with urine within 24 h, however, it remains longer in skin or testicles[48,49], which might induce skin tumours in female mice. AA undergoes enzymatic changes in organisms (Fig. 2). Firstly, it is subjected to the oxidation in cytochrome P450 2E1 (CYP2E1) to glycidamide (2,3-epoxypropionamide; GA), which is considered as an activation pathway. Both AA and GA might bind haemoglobin, blood plasma albumins, proteins (like protamine) and DNA;

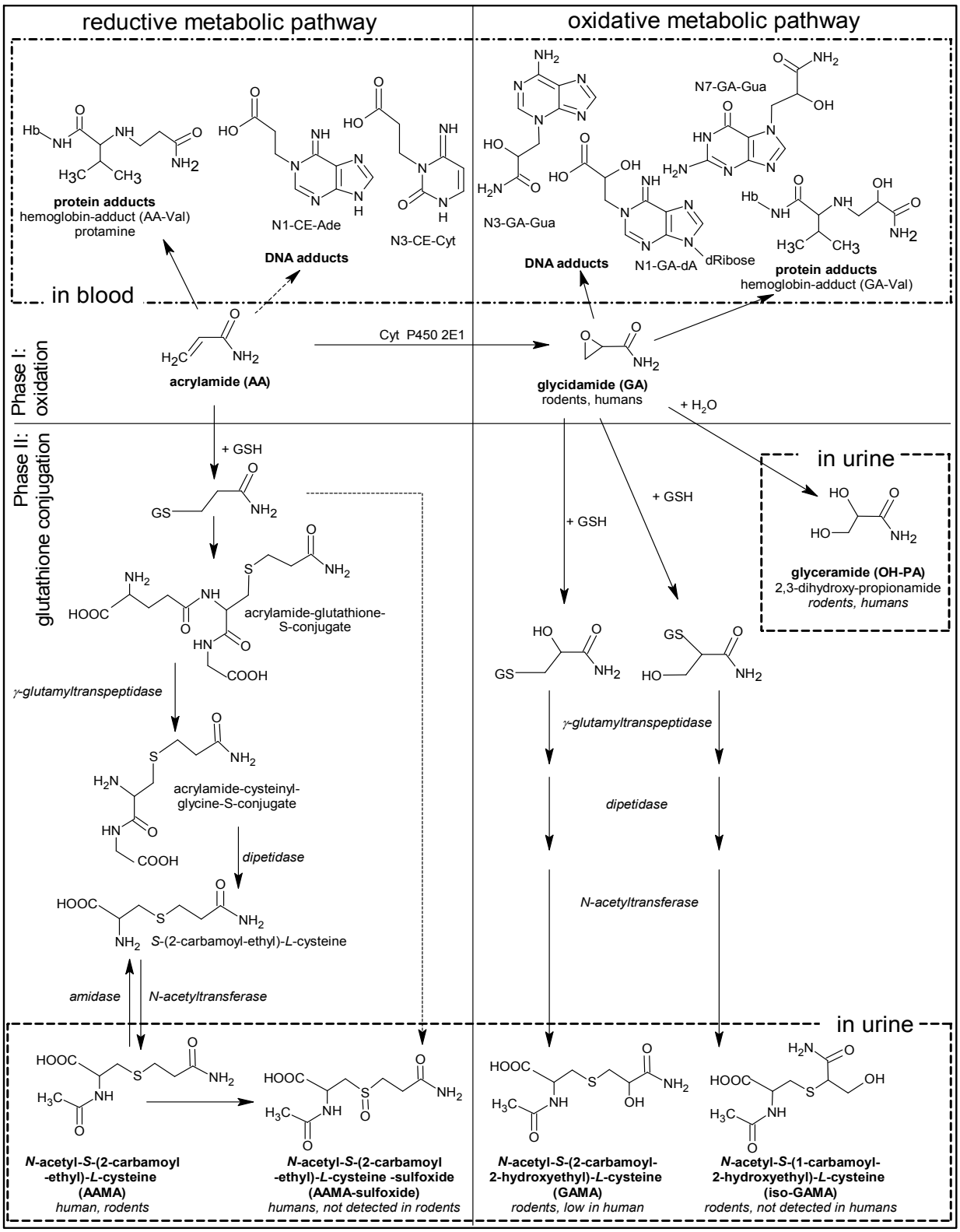

Fig. 2. Oxidative and reductive pathways of acrylamide metabolism and adducts detected in blood[8,50–55]

