Effects of bioactive molecules on the concentration of biogenic amines in foods and biological systems

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ABSTRACT

Biogenic amines (BAs) are a group of molecules naturally present in foods that contain amino acids, peptides, and proteins as well as in biological systems. In foods, their concentrations typically increase during processing and storage because of exposure to microorganisms that catalyze their formation by releasing amino acid decarboxylases. The concentrations of BAs above certain values are indicative of unsafe foods due to associate neuronal toxicity, allergic reactions, and increase risks of cardiovascular diseases. There are therefore various strategies that focus on the control of BAs in foods mostly through elimination, inactivation, or inhibition of the growth of microorganisms. Increasingly, there are works on bioactive compounds that can decrease the concentration of BAs through their antimicrobial activity as well as the inhibition of decarboxylating enzymes that control their formation in foods or amine oxidases and N-acetyltransferase that control the degradation in vivo. This review focuses on the role of food-derived bioactive compounds and the mechanism by which they regulate the concentration of BAs. The findings are that most active molecules belong to polyphenols, one of the largest groups of plant secondary metabolites, additionally other useful compounds are present in extracts of different herbs and spices. Different mechanisms have been proposed for the effects of polyphenols depending on the model system. Studies on the effects in vivo are limited and there is a lack of bioavailability and transport data which are important to assess the importance of the bioactive molecules.

1. Introduction

It is an established fact that foods provide nutrients that nourish our body and keep our system in proper working conditions. Meanwhile, from early civilization, certain foods are known to confer additional health benefits to human like the prevention and treatment of diseases [1, 2]. Today, foods with beneficial effects are commonly referred to as functional foods, and although no consensus definition exists, they are generally recognized to provide a health benefit beyond basic nutrition [3]. Most research works on the health-promoting effects of active food-derived molecules have focused on chronic conditions such as hypertension, diabetes, cardiovascular diseases, or cancer [4, 5, 6, 7]. There are also increasing works on their role in neuronal and mental health [8, 9]. One of the areas of interests is the role bioactive compounds may have in the control of substances whose presence or certain concentrations may be detrimental to either the quality of foods or to human health. Biogenic amines (BAs) fall within this category. BAs are nitrogen containing molecules found in raw or processed foods and in biological systems [10, 11]. In foods and beverages, they can be formed during fermentation processes via a decarboxylation of the amino acid functional group. In biological systems, the concentration of BAs is dependent on the consumed amount from foods, the activity of decarboxylases and the overall metabolism that involves catechol-O-methyltransferase, N-acetyltransferase, and amine oxidases [12, 13]. Antioxidative properties have been reported for some BAs [14, 15]. The complexation of caffeic acid with spermine and spermidine for example, increases its ability to scavenge ABTS radicals while also decreasing the growth of tumor cells by 15–25% [16]. Meanwhile, increased concentrations in foods are related to spoilage which is caused by an increase activity of microbial decarboxylases and subsequently toxicity associated for example with higher concentrations of histamine, tyramine, and nitrates 

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on the use functional ingredients and food-related bioactive compounds. This is different from other reviews that focus on the control of BAs using mostly temperature, antimicrobials, irradiation, high hydrostatic pressure, starter culture, or non-producing decarboxylating microorganisms [20, 21, 22].

2. Biogenic amines

Biogenic amines (BAs) are low molecular weight nitrogen-containing organic compounds. They are formed by the action of proteases secreted by living microorganisms, during the storage of foods or processes such as fermentations. There is a diversity in structures of BAs dependent on whether the substrate is an amino acid, an aldehyde, or a general nitrogen-containing compound. Their formation typically proceeds via a decarboxylation, amination or transamination reactions catalysed by enzymes (decarboxylases, aminases) produced by microorganisms in foods and during normal metabolic processes in living cells [23].

The vast majority of biogenic amines are derived from amino acids and depending on the substrate, they are classified into mono-, di-, and polyamines (Figure 1). Monoamines of interest tyramine and phenylethylamine are produced from tyrosine and phenylalanine by the action of tyrosine and phenylalanine decarboxylase, respectively (Figure 1). Diamines, histamine, tryptamine and cadaverine are produced from direct decarboxylation of histidine, tryptophan, and lysine, respectively (Figure 2). In contrast, the other diamine putrescine is formed through complex metabolic pathways that can involve up to eight different enzymes depending on the type of microorganisms involved in its formation [24]. In some bacteria for example, putrescine is formed from arginine by the action of arginine decarboxylase followed by that of Agmatinase and putrescine carbamoyl transferase, or from the action of arginase followed by ornithine decarboxylase. A summary of the formation of putrescine is shown in Figure 3.

