Bacterial Production and Control of Biogenic Amines in Asian Fermented Soybean Foods

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Abstract: Fermented soybean foods possess significant health-promoting effects and are consumed worldwide, especially within Asia, but less attention has been paid to the safety of the foods. Since fermented soybean foods contain abundant amino acids and biogenic amine-producing microorganisms, it is necessary to understand the presence of biogenic amines in the foods. The amounts of biogenic amines in most products have been reported to be within safe levels. Conversely, certain products contain vasoactive biogenic amines greater than toxic levels. Nonetheless, government legislation regulating biogenic amines in fermented soybean foods is not found throughout the world. Therefore, it is necessary to provide strategies to reduce biogenic amine formation in the foods. Alongside numerous existing intervention methods, the use of Bacillus starter cultures capable of degrading and/or incapable of producing biogenic amines has been proposed as a guaranteed way to reduce biogenic amines in fermented soybean foods, considering that Bacillus species have been known as fermenting microorganisms responsible for biogenic amine formation in the foods. Molecular genetic studies of Bacillus genes involved in the formation and degradation of biogenic amines would be helpful in selecting starter cultures. This review summarizes the presence and control strategies of biogenic amines in fermented soybean foods.

Keywords: food safety; biogenic amines; fermented soybean foods; intervention methods; control; starter culture; Bacillus spp.

1. Introduction

Microbial fermentation is one of the oldest and most practical technologies used in food processing and preservation. However, fermentation of protein-rich raw materials such as fish, meat, and soybean commonly provides abundant precursor amino acids of biogenic amines. Even though most fermented foods have been found to be beneficial to human health, biogenic amines produced through fermentation and/or contamination of protein-rich raw materials by amino acid-decarboxylating microorganisms may cause intoxication symptoms in human unless they are detoxified by human intestinal amine oxidases, viz., detoxification system [1,2]. Thus, the presence of biogenic amines in fermented foods (and non-fermented foods as well) has become one of the most important food safety issues.

According to old documents, the cultivation and use of soybeans, dating back to B.C., were launched in Manchuria on the north side of the Korean Peninsula and have spread to other regions of the world. Hence, a variety of fermented soybean foods have been developed and consumed in north-east Asian countries around the Korean Peninsula, and consequently humans in this region have steadily taken the fermented foods for a long period of time from hundreds to thousands of years, depending on the types of fermented soybean foods consumed [3]. Presently, fermented soybean foods
are of public interest and consumed more frequently even in western leading countries because the fermented foods, particularly fermented soybean pastes, not only have been believed by many people, but also have been scientifically proven by researchers to have health-promoting and -protective effects [4]. However, much less attention has been paid to the safety issues of fermented soybean foods [5].

Fermented soybean foods, including various types of fermented soybean pastes and soy sauces, are commonly made from whole soybeans containing abundant amino acids through microbial fermentation. If the fermenting (or sometimes contaminating) microorganisms are significantly capable of decarboxylating amino acids, the resultant fermented soybean foods may contain unignorable amounts of biogenic amines. Indeed, the presence of biogenic amines seems to be quite frequent and inevitable in fermented soybean foods. Therefore, the present review provides information on the presence, bacterial production, and control strategies of biogenic amines in fermented soybean foods, especially focusing on fermented soybean pastes usually considered as healthy foods.

2. A Brief on Biogenic Amines

Biogenic amines are defined as harmful nitrogenous compounds produced mainly by bacterial decarboxylation of amino acids in various foods. The bacterial decarboxylation of amino acids to biogenic amines have been well illustrated in literature and can be found elsewhere [6–8]. Biogenic amines are also endogenous and indispensable components of living cells, and consequently most food materials, including fruit, vegetables, and grains, contain different levels of biogenic amines depending on their variety, maturity and cultivation condition [7]. Usual intake of dietary biogenic amines generally causes no adverse reactions because human intestinal amine oxidases, such as monoamine oxidase (MAO), diamine oxidase (DAO) and polyamine oxidase (PAO), quickly metabolize and detoxify the biogenic amines. If the capacity of amine-metabolizing enzymes is over-saturated and/or the metabolic activity is impaired by specific inhibitors, vasoactive biogenic amines, including histamine, tyramine and β-phenylethylamine, may cause food intoxication and in turn be considered to be toxic substances in humans [1,2]. Furthermore, the toxicity of biogenic amines can be enhanced by putrefactive biogenic amines such as putrescine and cadaverine [9]. The most common symptoms of biogenic amine intoxication in human are nausea, respiratory distress, hot flushes, sweating, heart palpitation, headache, a bright red rash, oral burning, and hypo- or hypertension [10]. Figure 1 schematically illustrates the detoxification and toxicological risks of biogenic amines.