although, glycidamide is much more reactive toward DNA than acrylamide. Up to day, DNA adducts of acrylamide have not been detected in human cells, but it has been proven in *in vitro* studies that AA can bind to DNA of calf thymus. After 40 days of exposure to AA, some DNA adducts were detected at very low concentrations and *N*1-(2-carboxyethyl)-adenine (N1-CE-Ade) and *N*3-(2-carboxy-ethyl)-cytosine (N3-CE-Cyt) dominated[9].

The conversion of AA to glycidamide by CYP2E1 was confirmed in humans and rodents in both *in vitro* and *in vivo* studies. Although this process seems to be minor pathway in humans, in rodents approx. 30% (rats) to 60% (mice) of excreted metabolites are GA derivatives[2,52]. Highly reactive GA might be detoxified *via* hydrolysis to less reactive glyceramide (2,3-dihydroxypropionamide) mediated by the epoxide hydrolase[56]. Glyceramide, which is soluble in water, seems to be the main metabolite of the oxidative metabolic pathway in humans (Fig. 2) and it is excreted with urine reaching maximum levels between 8 to 22 h after AA intake[57].

Both acrylamide and glycidamide might be conjugated with glutathione (GSH) due to the activity of glutathione-S-transferases (such as GSTM1, GSTT1, and GSTP1), and then transformed into conjugates of mercapturic acids, which are excreted with urine – it is considered as the deactivation pathway. In both cases the GSH conjugation might lead to decreasing the availability of that tripeptide like it occurs in hepatocytes of male rats[58,59]. In humans, lowering glutathione level is rather related to hydrolysis processes[58]. The products of glutathione conjugation with AA detected in urine are *N*-acetyl-*S*-(2-carbamoylethyl)-*L*-cysteine (mercapturic acid of acrylamide, AAMA) and *N*-acetyl-*S*-(2-carbamoylethyl)-*L*-cysteine-sulfoxide (AAMA-sulfoxide), while GA metabolites are *N*-acetyl-*S*-(2-carbamoyl-2-hydroxyethyl)-*L*-cysteine (GAMA) and *N*-acetyl-*S*-(1-carbamoyl-2-hydroxyethyl)-*L*-cysteine (*iso*-GAMA). Moreover, significant differences in the profiles of AA metabolites between mice, rats and people were demonstrated[58]. In humans, acrylamide is metabolized mainly *via* reductive pathway and more than 51% of ingested dose is excreted as AAMA, while about 13-14% as AAMA-sulfoxide, which was detected only in humans[52]. Oxidative metabolic pathway leads to the generation of glyceramide, GAMA and *iso*-GAMA, but in humans this pathway has less significance and only small part of AA dose is excreted as oxidated metabolites, mainly as glyceramide (5.4%) and GAMA (4.6%). The third metabolite, *iso*-GAMA, was detected in some studies at very small amounts in urine and constituted 0.8% of initial AA dose[57], while in others, *iso*-GAMA was not detected in samples of human urine at all[52]. On the other hand, acrylamide in rodents is metabolized both *via* reductive and oxidative pathways and in urine AAMA and GAMA are detected at similar levels (each about 30-40% of AA dose), but AAMA-sulfoxide is not generated. Due to this fact, it might be stated, that animal model is not very useful for examining AA metabolism in humans, which makes an interpretation of results gathered on the toxicity of that substance more difficult. Possible solution might be creating adequate *in vitro* model considering changes that AA is subjected to in human digestive tract or body cells.