The three common polyamines are agmatine, spermidine and spermine. Agmatine synthesized from arginine via the action of arginine decarboxylase is also an intermediate in the synthesis of putrescine (Figure 4). Methionine provides the aminopropyl groups necessary for the formation of spermidine and spermine from putrescine [25] as illustrated in Figure 4. The action of adenosyl transferase followed by that of S-adenosylmethionine (SAM) decarboxylase converts methionine to decarboxylated S-adenosyl-methionine. In the next step, a transfer of an aminopropyl from decarboxylated S-adenosyl-methionine to putrescine generates the tri amine spermidine while another transfer leads to spermine (Figure 4).

Many literature works have reported that BAs can also be formed by amination and transamination of carbonyl compounds (aldehydes, ketones). However, the search of the literature did not identify any biogenic amine in foods or in biological systems that are formed from an aldehyde or a ketone. Transamination reactions in the literature are instead related to reversible amination and deamination that mediate the redistribution of amino groups amongst amino acids with an α-keto acid serving as an amino acceptor. In human, there are other BAs (dopamine, norepinephrine or noradrenaline, epinephrine or adrenaline, and serotonin or 5-hydroxytryptamine) that act as neurotransmitters and their formation was summarized by Purves et al. [26]. In brief, hydroxylation of tyrosine forms dihydroxyphenylalanine (DOPA) which upon the action of DOPA decarboxylase yields dopamine, subsequent action of dopamine

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Figure 1. Formation of tyramine and phenylethylamine. (i): In the resting state of the enzyme, the co-factor, pyridoxal 5'-phosphate of tyrosine or phenylalanine decarboxylase forms an internal aldimine (or Schiff base intermediate); (ii): The activated intermediate then reacts with the amine of the amino acid to form an intermediate structure, which then decarboxylates and generate the biogenic amine via transaldimination.

Figure 2. Formation of diamines histamine, tryptamine, and cadaverine by pyridoxal 5'-phosphate dependent histidine (HDC), tryptophan (TDC), and lysine decarboxylase, respectively.
β-hydroxylase catalyzes the formation of norepinephrine while further action of phenylethanolamine-N-methyltransferase leads to the formation of adrenaline. Serotonin is formed from tryptophan via a two-step process catalyzed by tryptophan-5-hydroxylase and a decarboxylase.

3. Analysis of biogenic amines

There are several procedures to analyse BAs which have been documented in literature review publications [27, 28, 29]. They include gas chromatography, thin layer chromatography, high-performance liquid chromatography (HPLC) with precolumn or post column derivatization, capillary electrophoresis as well as biosensors [29, 30]. The chromatographic system can be coupled to a mass spectrometer for enhanced precision and selectivity. The first step is typically a sample processing to remove interfering molecules, a pre-concentration of the analyte, or the derivatization of the analyte for improved detection and selectivity. The derivatizing agents commonly used are dansyl chloride and ortho-phthaldehyde for either ultraviolet or fluorescent detection but, 6-aminouquinolyl-N-hydroxysuccinimidyl carbamate, 9-Fluorenylmethoxy carbonyl, benzoyl chloride are also used [5]. Some derivatizing reagents such as dansyl chloride can react with phenols, alcohols and secondary amines which then can interfere with the analysis of BAs. Stable isotope dilution procedures to quantify BAs by HPLC and capillary electrophoresis can overcome the issues associated with the non-specificity of the derivatizing reagent [31, 32].

Solid food samples (e.g., fish, meat, cheese, sausage, vegetables) for HPLC and capillary electrophoresis are often solubilized in acidic solvents (0.1–0.6 M) made of trichloroacetic acid, perchloric acid or hydrochloric acid to precipitate and remove proteins. The extracts are then derivatized and analyzed directly or clean-up with solid phase extraction cartridges before the analysis. Beverages such as wines and beers can be analyzed with or without derivatization but treatment with acid is important for dairy beverages and juices. Treatments of wine samples with polyvinylpyrrolidone to remove phenolic components have been shown to be sufficient for the detection of BAs without any further processing. Biological samples (urine, plasma) are often acidified to about pH 2 to precipitate the proteins followed by their removal by centrifugation. The deproteinated biological sample can be analyzed either directly [33], after clean-up with solid phase extraction cartridges [34] or after derivatization [35].

A review on methods to analyse BAs in foods concluded that, out of seven hundred publications, 72% of procedures were based on HPLC, 18% on electrophoresis and 10% on gas chromatography [29]. The popularity of HPLC methods is due to the diversity of derivatizing reagents, the separation efficiency (many liquid and solid options) and their coupling to high performance mass spectrometers. The less use of gas chromatography can be attributed to the low volatility of BAs.

4. Biogenic amines in foods

In theory, they can be found in all foods that contain amino acids, peptides or proteins and which are exposed to conditions enabling the production of required enzymes as well as conditions for transamination reactions [36]. The nature of the BAs and their concentrations typically vary with the type of foods, and the processing or storing conditions. There are therefore differences in BAs present for example in meat versus fish, dairy, beverage or vegetable products which have been summarized...
in review articles [11, 37]. These reviews showed that food commonly investigated for BAs in terms of frequency are fish, meat, wine, and cheese products while vegetable products are less frequently investigated. The determination of BAs is important because they can serve as markers of food freshness, and indicators of improper processing and storage of foods.