![Diagram of biogenic amine detoxification and toxicological risks](image_url)

**Figure 1.** Detoxification and toxicological risks of biogenic amines. *: Metabolic inactivation of biogenic amines through oxidative deamination by oxidases. †: Incapacitation of intestinal detoxication system through saturation by biogenic amines or inhibition by antidepressant medications. BA: Biogenic amines.
The biosynthesis, toxicity and physiological effects have been well reviewed in recent articles [11,12], and will not be summarized here. In addition, it is worth mentioning that in particular, vulnerable people who are immune compromised, such as the elderly, children, and infants, may exhibit intolerance to even low levels of biogenic amines and suffer more severe symptoms [13]. The maximum tolerance levels of vasoactive biogenic amines (mostly histamine in fish and fish products) have established and proposed by government agencies or individual researchers as described below (refer to Table 1), but may need to be further studies and subdivided, considering the vulnerable people.

3. Legal Limits and Toxic Levels of Biogenic Amines in Foods

Early in 1980, the U.S. Food and Drug Administration (FDA) first established regulations for tuna and mahimahi that consider 200 mg histamine/kg as an indication of prior mishandling and 500 mg histamine/kg as an indication of a potential health hazard [14]. Early in 1990, the European Economic Community (EEC) also established regulation for fish species of the Scombridae and Clupeidae families and fixed a three-class plan for maximum allowable levels of histamine in fresh fish ($n = 9; c = 2; m = 100$ ppm; $M = 200$ ppm) and enzymatically ripened fish products ($n = 9; c = 2; m = 200$ ppm; $M = 400$ ppm) where $n$ is the number of units to be analyzed from each lot, $m$ and $M$ are the histamine tolerances, and $c$ is the number of units allowed to contain a histamine level higher than $m$ but lower than $M$ [15]. In 1996, Shalaby [16] suggested the guidelines for histamine content of fish as follows: <50 mg/kg (safe for consumption), 50–200 mg/kg (possibly toxic), 200–1000 mg/kg (probably toxic), >1000 mg/kg (toxic and unsafe for human consumption) based on the review of the regulations and other literature. In the meantime, values of 100–800 mg/kg of tyramine and 30 mg/kg of β-phenylethylamine were reported to be toxic doses in food, respectively, and 100 mg histamine per kg of food and 2 mg histamine per liter of alcoholic beverage were suggested as upper limits for human consumption [6]. The upper limits and toxic doses (stated right above) suggested by Brink et al. [6] have been steadily used by numerous investigators as threshold values to assess human health risks derived from exposure to vasoactive biogenic amines in foods because there have been no other reports describing the guidelines for respective vasoactive biogenic amines in general foods, except for histamine (particularly in fish; not applicable to other foods).