It should be underlined that decreasing concentration of available glutathione in its reduced form (GSH) obtained after conjugation with AA, might be responsible for acrylamide cytotoxic effect[60–62], which is probably related to the accumulation of excessive quantities of reactive oxygen species (ROS) and initiation of oxidative stress in cells/organism.

Another possible pathway of AA decomposition is its degradation by microbial amidases. Some microorganisms that can use acrylamide as a sole carbon source to grow, conduct this process. Acrylamide, an aliphatic amide, is deaminated giving ammonia and acrylic acid. That process is catalyzed by amidase or amidohydrolase. Then acrylic acid can be reduced to propionate or transformed to β-hydroxypropionate, lactate or CO_2 (Fig. 3)[63–65]. So far, the participation of intestinal microbiota in chemical changes of AA and GA has not been investigated. On the other hand, it has been shown that various bacteria, including those that reside in human intestine might degrade both mentioned compounds. Hence, it might be concluded that in the next years it will be a new research direction.

Acrylamide degradation by microorganisms

So far, various species and strains of microorganisms that are able to degrade AA have been isolated from different environments (Table 1). They were proven to decompose acrylamide in a very broad range of concentrations (from 1 to 40 mM[67–75]), and it was reported that bacteria are clearly more

efficient in that process than yeasts. In case of moulds, there are very few papers describing acrylamide degradation by this group of microorganisms and they are only related to *Aspergillus* sp. It is worth highlighting that among presented strains there are certain species that naturally occur in human organism or those that are delivered with food such as *Escherichia coli* [76,77], *Enterococcus faecalis* [78], *Bacillus clausii* [79], and *H. pylori*[80].

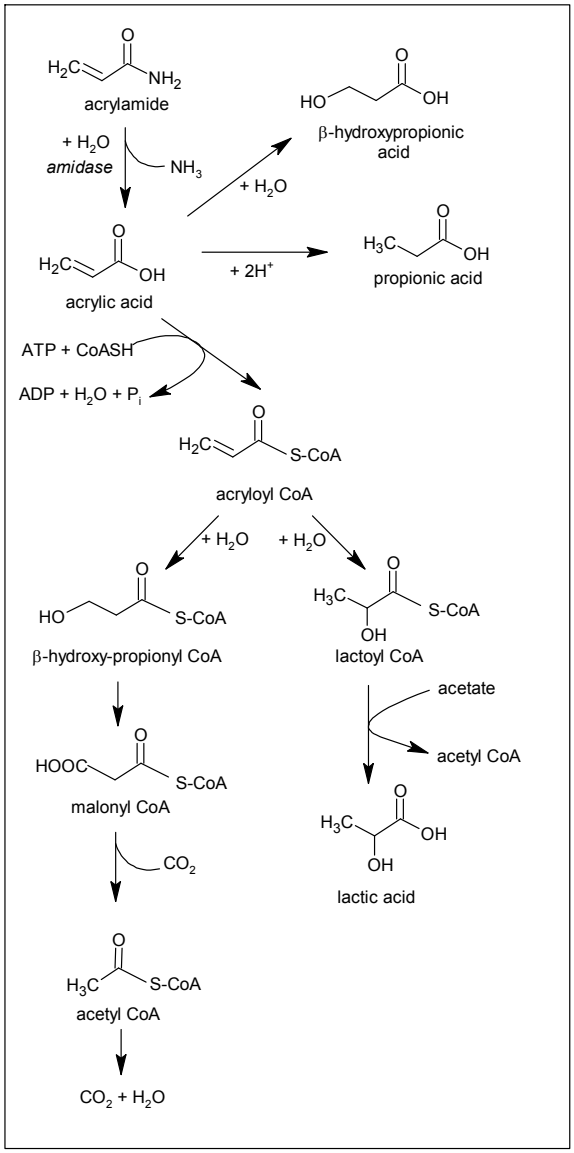

Fig. 3. Deamination of acrylamide by amidase and possible biological fates of obtained acrylic acid[65,66]

The most important enzymes engaged in acrylamide degradation are amidases, which catalyze the AA hydrolysis to ammonia and acrylic acid (Fig. 3)[69,81]. Amidases (acylamidase, amidohydrolase, EC 3.5.1.4) enable growth of microorganisms in the environment where linear aliphatic amides occur as the only carbon and nitrogen sources. The activity of those enzymes is enhanced by specific substrates present in various environments, *i.e.* acetamidase is induced by acetamide and formamidase by formamide[82]. Some microorganisms produce amidases demonstrating high substrate specificity, whereas others synthesize amidases able to hydrolyze various substrates. Table 1 presents bacteria and fungi, for which amidase production have been confirmed along with the name of detected enzyme and its preferred substrates.