4.1. Biogenic amines in seafoods

In seafood products, the most commons BAs are histamine, tyramine, cadaverine, and putrescine [38]. Their concentrations are affected by the conditions under which they are stored (temperature, time duration) because of a direct relationship with the growth of microorganisms [39]. The most abundant BA in seafood products is histamine followed by phenylethylamine due to higher concentrations of free histidine and phenylamine, respectively. The amounts of histamine in freshly captured fish are generally less than 1 mg/kg [40]. Meanwhile, toxic levels of histamine more than 10 mg/kg (Food and Drug Administration) regulatory limit (50 mg/kg) [41] has caused the condition known as fish scumbroid syndrome. *Morganella psychrotolerans* and *Photobacterium phosphoreum* microorganisms are commonly associated with the production of histamine in seafood products [42, 43]. A review by Visciano et al., summarized the content of biogenic amines in raw and processed seafood stored under different conditions [10]. In raw products, the concentrations range from not detected to 49.3 mg/kg with spermine and spermidine generally being the most abundant, histamine up to 19.5 and tyramine up to 46.9 mg/kg. In processed concentrations of tryptamines as high as 5487 mg/kg were reported in fish paste [10].

4.2. Biogenic amines in meat and dairy products

Fermented meats as well as other fermented food products typically contain higher amounts of BAs due to an increase concentration of free amino acids, the main precursors of their formation during the fermentation process. In dry sausages, tyramine (up to 600 mg/kg) and putrescine (up to 450 mg/kg) are the most abundant BAs [44]. There are reviews on biogenic amines in meat products [45, 46, 47]. In raw fresh meats, concentrations of BAs ranged from not detectable to the following values for individual BAs [47]. Histamine (0.5–27 mg/kg), tyramine (0.0–15.6 mg/kg), spermine (0.1–42 mg/kg), spermidine (0.0–10 mg/kg) and putrescine (0.5–12 mg/kg). There is a variation in concentration depending on the meat type (e.g. beef versus pork or poultry) but also on the animal part (e.g. leg versus breast). Storage and processing significantly increase the concentrations.

In cheese, native microorganisms with decarboxylase activities are responsible for the generation of low amount BAs but BA concentrations typically increase during ripening because of partial proteolytic cleavage of casein and the subsequent increase in free amino acids with histamine being the BA of concern [48]. In raw or pasteurized cow milk, BAs are low and often not detected. In cheese concentration of tyramine can increase to more than 830 mg/kg and that of histamine to 260 mg/kg [48]. A recent review article reported the concentration of histamine in other fermented milk products as 7 mg/kg in sour cream, 13–21 mg/kg in yogurt and 4 mg/kg in kefir [49].

4.3. Biogenic amines in plant-based foods

In plant-based foods, those that are fermented are the most studied for the presence of biogenic amines. Examples include fermented soy products (e.g. tofu, sauces) in which BAs over the regulatory limit have been detected. In fermented soy products, the hydrolysis of proteins provides the required substrate for the synthesis of BAs. A study by Yongmei et al. reported that tyramine was the most prevailing amine in soy sauce followed by spermidine, histamine, and cadaverine with a total content of 41.7–1357 mg/L [50]. Other works have reported total content of 56–634 mL/L for soy sauce [51]; 30–82 mg/kg for tofu with spermidine being the most abundant [52]. Fermented cabbage known as sauerkraut also contains BAS specifically, histamine, tyramine, putrescine, cadaverine, spermine, and spermidine [53]. The BAs in wine are believed to be influenced by both the nature of grapes and the vinification process. For example, only putrescine and tyramine were found in musts from sterilised grapes while musts from non-sterilised grapes contained cadaverine, tyramine and agmatine [54]. This is likely because sterilization inactivates some enzymes that can release peptides and amino acids or act as decarboxylases. Putrescine has been reported to be the most abundant BA in wine [55] while spermidine and putrescine have been identified as two dominant BAs in grapes and must [56].