At present, histamine is the only biogenic amine for which the U.S. FDA has set a guidance level, i.e., 50 mg/kg of histamine in the edible portion of fish [17], whereas the European Commission (EC) has established regulatory limits of 100 mg/kg for histamine in fish species and 400 mg/kg for histamine in fish sauce produced by fermentation of fishery products [18]. In the meantime, the European Food Safety Authority [19] reported that although a dose of 50 mg histamine is the no-observed-adverse-effect level (NOAEL), healthy individuals do not experience symptoms unless they ingest a larger amount of histamine than NOAEL. Then, the Food and Agriculture Organization/World Health Organization [20] announced 200 mg histamine/kg as the maximum allowable level for consumption of fish and fish products. According to the Codex standard [21], 200 mg/kg of histamine in fish and fish products and 400 mg/kg of histamine in fish sauce are set as the hygiene and handling indicator levels in the corresponding products, respectively. In addition, the governments of several countries in Asia and Oceania have lately established regulatory limits for histamine in fish and fish products [22–24]. Legal limits and toxic levels set by government agencies or individual researchers for biogenic amines in food products are listed in Table 1. Although several food scientists have referred the suggestion of Brink et al. [6], as described above, there have not been government regulations on maximum allowable levels of biogenic amines, other than histamine, in history. Besides, any government legislation or guidelines on the contents of biogenic amines in fermented soybean foods are not found throughout the world.
Table 1. Legal limits and toxic levels set by agencies for biogenic amines in food products.

| Agency                  | Food                      | Toxicty Classification | Biogenic Amines (mg/kg) | Governing Entity | Ref. |
|-------------------------|---------------------------|------------------------|-------------------------|------------------|------|
|                         |                           |                        | PHE         | HIS | TYR |                        |                  |
| Government              | Fish ² and fish products | Defect action level    | 50                      | United States    | [17] |
|                         |                           | Toxicty level          | 500                     |                  |      |
|                         |                           | Maximum allowable level | 200                    | Australia and New Zealand | [22] |
|                         |                           | Maximum allowable level | 200                    | Korea            | [23] |
|                         |                           | Maximum allowable level | 400                    | China            | [24] |
| International           | Fish ³ and fish products | Maximum allowable level | 200                    |                  |      |
| organization            |                           |                        |                        |                  |      |
|                         | Fresh fish ⁴              | Defect action level    | 100                    | Europe           | [15] |
|                         |                           | Maximum allowable level | 200                    |                  |      |
|                         | Enzymaticallyripened fish| Defect action level    | 200                    |                  |      |
|                         | products ⁴               | Maximum allowable level | 400                    |                  |      |
|                         | Fish ²                    | Regulatory limit       | 100                    |                  | [18] |
|                         | Fish sauce ⁵             | Regulatory limit       | 400                    |                  |      |
|                         | Fish ² and fish products  | Maximum allowable level | 200                    | [20]             |      |
|                         |                           | Decomposition indicator | 100                    |                  |      |
|                         |                           | Hygiene and handling indicator | 200       |                  | [21] |
|                         | Fish sauce ⁶             | Hygiene and handling indicator | 400       |                  |      |
| Independent             | General foods             | Toxicty threshold      | 30                      | 100              | 100-800 | [6] |
| research                | Fish ²                   | Safe for consumption   | <50                     |                  |      |
|                         |                           | Possibly toxic         | 50–200                  |                  |      |
|                         |                           | Probably toxic         | 200–1000                |                  |      |
|                         |                           | Toxic and unsafe for human consumption | >1000     |                  | [16] |

¹ PHE: β-phenylethylamine, HIS: histamine, TYR: tyramine; ² Scombridae, Clupeidae, Engraulidae, Pomatomidae, Scombresosidae and other fish species well known for high histamine content; ³ fish species without high histamine content; ⁴ Scombridae and Clupeidae families only; ⁵ produced by fermentation of fishery products; ⁶ prepared from fresh fish.

4. Fermented Soybean Foods and Vasoactive Biogenic Amines

Fermented soybean foods have not only been commonly consumed as they are, but have also been frequently used in a variety of processed products, which make them become a necessity in the household in Asian cultures. Moreover, fermented soybean food products have recently gained popularity, crossing from Asian communities to mainstream markets, in many western countries due to the healthy functions of the foods [3,4]. Aside from soy sauces, the most popular fermented soybean foods produced mainly by bacterial fermentation (sometimes with molds) are Natto, Miso (Japanese fermented soybean pastes), Cheonggukjang, Doenjang, Gochujang (Korean fermented soybean pastes), Chunjang, Doubanjiang, Douchi (Chinese fermented soybean pastes) and Tempeh (an Indonesian fermented soybean paste). Some other soybean foods such as Sufu (a Chinese fermented Tofu) and Tauco (an Indonesian fermented yellow soybeans) prepared by mold fermentation are also available in local area (but were excluded from this review due to great differences in the microorganisms involved in fermentation processes as well as little data available in literature). The safety issues of traditional fermented soybean foods have heretofore been overlooked because humans have consistently taken the foods at least for centuries or millennia. However, considering that fermented soybean foods contain not only abundant dietary amino acid precursors of biogenic amines, as mentioned at the beginning of this article, but also significant biogenic amine-producing microorganisms, mainly bacterial species, it is critically important to assess the levels of biogenic amines in the foods.