As it was shown, most of tested enzymes demonstrated satisfactory efficiency in decomposing acrylamide or other substances, which might potentially contaminate environment or food. *Helicobacter pylori*, bacteria living in human stomach, produces amidase (AmiE) and can use acrylamide to release of ammonia in direct cell surrounding. It is sought that combination of urease and amidase activities enables survival of *H. pylori* under unfavourable conditions in stomach[83,84]. Some bacteria, including typical representative of intestinal microbiota - *Escherichia coli*, also produce other enzymes that catalyze the hydrolysis of non-protein C-N bonds in linear molecules; for example, penicillin amidase (EC 3.5.1.11) catalyzes decomposition of penicillin to carboxylic acid and 6-aminopenicillanic acid, which exerts weaker antibacterial activity. Amidases play an important role in the proliferation of cells and separating young cells (*e.g.*, amidases of *E. coli* AmiA, AmiB and AmiC), however, the substrate for those enzymes is peptidoglycan. There are also other enzymes that operate similarly. One of them is N-acetylmuramidase (AcmA, EC 3.5.1.28), enzyme synthesized by various strains of *Lactococcus lactis,* that demonstrates autolytic activity. It has been already applied in cheese maturation because as the result of cell autolysis the release of bacterial peptidases occurs leading to the formation of peptides and amino acids providing desired aroma and flavour of cheese[61,111].