5. Properties and functions of biogenic amines

5.1. Role in food quality and safety

In foods, the concentration of BAs is mainly associated with quality such as freshness, acceptability indicators, storage conditions and safety [57, 58]. In foods like fish, meat, and wines BAs are often determined a part of a quality control process because their excess amounts are associated with toxicological issues mostly with the nervous or vascular systems [59, 60]. The legal limit of BAs in food varies depending on the type of food, the chemical nature, and the country. In the USA for example, the limit of histamine is 50 mg/kg of flesh meat or fish, compared to 100 mg/kg in the European Union and South Africa, or 200 mg/kg in Australia and New Zealand [40]. The relationship between types of BAs was used to generate a chemical index for tuna decomposition in which, the sum of histamine, putrescine, cadaverine, and tyramine below 50 mg/kg is considered an acceptable sensory characteristic of tuna products [61]. In the case of meat products, the biogenic amine index (BAI) that consists of the sum of putrescine, cadaverine, histamine, and tyramine is instead recommended as a quality indicator [62, 63]. In that index, a value below 5 mg/kg is equivalent to good quality (i.e. fresh), between 5–20 mg/kg acceptable, 20–50 mg/kg low quality, and above 50 mg/kg spoiled meats [63, 64]. In beer beverages, Loret et al. [65] proposed a different index based on the ratio of BAs mostly produced by bacterial decarboxylases (tyramine, putrescine, cadaverine, histamine, phenylethylamine, and tryptamine) to the agmatine that mostly originates from the raw malt material [66]. They concluded that an index below 1.5 was of high quality while a value above 10 was a consequence of a poor hygienic fermentation process (i.e., presence of high level of decarboxylating bacteria).

5.2. Role in foods as bioactive molecules

Although, the presence of BAs is mainly used as quality indicators, they may provide some functionalities to foods specifically, those with aromatic moieties or proton donating abilities in their structures [67]. In a linoleic acid model system for example, tyramine, tryptamine and phenylethylamine inhibited the formation of hydroperoxide [14] indicating that in foods BAs can have antioxidant activities. Higher amounts of serotonin, putrescine and spermidine for example in fruits (e.g. grapes, bananas, plums) increase their resistance to oxidative damage which then enhances their quality postharvest by preserving the integrity of cell membranes during storage [68, 69, 70]. The concentration of dopamine in banana peel was 8-fold higher compared to naringin, the second most abundant molecule [71]. Dopamine was then identified as the most antioxidant molecule in those banana peels. In grapes that contained higher concentrations of putrescine, there was less incidence of decay, browning, and cracking during cold storage [72]. The conjugation of BAs with other molecules in foods can enhance their biological activity. In goji berries for example, N-feruloyl tyramine dimer and N-trans-and N-cis-feruloyl tyramine were identified as molecules that contributed to the ability of the extract to scavenge 2,2-diphenyl-1-picrylhydrazyl (DPPH) radicals [73]. The N-trans-feruloyl tyramine scavenged 12% more radical than butylated hydroxyanisole, a reference antioxidant.
molecule [73]. The presence of amide compounds is not limited to the berries or to tyramine. These types of amides are formed by reactions between esters of hydroxycinnamic acids and the BAs. Tyramyl amides have been reported in fruits, in garlic, and in onion [74, 75] but also in pepper and tomatoes [76] where they may contribute to antioxidant (scavenge radicals, inhibit lipid oxidation) and antimicrobial activities. N-E-coumaroyl tyramine and N-E-feruloyl tyramine both from *Lycium barbarum* fruits scavenged 96% of DPPH radicals and inhibited lipid induced oxidation (83–96%) in rat liver microsomes at 0.1 mM concentrations [74]. Putrescine, spermidine and agmatine amides which are in most cases, coumaroyl, feruloyl, and sinapoyl-substituted amines have been purified from corn bran, corn bread and other cereal products [77, 78]. Many have been found to possess radical scavenging and anti-inflammatory activities [79, 80, 81]. For example, N,N'-diferuloylputrescine obtained from corn bran showed potent inhibition of DPPH radicals (IC₅₀ = 38.46 μM) and superoxide anion radicals (IC₅₀ = 291.62 μM) [80]. These data suggest that aromatic BAs at the safe concentration level as well as hydroxycinnamic derivatives of both aromatic and aliphatic BAs may provide some stability to foods by acting as antioxidant or antimicrobial agents. It will be interesting to establish the functional relation between foods and BAs in the presence or absence of contaminating microorganisms.

5.3. **Role of biogenic amines in human**

Biogenic amines at the right concentration are important sources of nitrogenous compounds for human with the most active ones being histamine and tyramine. The concentration of BAs in a biological system is dependent on dietary sources, endogenous synthesis, and metabolic degradation. A total concentration of BAs of safe foods should not exceed 1000 mg/kg with threshold values of 50, 100, 30 mg/kg for histamine, tyramine, and phenylethylamine [52, 59, 82]. Tyramine and histamine are involved for example in the control of circadian rhythm, attention, gastric acid secretion, cell growth and differentiation [28, 83]. Polyamines, putrescine, spermine and spermidine also play essential roles in cell growth and differentiation [38, 84]. The polyamines are positively charged and can affect the functions of nucleic acids (DNA, RNA) via strong ionic interactions.