Based on a critical review of published data (refer to Table 2) [25–37], it seems that the amounts of biogenic amines in most fermented soybean food products are usually within the safe levels for human consumption. It is noteworthy, however, that some specimens of the fermented soybean food products, including both fermented soybean pastes and soy sauces, have been reported to contain vasoactive biogenic amines greater than toxic dose of each amine. For instance, β-phenylethylamine has been detected at concentrations up to 185.6 mg/kg and 239.0 mg/kg in Doubanjiang and
Douchi, respectively [26,36], which are approximately 6–8 times higher than toxic dose of this amine (30 mg/kg) suggested by Brink et al. [6]. In another report, β-phenylethylamine was determined to be 8704.6 mg/kg in a Doenjang sample [34], but which is unreliably larger than those in other articles in which maximum β-phenylethylamine concentrations of 529.2 mg/kg and 544.0 mg/kg have been reported [28,32]; this report was thus excluded from further review. In the meantime, histamine has been detected at concentrations up to 952.0 mg/kg and 808.0 mg/kg in Doenjang and Douchi, respectively [28,36], whereas tyramine has been detected up to 1430.7 mg/kg and 2539.0 mg/kg in Doenjang and Cheonggukjang, respectively [28,33]. The maximum concentrations of histamine and tyramine are reported approximately 8–10 times higher than upper limit of histamine (100 mg/kg) and 14–25 times (on lower toxic dose basis; 2–3 times, upper dose basis) higher than toxic dose of tyramine (100–800 mg/kg), respectively, suggested by Brink et al. [6]. Like the fermented soybean pastes described above, some specimens of soy sauces have been reported to contain high levels of vasoactive biogenic amines, including β-phenylethylamine (up to maximum 121.6 mg/kg), histamine (398.8 mg/kg) and tyramine (794.3 mg/kg), which are much greater than toxic doses of respective amines [28]. As a counter-example, there is a report in which the amounts of respective vasoactive biogenic amines were very low or not detected in all samples (i.e., three batches) of commercial Natto, Miso, Tempeh, and soy sauce products; however, this report seems to insufficiently brief the presence of biogenic amines in the products because samples (batches) of only a single brand for each type of product were available in local stores [4]. The contents of biogenic amines in different types of fermented soybean food products reported in literature have been reviewed once in a book chapter in 2011 [38], and those in the representative fermented soybean food products reviewed herein are compiled in Table 2. After all, it seems likely that there may occasionally be a risk of food poisoning associated with eating fermented soybean pastes, especially when the pastes contain significant amounts of vasoactive biogenic amines, because some types of the pastes, for instance, Natto, Tempeh and sometimes Cheonggukjang, are taken not only as side dishes, but also main dishes. In the case of soy sauces, the risk to consumers may not be so great, considering the small quantity of intake per serve [29].