Table 1. Microorganisms proven to synthesize amidases

Microorganism [Reference]	Origin of microorganism(s)	Enzyme name(s)	Substrate(s)
Bacteria			
Arthrobacter sp. NJ-26[85]	activated sludge	D-amidase	D-alaninamide
Bacillus cereus DRY135[86]	soil, Malaysia	aliphatic amidase	acrylamide, methacrylamide, nicotinamide, acetamide, propionamide, urea
Bacillus clausii 1779[74]	soil	aliphatic amidase	acrylamide
Bacillus megaterium[87]	temple Puja wastes, India	penicillin amidase	carboxyl methyl cellulose
Bacillus megaterium ATCC 14945[88]	recombinant	penicillin G amidase	various mineral and organic nitrogen sources
Bacillus subtilis recombinant[89]	recombinant of *Bacillus sphaericus*	penicillin V amidase	ampicillin, tetracycline, chloramphenicol, penicillin V, 6-aminopenicillianic acid, phenoxyacetic acid
Blastobacter sp. A17p-4[90]	Kyoto University, Japan	half-amidase	succinimide, maleimide, 2-methylsuccinimide, glutarimide
Brevibacterium epidermidis ZJB-07021[91]	soil, China	*R*-stereospecific amidase	2,2-dimethylcyclopropanecarboxamide
Burkholderia sp. strain DR.Y27[71]	soil, Malaysia	amidases of short-chain aliphatic amides	acetamide, 2-chloroacetamide, urea, acrylamide, propionamide, methacrylamide, nicotinamide
Delftia tsuruhatensis ZJB-05174[92]	sewage	*R*-enantio-selective amidase	acrylamide, acetamide, 2,2-(*R,S*)-dimethylcyclopropane carboxamide, asparagine, nicotinamide, ε-caprolactam,
Enterobacter aerogenes[72]	domestic wastewater, Thailand	aliphatic amidase	acrylamide, acetamide, benzamide, butyramide, cyanoacetamide, formamide, iodoacetamide, lactamide, *N,N*-methylene bisacryalmide, propionamide, sodium azide, thioacetamide, urea
Enterococcus faecalis[78]	human stools	No data	oxalate
Escherichia coli and paracolon bacilli[93]	clinical isolates	Pen-amidase	penicillins, leucylnaphtylamide, L-leucinamide
Escherichia coli ATCC 11105[94]	Squibb Institute for Medical Research, USA	penicillin amidase	α-aminobenzocillins
Escherichia coli JM109[95]	recombinant	no data	ampicillin, isopropyl-β-D-thiogalactopyranoside
Helicobacter pylori 26695[80]	mutant	Amidase AmiE	acrylamide, formamide
Helicobcter pylori[83]	45 human clinical isolates	acrylamide aminohydrolase	propionamide, acrylamide, acetamide
Helicobacter sp.[84] *e.g., H. acinonychis, H. felis, H. pylori, H. muridarum*	11 isolates from gut or intestine of various animals and human	amidase AmiE, formamidase AmiF	acetamide, acrylamide, formamide
Moraxella osloensis MSU11[75]	paper mill effluent, India	aliphatic amidase	acrylamide
Nocardia globerula NHB-2[96]	forest soil, India	nitrilase, nitrile hydratase, amidase	propionitrile, benzonitrile, acetamide, acrylamide
Proteus rettgeri[97]	no data	penicillin amidase	penicillins, cephalosporins,
Pseudomonas aeruginosa[98]	recombinants	A and B amidase	succinate, formamide, lactamide, butyramide, phenylacetamide, ammonium sulphate, fluoroacetamide
Pseudomonas aeruginosa 8602[99]	recombinant	aliphatic amidase	succinate and acetamide
Pseudomonas aeruginosa 8602[100]	wild type and mutants	aliphatic amidase	succinate and acetamide
Pseudomonas putida[101]	soil	aliphatic amidase	acrylamide
Pseudomonas putida MTCC 6809[102]	rhizosphere of *Pisum sativum*,	extracellular amidase	acetamide, propionamide, acrylamide, butyramide

	India		
Rhodococcus equi A4[103]	no data	amidase conjugated with nitrile hydratase	benzonitrile, 3-cyanopyridine, *(R,S)*-3-hydroxy-2-methylenebutanenitrile, *(R,S)*-3-hydroxy-2-methylene-3-phenylpropanenitrile
Rhodococcus erythropolis No. 7[104]	soil	*R*-stereoselective amidase	isobutyramide, butyramide
Rhodococcus sp.[69]	soil, USA	aliphatic amidase	acrylamide, acetamide, butyramide, propionamide, isobutyramide
Rhodococcus sp. N-771[105]	recombinant	aliphatic amidase	various aldoximes
Genera and species not determined, strain BS16[106]	soil, Thailand	D-amino acid amidase	D-phenylalanine amide, D-*tert*-leucine
Fungi			
Aspergillus nidulans[70]	wild type and mutants	acylamide amidohydrolase	acrylamide
Candida famata[107]	gold mine effluent	aliphatic amidase	acetonitrile, acrylonitrile, butyronitrile, isobutyronitrile, methacrylnitrile, propionitrile, succinonitrile, valeronitrile, acetamide, isobutyamide, succinamide
Candida guilliermondii UFMG-Y65[68]	water from gold extraction circuit	nitrile hydratase, amidase	acetonitrile
Candida guilliermondii UFMG-Y65[108]	gold mine	nitrile hydratase, amidase	benzonitrile, acrylonitrile,
Candida utilis IGC 3093[67]	laboratory culture collection, Portugal	acylamide amidohydrolase	acetamide, nicotinamide, N-valeramide, propionamide, N-hexoamide, pirazinamide, acrylamide, N-butyramide, malnonamide, asparagine, isonicotinamide
Kluyvera georgiana[109]	domestic wastewater, Thailand	alipahtic amidase	acrylamide, iodoacetamide, thioacetamide, propionamide, cyanoacetamide, acetamide, formamide, butyramide, lactamide, urea, sodium azide
Kluyveromyces thermotorlerans MGBY 37[110]	traditional fermented foods and beverages of Himachal Prades, India	nitrile hydratase, amidase	3-cyanopiridine, nicotinamide, benzonitrile, benzamide, acrylonitrile, acrylamide, acetonitrile, acetamide