The concentrations of BAs above safe values are linked to various issues in the nervous, vascular and lung systems [23, 64]. There many are reviews dealing with the toxicological effects and poisoning related to the consumption of poorly processed or stored foods (fish, cheeses) that contain high concentrations of BAs. Total BAs concentration above 1000 mg/kg in the body system can cause either a mild allergic reaction or serious impairment of the respiratory, cardiovascular, and nervous systems [23, 59]. Physiological symptoms of the two most toxic BAs, histamine and tyramine include headache, migraine, hypertension, and respiratory disorders but similar symptoms have also been reported for phenylethylamine and tryptamine [85]. The most frequent BAs intoxication involved histamine. Its higher intake from poorly conserved fish products leads to what is known as scombroid fish poisoning because products are often derived from fishes of the *Scombridae* and *Scomberesocidae* families [58], while intake of tyramine poisoning from the consumption of unsafe cheese products is characterized as a cheese reaction [33]. In human, aliphatic BAs (putrescine and cadaverine, spermidine and spermine) are generally not directly toxic but they can enhance the toxicity of tyramine and histamine due to their inhibition of oxidases and N-methyltransferase involved in their metabolic turnover [86, 87].

The reaction of nitrates with cadaverine leads to N-nitrosopiperidine, while putrescine, spermine and spermidine are converted to N-nitrosopropylidine which are carcinogenic compounds [88, 89]. The above compounds and other N-nitrosylated compounds are synthesized in dried salted foods (meat and fish) but also come from cigarette’s smoke [90, 91]. N-nitrosopiperidine is an oesophageal carcinogen while N-nitrosopyrrolidine is an inducer of liver tumours as found in mice and rats [88]. A review by Gushgari et Halden [92] estimated human exposure to total nitrosamines from foods and drinks to be 1.9 ± 0.38 μg/day which is below the tolerable value of exposure in humans, 5–10 μg/kg of body weight per day [93]. N-nitrosopiperidine and N-nitrosopyrrolidine are classified as possibly carcinogenic to humans by the International Agency for Research on Cancer [92] meaning that despite animal data, quantitative human data are still not available.

6. **Role of functional ingredients and bioactive compounds in regulating the concentration of biogenic amines**

The intake of a small concentration of BAs through the diet is normally not harmful to health because the human body has a detoxification system to take care of these BAs very quickly in the intestine through the action of enzymes such as monoamine oxidase (MAO), diamine oxidase (DAO), and polyamine oxidase (PAO) which can metabolize dietary BAs in a healthy person. However, when a quantity in food is too high or if these enzymes are dysfunctional either genetically or due to the intake of inhibitors such as alcohol or certain antidepressant drugs, this mechanism may be hampered and allow greater concentration of BAs to enter the systemic circulation and exert a toxic effect on different organs [94, 95]. Bioactive compounds to control the concentration of BAs can work via several mechanisms, including the inhibition of their formation (e.g. inhibition of decarboxylases) or increase the metabolism of biogenic amines (e.g. greater expression of amine oxidases). Other methods to control BAs include the use of starter cultures that lack decarboxylating enzymes and additives that can act as antimicrobials.

6.1. **Reduction of biogenic amines in foods**

The concentration of biogenic amines in foods can be controlled by a strict adherence to cold chain because their formation is temperature dependent and decreases at low temperature through the inhibition of microbial growth and the reduction of the activity of decarboxylating enzymes [96, 97, 98]. Temperature control meanwhile is not enough since some bacteria produce BAs at temperatures below 5 °C. Methods that consist of modified atmosphere packaging, high hydrostatic pressure, or irradiation have developed and are summarized in the literature [21]. Other methods to control BAs include the use of starter cultures that lack decarboxylating enzymes but can also degrade for example histamine [99, 100].

The other alternative is the use of phytochemicals (secondary metabolites) in purified forms or as extracts to regulate the concentration of BAs in foods (Table 1). Grape juices made with purple-flesheed sweet potato (10 and 30%) lower serotonin and dopamine concentrations with a concomitant decrease of tyramine, histamine with the benefits being attributed to the presence of anthocyanins and catechins [101]. The addition of tea polyphenol extracts to freeze-chilled shrimps (immersed in 1% polyphenol solution for 30 min, −20 °C for 2 weeks and then 4 °C for 6 days) decreased the concentration of putrescine from 13.76 and 7.57 mg/kg meanwhile, there was no significant change in histamine concentrations [102]. A polyphenol rich-extract from cava lees, a winery by-product added to fermented sausages decreased cadaverine and putrescine concentrations by 21 and 40%, respectively [103]. There are studies conducted on the role of extract from spices such as garlic, onion, cinnamon, or ginger. Garlic extract applied during the ripening of a Korean seafood (anchovy) product reduced by 8.7% the total concentration of biogenic amines [104]. The mechanism was suggested to be due to the inhibition of the growth of *Bacillus licheniformis*, one of the known BAs producing microorganisms in the tested food [104]. The addition 0.3 mg/g extract of star anise, cassia, nutmeg, or cinnamon, during the preparation of dry fermented sausages showed a reduction of 19–28% in histamine, tryptamine, putrescine, spermidine, tyrosamine, and phenylethylamine concentrations [105, 106]. Possible mechanisms of extracts vary as they contain different molecules. The effects of cassia and fennel extracts were suggested to be due to high contents of estragole.
and trans-anethole which can affect the integrity of microbe cell membranes while that of clove is believed to be associated with the antimicrobial activity of the most abundant compound, eugenol. Another mechanism is the greater decrease of pH in the presence of species extracts [106] that will decrease microbial growth or inhibit the activity of decarboxylases. Polyphenols extracted from green tea and grape seeds as well as α-tocopherol, each evaluated at 300 mg/kg reduced the concentration of putrescine, cadaverine, histamine, tyramine and spermine in cured meats with tea extract having the greater which was associated with the inhibition of Enterobacteriaceae populations during ripening and storage [107]. Glucono-δ-lactone (1%) decreased histamine and putrescine in meat through a pH reduction [108]. Small organic acids like citric acid, succinic acid, and malic acid inhibited decarboxylase activity and the result was a decrease of histamine formation [21, 109]. Marination of pork with black currant juice decreased by 22.7–66.6% the concentration of putrescine, cadaverine, histamine, tyramine, and spermine in cured meats with tea extract having the greater which was associated with the inhibition of Enterobacteriaceae populations during ripening and storage [107]. Glucono-δ-lactone (1%) decreased histamine and putrescine in meat through a pH reduction [108]. Small organic acids like citric acid, succinic acid, and malic acid inhibited decarboxylase activity and the result was a decrease of histamine formation [21, 109].