### Table 2. Biogenic amine content in fermented soybean food products.

| Fermented Soybean Products | N 1 | TRP (mg/kg) | PHE (mg/kg) | PUT (mg/kg) | CAD (mg/kg) | HIS (mg/kg) | TYR (mg/kg) | SPD (mg/kg) | SPM (mg/kg) | Ref. |
|---------------------------|-----|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|------|
| Cheonggukjang             |     |             |             |             |             |             |             |             |             |      |
| | 7   | 6.7–236.4   | ND–40.8     | 4.7–121.3   | 2.5–28.2    | 1.3–54.3    | 0.7–483.1   | 39.6–59.2   | 7.1–14.7    | [28] |
| | 102 | NT 2        | NT          | NT          | ND–759.40   | ND–1913.51  | NT          | NT          | NT          | [34] |
| | 13  | NT          | NT          | NT          | ND–2398.0   | NT          | NT          | NT          |             | [31] |
| Chunjang                  |     |             |             |             |             |             |             |             |             |      |
| | 4   | 13.3–19.9   | 2.2–11.8    | 9.2–11.7    | 1.7–6.6     | 11.6–22.4   | 28.7–34.6   | 1.4–12.8    | ND–2.9      | [28] |
| | 4   | 19.57–31.55 | ND–6.79     | 3.26–28.59  | ND–2.04     | 1.85–272.35 | 19.78–131.27| 0.24–11.63  | ND–1.49     | [28] |
| | 14  | 6.1–224.1   | ND–529.2    | 9.9–1433.7  | 0.3–65.4    | 1.5–952.0   | 3.4–1430.7  | 4.2–23.3    | ND–10.2     | [28] |
| | 10  | ND–449.8    | ND–544.0    | 28.8–1076.6 | 2.7–144.1   | 1.4–329.2   | 12.5–567.6  | ND–30.3     | ND–9.8      | [32] |
| | 23  | ND–2008.1   | ND–8704.6   | ND–4292.3   | ND–3235.5   | ND–2794.8   | ND–6616.1   | ND–8040.4   | ND–9729.5   | [34] |
| | 7   | 13.5–45.9   | 3.3–65.0    | 46.7–168.2  | ND–12.9     | 71.1–382.4  | 46.4–190.7  | ND–24.7     | NT          | [28] |
| Douchi                     |     |             |             |             |             |             |             |             |             |      |
| | 7   | ND–62.43    | 1.43–185.61 | 1.13–129.17 | ND–0.17     | ND          | ND–25.75    | ND–0.18     | ND–1.69     | [28] |
| Gojuchajung                |     |             |             |             |             |             |             |             |             |      |
| | 26  | ND–440      | ND–239      | ND–596      | ND–191      | ND–808      | ND–529      | ND–719      | ND–242      | [36] |
| Miso                       |     |             |             |             |             |             |             |             |             |      |
| | 5   | 17.9–36.6   | 0.7–9.1     | 2.5–3.2     | ND–1.1      | 0.6–1.3     | 2.1–4.9     | 1.6–3.4     | 1.4–1.8     | [28] |
| | 7   | ND–8.1      | 1.5–24.8    | 10.4–36.4   | ND–18.1     | 2.2–59.0    | 2.9–126.8   | ND–14.5     | NT          | [29] |
| | 5   | 21.6–23.7   | 0.7–8.1     | 16.4–23.2   | 2.6–3.2     | 0.8–11.1    | 2.0–95.3    | 9.5–21.9    | 1.3–3.1     | [28] |
| | 40  | ND–762      | ND          | ND–12       | ND–201      | ND–221      | ND–49       | ND–216      | [31] |
| | 22  | ND–9.71     | 2.38–117.6  | 2.69–14.09  | ND–1.31     | ND–24.42    | ND–66.66    | ND–28.31    | ND–2.85     | [27] |
| | 39  | ND–301.0    | ND          | ND–270      | ND–42.0     | ND–457.0    | ND–45.0     | ND–124.0    | ND–71.0     | [55] |
| | 21  | ND–45.80    | ND–51.50    | ND–43.10    | ND–36.80    | ND–34.40    | ND–200.30   | 246.50–478.10 | 18.80–80.10 | [57] |
| | 11  | ND–45.8     | 1.5–121.6   | 2.5–1007.5  | 0.7–32.3    | 3.9–398.8   | 26.8–794.3  | 1.5–53.1    | ND–16.1     | [28] |