The ability to synthesize amidases by bacteria present in digestive tract (*Escherichia coli*[76,77], *Enterococcus faecalis*[78], *Bacillus clausii*[79], *H. pylori)* means that potentially there might be mechanisms leading to acrylamide degradation in human organism. So far, there have been no reports examining whether bacteria that synthesize amidases able to degrade amide bonds in peptidoglycan are also able to degrade acrylamide; however, this possibility cannot be excluded. It seems that analysing the potential to detoxify human organism by intestinal microbiota after AA ingestion could become an interesting research direction in the future.

Amidase activity and synthesis increase significantly under the following conditions: neutral[102,105] or slightly alkaline pH[69,85,108,112], temperature ranging from 30°C[102,105,108] to above 40°C[69,112], the presence of reducing substances (sodium sulphide, sodium thiosulphate, 2-mercaptoethanol, *L*-cysteine)[105] and electron acceptors (flavines, sulphides and vitamin K_3)[105]. Ferric ions stimulate amidases production[69], whereas partial inhibition of those enzymes might be caused by magnesium ions, while complete inhibition was observed in the presence of nickel, mercury[101], zinc[113], copper and cobalt[112], specific magnesium chelators, and thiol blocking reagents[69]. Moreover, heavy metals did not influence the activity of amidases synthesized by some microorganisms, e.g., *Pseudomonas putida* MTCC 6809[102]. It was indicated that succinic acid might inhibit amidase synthesis, whereas *N*-acetylacetamide induces that process[99,100]. Moreover, in case of *Aspergillus nidulans*, acetamidase is able to degrade acrylamide but its synthesis is not induced by that substance[70].

Among other amidases, which have not been presented in Table 1, it is worth mentioning *L*-asparaginase and *L*-glutaminase that might play significant role in interactions between microorganisms and food compounds. They exert prominent anticancerogenic activity and they have been accepted in therapies against those diseases[114]. It was confirmed that they are produced by various microorganisms, including both bacteria and fungi,

specially yeasts[115]. Deamination of asparagine and glutamine by those enzymes decreases acrylamide formation.

Various bacteria can also play a key role in generating acrylamide in food during thermal processing. Baardseth et al.[41] have applied lactic acid fermentation carried out by *Lactobacillus plantarum* for reducing the quantity of simple sugars that are present in potato rods prepared for the production of French fries. Thanks to this, they managed to decrease the content of AA in finished products. On the other hand, it is important to bear in mind that there is a possibility to form acrylamide from lactic acid and NH_3 (Fig. 1)[40]. Blom et al.[116] and Bartkiene et al.[117], who applied selected strains of lactic acid bacteria (LAB) along with glucoamylase from *Aspergillus niger* for the production of various rye breads also noted significant decrease of AA content in final products. Another example of applying LAB is the study carried out in male mice. It was demonstrated that in animals subjected to the exposure of acrylamide or 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP) the pre-treatment with mixture of various bacteria belonging to the *Bifidobacterium* genus caused significant decrease in DNA damage in liver or colon[118]. However, as it was stated before, animal model might not reflect adequately how those processes are carried out in humans. Seiquer et al.[119] indicated that the diet rich in the products of Maillard reaction led to significant quantitative changes of particular microorganisms residing in gut in the studies on intestinal microbiota of humans and rats. In both tested populations, the negative correlation was observed between the number of *lactobacilli* and hydroxymethylfurfural but also between the number of *bifidobacteria* and the ingestion of Amadori compounds.