| Food                          | Treatment                                                                 | Duration            | BA detected                                                                 | Effect on treatment          | Reference |
|-------------------------------|---------------------------------------------------------------------------|---------------------|------------------------------------------------------------------------------|------------------------------|-----------|
| Sausage                       | 0.3 mg/g ethanol extract of star anise, clove, cassia, fennel, bay leaf, or nutmeg (74 volatile compounds) | Fermented, 8 days   | Tryptamine, putrescine, spermidine, phenylethylamine, tyrosamine, and histamine | 18%-28% reduction            | [105]     |
| Fish sauces                   | Ginger, anise, garlic, or cinnamon ethanol extract (2%)                    | Fermented 15 days 30 ºC | Histamine, putrescine, tyramine, spermidine                                  | 18%-37% reduction            | [136]     |
| Cereal based fermented food   | 0.5-2% commercial pomegranate seed extract powder                          | 15 days 30 ºC       | Total BAs (putrescine, cadaverine, spermidine, spermine, histamine, tyramine) | 36-53% reduction             | [137]     |
| Shrimp paste                  | Commercial tea polyphenols (0.3%)                                         | Stored 120 days 25 ºC | Putrescine, cadaverine, histamine, phentylethylamine, tryptamine, tyramine    | 54-68% reduction             | [138]     |
| Fermented pork product (Nham)| Ginger extract                                                             | 7 days 30-50 ºC     | Histamine                                                                    | 65% reduction total BAs      | [139]     |
| Atlantic salmon fillets       | Phlorentin 2-4 mg/ml                                                        | Stored 3 days 4 ºC  | Histamine, putrescine, cadaverine, tyramine                                  | 10-16% reduction             | [114]     |
| Mackerel                      | Gallic acid (5%)                                                           | Stored 12 days, 4 ºC | Histamine                                                                    | 63-84% reduction             | [113]     |
| Cured Bacons                  | Commercial green Tea Polyphenol 300 mg/kg                                  | 12 days 13-31 ºC    | Putrescine, cadaverine, spermine, tyramine, histamine                        | 23-71% reduction             | [107]     |
| Sauerkratz (shredded and salted cabbage fermentation) | Shredded onion (10 g/kg), or caraway seed (350 g/kg) | Fermented 14 days (18 ºC or 31 ºC) Stored 12 wk (4 ºC) | Cadaverine, spermine, tyramine, histamine                                   | 2-3 fold reduction           | [53]      |
| Dry-fermented sausage         | Green tea extract (0.15 and 0.3 g/kg)                                      | 15 days 18-26 ºC    | Putrescine, histamine, tyramine                                              | 34-36% reduction             | [140]     |
| Camel meat                    | 0.5-2.5% Gingerol                                                          | 30 min, Room temperature | Total BAs (cadaverine, histamine, putrescine, spermine, tyramine)            | 47-91 reduction              | [141]     |
| Fish (Rainbow rout)           | 3% rosemary oil                                                            | Stored 9 days, 4 ºC | Histamine, tyramine, cadaverine, putrescine                                  | 86%-94% reduction            | [142]     |
| Sardine fillets               | Rosemary ethanol extract (1%)                                              | Stored 20 days, 3 ºC | Histamine, cadaverine, putrescine                                            | 18-25% reduction             | [143]     |
| Harbin dry sausage            | Spices ethanol extract 0.3 g/kg (cinnamon, clove, or anise)                | Fermented, 9 days   | Cadaverine, putrescine, tyrosamine, phenylethylamine, histamine, tryptamine  | 11-22% reduction             | [106]     |
| Sardine fillets               | Mint ethanol extract (1%)                                                  | 21 days 3 ºC        | Putrescine, cadaverine, spermidine, histamine, tyramine                      | 27-66% reduction             | [144]     |
concentration of total BAs, putrescine, cadaverine, or tyramine during storage (10 days) at refrigerator temperatures [110].