1 Quantity of samples examined; 2 TRP: tryptamine, PHE: β-phenylethylamine, PUT: putrescine, CAD: cadaverine, HIS: histamine, TYR: tyramine, SPD: spermidine, SPM: spermine; 3 the range from minimum to maximum (the same number of digits is used after the decimal point in the values, as was presented in the corresponding references); 4 NT: not tested; 5 ND: not detected.
It is also worth pointing out that some specimens of fermented soybean food products have been found to contain relatively high levels of putrescine and cadaverine (Table 2). The putrefactive biogenic amines have been known to enhance the toxicity of vasoactive biogenic amines in foods [9]. Therefore, comprehensive monitoring and reduction strategies are required to reduce the risk of ingesting putrefactive biogenic amines as well as vasoactive biogenic amines in fermented soybean foods, which may come from the understanding of why there are differences in the amounts and diversity of biogenic amines between the types or batches of the food products. It is probably that the differences may be attributed to (i) the ratio of ingredients used in raw material, (ii) physicochemical and/or microbial contribution, and (iii) conditions and periods of the entire food supply chain [5]. Since fermented soybean foods have their own unique raw materials, physicochemical properties, and production processes, the present review focuses on bacterial contribution to biogenic amine formation conserved across most fermented soybean foods.

5. Bacterial Activity to Produce Biogenic Amines in Fermented Soybean Foods

It has been known that most fermented soybean foods, except for several types of soybean foods prepared by mold fermentation, are mainly fermented (or contaminated) by *Bacillus* species (particularly *B. subtilis*) [5,39,40], which, in turn, leads to biogenic amine formation in the fermented foods, although the abilities of *Bacillus* strains to produce biogenic amines are diverse depending on the types and/or batches of the food products from which the strains are isolated (refer to Table 3) [25,26,31,35–37]. In the studies, the reported ranges (mean ± standard deviation; minimum—maximum) of biogenic amines produced by *Bacillus* spp. in assay media, when cultured for 24 h with proper precursor amino acids, are as follows: histamine 0.22 ± 0.65–29.9 ± 13.4 µg/mL, tyramine 0.3 ± 0.5–30.6 ± 21.7 µg/mL, β-phenylethylamine not detected (ND)—11.2 ± 9.17 µg/mL, tryptamine 0.20 ± 0.45–6.17 ± 3.98 µg/mL, putrescine ND—7.59 ± 3.06 µg/mL, cadaverine ND—1.8 ± 1.1 µg/mL, spermidine 0.40 ± 0.20–9.26 ± 5.73 µg/mL, spermine 1.29 ± 0.86–27.2 ± 12.7 µg/mL. Among the *Bacillus* strains reported, *B. subtilis* strains isolated from Natto exhibited the strongest abilities to produce respective biogenic amines. Table 3 reveals the abilities to produce biogenic amines of different bacterial species isolated from representative types of fermented soybean food products.

Table 3. Production of biogenic amines by bacteria isolated from fermented soybean food products.