Serrano-Niño et al.[120] tested 14 various species of LAB and they proved that some among them demonstrated the ability to decrease AA concentration, especially at pH 8 (which is close to the conditions in human intestine). *Lactobacillus casei* strain 334 managed to bind 29.12% of acrylamide within 4 h from the solution at the concentration 5 µg AA/ml, while after 12 h of incubation *Lb. reuteri* strain *NRRL 14171* bonded 24.01% and *Lb. casei* Shirota bonded 24.95% of introduced acrylamide. Unfortunately, it has not been determined whether those microorganisms managed to synthesize amidases. So far, the interaction between health-promoting gut microbiota and AA has not been described. Therefore, we cannot assess their potential for detoxifying food contaminated with acrylamide and explain the phenomena occurring in human organism after the ingestion of food products containing that substance.

Protective impact of selected diet compounds

The reduction of negative influence of acrylamide on organisms is not tantamount to the necessity of degrading that compound before ingestion. Proteins present in food (*e.g.*, chicken egg albumin) bind acrylamide, which reduces its absorption by intestinal cells and eventually decreases its final concentration in body cells and tissues[121]. Replacing some part of flour in baked goods with amaranth proteins, which are rich in lysine and sulphur amino acids[122] has caused the reduction of AA amount generated during thermal processing. Legume proteins also protect organisms by limiting AA formation. It is probably due to the starch stabilisation and reduction of D-glucose release but also by participation of those proteins in dislocating electrons, which prevent breakages of carbon chains and formation of 3-carbon compounds that might be AA precursors[16,34].

There are various substances, which might alleviate or inhibit toxicity of AA and its derivatives in human organisms. All of them demonstrate high antioxidant potential, including 5-aminosalicylic acid, which showed protective properties to leucocytes in testicles of male rats that had been exposed to AA[123] and *L*-carnitine that decreased AA mutagenicity[124]. Moreover, *N*-acetyl-*L*-cysteine (NAC, GSH precursor) efficiently acted against adverse influence of AA and GA on intestinal and liver cells[59,125] because it reduced acrylamide-induced infiltration of neutrophils, balanced the oxidant-antioxidant status, and regulated the generation of inflammatory cytokines to protect tissues.

Antioxidants play an important protective role against the influence of acrylamide. Cyanidin-3-*O*-glucoside efficiently reduced AA-induced oxidative stress in MDA-MB-231 cells through the reduction of radical products generation, and by decreasing the activities of pro-oxidative enzymes such as glutathione peroxidase, glutathione *S*-transferase and CYP2E1, with simultaneous activation of γ-glutamyl cysteine synthase[126]. Pan et al.[127] demonstrated that melatonin exerted protective effect against AA-induced oxidative damage. Melatonin decreased DNA fragmentation, reduced ROS and malondialdehyde generation and influenced the synthesis and activity of enzymes.

It has been shown, that some substances holding antioxidant properties, *e.g.*, tymochinon[128], rutin[129] and *Acolus calamus* extracts[130] can erase or reduce neurotoxic effects induced by the exposure to AA. The activity of those natural compounds results in restoring normal walk, regenerating cortex brain cells, reducing the risk of paralysis and, as in case of the substances mentioned before, reversing effects of an oxidative stress.

Various herbs and medicinal plants also demonstrate protective activity against acrylamide toxicity, *e.g.*, *Panax ginseng* extract[131]. Extracts of pimento, black pepper, marjoram and oregano decreased the AA quantity formed in potatoes under thermal processing (20 min, 180°C) and that influence was correlated with their antioxidant activity[132]. Crocin, which is present in saffron, when delivered at concentrations 10-50 μM before exposition to AA, weakened harmful influence of acrylamide to PC12 cells by inhibiting their apoptosis and decreasing the ROS generation[133]. Allicin present in garlic exerts protective impact towards liver cells mainly through decreasing the amount of reactive oxygen species, enhancing the activity of superoxide dismutase or GSH level and due to its ability to prevent the epoxidation of AA to GA through inhibition of P450 enzyme. Allicin at the concentration of 15 μM effectively inhibited AA-caused hepatocyte damage by decreasing the level of maleic dialdehyde and 8-hydroxy-deoxyguanosine (DNA damage marker)[134]. Similar effects were observed in case of delivering garlic and karkadé before acrylamide ingestion[135].