Polyphenols are one of the groups of bioactive molecules used to control the formation of BAs in food. The inclusion of ferulic acid and its complex to smoked horsemeat sausages decreased the formation of tyramine via the inhibition of tyrosine decarboxylase and tyrosine/tyramine antiporter genes expression [111]. The addition of a mixture of quercetin, 4-hexylresorcinol, and cinnamic acid coupled with modified atmosphere packaging had a significant effect on the reduction of tyramine in pork shrimp stored at 4 °C but not on putrescine and cadaverine [112]. A coating of mackerel with a solution of gallic acid (5%) reduced histamine concentration from 529 to 83 mg/kg after 12 days storage at 4 °C which was associated with reduce microbial growth [113]. In a related work, phloretin (4 mg/mL), a polyphenol (flavonoid) from apples reduced tyramine and histamine values from 21 and 16 mg/kg to 0.50 and 0.43 mg/kg, respectively in Atlantic salmon fillets [114]. In wine, the addition of naringenin (0.3 mg/mL), a polyphenol present in fruits and grains reduced by 71% the concentration of histamine. In the studies of polyphenols, the mechanism of BAs reduction is generally associated with their antimicrobial activity. Compounds such as epicatechin, epigallocatechin, epicatechin gallate, and epigallocatechin gallate have been shown to reduce by 60–76% the concentration of putrescine and cadaverine in fermented soy foods [115]. Additionally, in many cases, there were reports of increased oxidative stability characterized by inhibition of the oxidation of lipids.

6.2. Reduction of biogenic amines in biological systems

The control of BAs in biological systems is associated with both synthesis and metabolic pathways leading to their utilisation, degradation, and elimination. Functional ingredients can then target the decarboxylases or monoamine and polyamine oxidases. Apart from BAs commonly found in foods, two other ones are important in biological systems. They are dopamine formed via hydroxylation of tyrosine followed by a decarboxylation; and serotonin or 5-hydroxytryptamine which is formed via hydroxylation of tryptophan followed by a decarboxylation [26].

Biogenic amines functions include their beneficial role in cellular communications, neurotransmission or as sources of amines. They also possess pathological roles in stress, allergy, neurological and cardiovascular disorders. Research on the effect on BAs in vivo are then often associated with these conditions.

Food-derived molecules can affect the concentration of BAs in biological systems through several mechanisms as summarized in Table 2. The inhibition of decarboxylases is a common target, specifically for polyphenol-type compounds. Epigallocatechin gallate (main polyphenol in green tea) decreased the formation of histamine by inhibiting histamine producing mast cells degranulation and tyrosine phosphorylation which was then linked to up to 60% inhibition of the activity of histidine decarboxylase [116, 117, 118]. These were cellular cultures or ex vivo works, and so, the true effects of the catechins will depend on their absorption and bioavailability. The inhibition of kidney dopa-decarboxylase which is responsible for the formation of dopamine and serotonin from 3-hydroxytyrosine and 5-hydroxytryptophan, respectively has been reported [119]. The protective effect of epigallocatechin gallate was further demonstrated in mice, where it reduced skin tumor through an interaction with the higher concentrations of polyamines (putrescine, spermidine and spermine) produced in tumor cells contribute to growth and differentiation [120, 121]. Epigallocatechin gallate reduces the skin tumor by inhibiting (50%) the activity of ornithine decarboxylase. Mangiferin, a polyphenol from mango fruits is believed to be neuroprotective because it can reduce by 13% the concentration of dopamine in aged mice, restore brain acetylcholinesterase to normal level, and protect neurons and oligodendrocytes (myelinating cells of the central nervous system) from excitotoxicity [122, 123]. In spontaneously hypertensive rats, the antihypertensive activity of orally administered flavodil, a flavone derivative was associated with up to 75% depletion of biogenic amines including serotonin in heart tissues and a 20% decrease of BAs in the brain after acute or chronic treatment with 35–75 mg/kg [124].