Protective effects were also demonstrated in case of purified antioxidants, including polyphenols that are quite common in food products. Myricitrin (2.5–10 μg/ml) significantly inhibited AA cytotoxicity against cells of human intestine – Caco-2 by inhibiting ROS formation[136]. On the other hand, geraniol and curcumin (at concentrations 5–10 μM) significantly reduced AA-induced mortality of *Drosophila melanogaster,* decreased the level of markers related to oxidative stress and restored the level of GSH and total thiols[137]. Curcumin at the concentration 2.5 μg/ml significantly reduced genotoxic and cytotoxic effects of AA against Hep-G2 cells by limiting ROS production, DNA fragmentation and formation of micronuclei[138]. Similarly, procyanidin B2 and cocoa polyphenolic extract decreased AA toxicity through improving the redox status in Caco-2 cells and by blocking apoptosis pathways activated by acrylamide[139]. On the other hand, sulforafan (SFN), the compound of broccoli holding anticancerogenic activity, reduced GSH-dependent AA detoxification through the formation of GSH-SFN adducts that are more stable than GSH-AA adducts, which resulted in the reduction of free GSH pool[140].

The addition of flavonols (tricin, apigenin, luteolin) and izoflavonols (daidzin, genistin, daidzein, genistein) decreased AA formation with maximum inhibition ranging from 19.6% to 52.1% and the efficiency of inhibition was strongly correlated with the number of free hydroxyl groups in flavonoids[141]. Flavonoids, as strong antioxidants, can react with intermediates and products of Maillard reaction (*e.g.*, 3-aminopropionamide) causing the inhibition of AA formation[142]. However, some antioxidants such as chlorogenic acid can cause sugar decomposition, which promotes 5-HFM generation and eventually, acrylamide formation[143]. The final effect depends on the concentration of antioxidants[144] and food composition, including water content, food matrix, pH or polarity of reaction environment.

It was proven that in the environment rich in asparagine but low in sugars, antioxidants containing reactive carbonyl groups (*e.g.*, curcumin, sylimarin) reacted with asparagine and enhanced acrylamide synthesis (Fig. 1)[145,146]. In turn, antioxidants (*e.g.*, epicatechin) able to capture and inhibit compounds containing carbonyl groups, restricted their availability and decreased the quantity of produced AA[147]. Antioxidants (*e.g.*, naringenin) might also inhibit AA formation by reacting with its precursors, mainly amide compounds, including asparagine[27]. It was demonstrated that the influence of antioxidants on AA formation depends also on their stability[148]. Stable compounds (BHA, BHT, TBHQ) did not have any influence or even caused stimulation of AA formation. The less stable are antioxidants and more susceptible to their transformation into oxidized derivatives (quinones), the more effectively they reduce AA formation. It seems that decreasing AA formation is carried out in three different pathways[148]. The first one is based on elimination of existing AA, and it might be carried out by attacking the alkene bond of acrylamide by free radicals generated or as a result of direct reaction of AA with oxidized forms of antioxidants (*e.g.*, ferulic acid, epigallocatechin gallate, vitamin C). The second one is performed through the reaction of oxidized antioxidants with the main acrylamide precursor – asparagine and by decreasing the amount of that amino acid. The third one is based on the inhibition of carbonyl compounds generation during heating fats. Antioxidants that prevent lipid oxidation reduced the

formation of AA precursors, which in reaction with asparagine would form AA[149].

Conclusions

Interactions between acrylamide, microorganisms, and food components are still very interesting topics for scientist. The process of acrylamide formation in food can be both enhanced and inhibited by various food components or additives. Moreover, microorganisms, which are present in raw materials (added to food during technological processes) or those that reside in gastrointestinal tract can influence the AA level and its toxicity, by interacting with its synthesis or degradation. In the near future, it is expected to note an increase in the number of scientific studies on detoxification of acrylamide by carefully selected microorganisms added to food. It is also highly possible that as the result of such researches, new functional products will be designed.

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