The mechanisms of several neurotoxic molecules include lowering the concentration of the hormonal biogenic amines (dopamine, serotonin, noradrenaline). As such, food bioactive compounds that can counter the effects of the neurotoxins and prevent the decrease of the neurotransmitter BAs are considered beneficial. Intraperitoneal (i.p.) administration to mice of oleaneprope (8–32 mg/kg), a main bioactive phenolic compound in olives reverses corticosterone-induced depression [125] while in rats, resveratrol (20 mg/kg body weight) prevented fluoride-induced brain toxicity [126]. Oleuropein totally prevented the decrease of dopamine and serotonin while resveratrol maintained 89–97% of their values depending on the brain region compared to 66–74% only in its absence. Chronic administration of catechin (20 mg/kg daily for 28 days) improved the monoaminergic system in old rats with or without exercise [127, 128]. The benefits were characterized by increased dopamine (25%–26%), increase visuo-spatial working and episodic memory [127]; increase in motor coordination, spatial memory, and serotonin (72%) [126]. In addition to maintaining the right concentrations of BAs, other possible mechanisms of the polyphenols can include inhibition of the synthesis or the activity of decarboxylases, dopamine β-hydroxylase or tyrosine hydroxylase. Alternatively, the polyphenols can scavenge free radicals thereby, prevent them from lowering the BAs through oxidative damage.

Enzymes such as amine oxidases are also important in the physiological regulation of biogenic amines and in their metabolic turnover. The most common are mono amine oxidases A and B. Mono- and polyamine oxidases are flavoenzymes responsible for the oxidative deamination of BAs into corresponding imine followed by non-enzymatic hydrolysis to waste products (carbonyl compounds and ammonia) [129, 130]. In the case of biogenic amine food intoxication, a greater activity of these enzymes is beneficial for the BAs turnover while in the case of neurotoxicity from other molecules or in the case of neurodegeneration, inhibition of the transferase and amine oxidases will prevent the decrease of BAs and maintain optimum physiological levels. For neuronal diseases such as depression and neurodegeneration, inhibitors of the amine oxidases will provide some benefits. In a Parkinson’s disease mouse model for example, neurodegeneration was associated with an increase in activity of monoamine oxidase-B and a concurrent decrease of dopamine and, when curcumin (80 mg/kg i.p.) and tetrahydrodcurcumin (60 mg/kg i.p.) were administered they protected the neurons through a significant prevention the depletion of dopamine due the inhibition of the activity of the amine oxidase [131]. In a related work, curcumin (40 mg/kg i.p.) and its combination with piperine (2.5 mg/kg) attenuated chronic stress by reversing the increase in activity of both monoamine oxidases A and B in the brain with concomitant reversal of the decrease of serotonin and dopamine concentrations [132]. Berry extracts, standardized in a drink and given to young adults (8.75 mg of polyphenols/kg of bodyweight) inhibited blood monoamine oxidase-A which then limited the conversion of noradrenaline to 3,4-dihydroxyphenylglycol although, there were no changes in dopamine and serotonin contents in the blood [133].

Polyamines are poly-cationic molecules, and their function is associated with ionic interactions. A physiological way to regulate the concentration of polyamines is through their conversion to neutral molecules or to decrease their positive charge via acetylation reactions. Active ingredients that inhibit either polyamine oxidase or N-acetyltransferase have then been investigated for their role in the regulation of polyamine concentrations. In a work by Gossé et al. [134] on human colon cancer-derived metastatic cells, apple procyanidins decreased the formation of polyamines (spermidine, spermine) by inhibiting the activity of ornithine decarboxylase and S-adenosyl-L-methionine decarboxylase while also inducing the expression of N-acetyltransferase. The overall consequence was an increase concentration of polyamines together with an increase apoptosis. There are other data on the inhibition of amine oxidases and transferases by bioactive foods molecules, but they lack the
correlation with biogenic amine contents which is the subject of this paper. Inhibitors of monoamine oxidases are considered neuroprotective agents in neurodegeneration because of their ability to prevent the decrease of BAs while the inhibition of polyamines oxidases can be useful to control tumours. Neurodegeneration and tumour development are however complex issues with unclarified aetiologies and associations with other factors such as elevated oxidative stress, inflammation, apoptosis, dysfunction of mitochondria, excitotoxicity, impaired ubiquitine-proteasome system [135].

7. Conclusion and perspectives

Biogenic amines are a group of amine compounds with important functions in plants and humans. High concentrations in food, specifically those of monoamines are however associated with toxicological effects in human. The control of biogenic amines is done through optimization of handling and processing conditions, the use of antimicrobials, inhibitors of decarboxylates, amine oxidases, and N-transferases. Bioactive compounds mostly polyphenols have been proven useful in food products due to their antimicrobial and decarboxylase inhibitory properties.

In foods, the bioactive compounds tested are combined with temperature control meanwhile it may be of interest to also determine their effects in combination with other conditions such as modified atmosphere packaging and high hydrostatic pressure. In addition, the standardization of polyphenol extracts is important to determine the contribution of individual molecules. In biological systems, the bioactive compounds have a potential, but their effects are going to be limited by their absorption and bioavailability. More studies are needed in human or biological systems. Additionally, not all cells are able to produce biogenic amines, hence the need to develop approaches that can target the bioactive compound to the specified cells which might be challenging.
Declarations

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Additional information

No additional information is available for this paper.

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