| Fermented Soybean Products | Isolates | N | TRP µg/mL | PHE µg/mL | PUT µg/mL | Biogenic Amines (µg/mL) 1 | Ref. |
|---------------------------|----------|---|-----------|-----------|-----------|--------------------------|-----|
| Doubanjiang               | *Bacillus subtilis* | 2 | 1.1 ± 1.4 | 6.6 ± 3.2 | 11.2 ± 9.17 | Histamine: 0.22 ± 0.65–29.9 ± 13.4, | [25] |
|                           | *Bacillus subtilis* | 2 | 0.4 ± 0.2 | 0.6 ± 0.5 | 0.9 ± 0.3 | Tyramine: 0.3 ± 0.5–30.6 ± 21.7, | [26] |
|                           | *Bacillus subtilis* | 2 | 0.2 ± 0.1 | 0.6 ± 0.5 | 0.9 ± 0.3 | Tryptamine: 0.20 ± 0.45–6.17 ± 3.98, | [25] |
|                           | *Bacillus subtilis* | 2 | 0.2 ± 0.1 | 0.6 ± 0.5 | 0.9 ± 0.3 | Putrescine: ND—7.59 ± 3.06, | [25] |
|                           | *Bacillus subtilis* | 2 | 0.2 ± 0.1 | 0.6 ± 0.5 | 0.9 ± 0.3 | Cadaverine: ND—1.8 ± 1.1, | [25] |
|                           | *Bacillus subtilis* | 2 | 0.2 ± 0.1 | 0.6 ± 0.5 | 0.9 ± 0.3 | Spermidine: 0.40 ± 0.20–9.26 ± 5.73, | [25] |
|                           | *Bacillus subtilis* | 2 | 0.2 ± 0.1 | 0.6 ± 0.5 | 0.9 ± 0.3 | Spermine: 1.29 ± 0.86–27.2 ± 12.7, | [25] |
|                           | *Bacillus subtilis* | 2 | 0.2 ± 0.1 | 0.6 ± 0.5 | 0.9 ± 0.3 | Tryptamine: 0.20 ± 0.45–6.17 ± 3.98, | [25] |
|                           | *Bacillus subtilis* | 2 | 0.2 ± 0.1 | 0.6 ± 0.5 | 0.9 ± 0.3 | Putrescine: ND—7.59 ± 3.06, | [25] |
|                           | *Bacillus subtilis* | 2 | 0.2 ± 0.1 | 0.6 ± 0.5 | 0.9 ± 0.3 | Cadaverine: ND—1.8 ± 1.1, | [25] |
|                           | *Bacillus subtilis* | 2 | 0.2 ± 0.1 | 0.6 ± 0.5 | 0.9 ± 0.3 | Spermidine: 0.40 ± 0.20–9.26 ± 5.73, | [25] |
|                           | *Bacillus subtilis* | 2 | 0.2 ± 0.1 | 0.6 ± 0.5 | 0.9 ± 0.3 | Spermine: 1.29 ± 0.86–27.2 ± 12.7, | [25] |

1 Quantity of bacterial samples examined; 2 TRP: tryptamine, PHE: β-phenylethylamine, PUT: putrescine, CAD: cadaverine, HIS: histamine, TYR: tyramine, SPD: spermidine, SPM: spermine; 3 *Bacillus* spp. were identified to be *B. subtilis* (91.0%), *B. coagulans* (4.5%), *B. licheniformis* (1.1%) and *B. firmus* (1.1%); 4 mean ± standard deviation (the same number of digits is used after the decimal point in the values, as was presented in the corresponding references); 5 ND: not detected; 6 NT: not tested.
In addition to the aforementioned Bacillus spp., Lactobacillus sp. and Enterococcus faecium, which had been isolated from raw materials of Miso, were proposed to produce histamine and tyramine in Miso, respectively, through a qualitative detection using BCP (Bromo-cresol purple) agar plates and subsequently a quantitative test using liquid media [41,42]. In the quantitative test with incubation for 90 days, the strains of Lactobacillus sp. and E. faecium produced histamine and tyramine up to approximately 100 µg/mL and 150 µg/mL, respectively. Although Lactobacillus species are not commonly involved in the preparation of fermented soybean foods, diverse species of Lactobacillus have also been reported to be responsible for the formation of biogenic amines, including histamine, in lactic fermented foods [12]. E. faecium and E. faecalis have been found to possess tdc gene and produce tyramine in fermented foods, including dairy products, fermented sausages, wine and fermented soybean foods [12]. Thus, E. faecium strains have been used as target organisms for studies on the reduction of tyramine in fermented soybean foods [33,43], even though Enterococcus spp. are present as contaminants at relatively low levels (maximum up to 10^6 CFU/g) in the foods [44–46]. In the meantime, the absence of hdc gene encoding histidine decarboxylase was reported in both E. faecium and E. faecalis in one study [47], while histidine decarboxylase-positive E. faecium and E. faecalis strains were detected by a PCR (polymerase chain reaction) method in another study [48]. It is interesting to note that the PCR screening method used in the latter study employed the primers developed in the former study, which makes it difficult to conclude whether the species possess hdc gene or not.

As shown in Table 4, at present the Gene Bank database of the National Centre for Biotechnology Information (NCBI, National Center for Biotechnology Information, U.S. National Library of Medicine, Bethesda, MD, USA) provides the sequences of tdc, odc, and ldc genes in E. faecium and tdc and ldc genes in E. faecalis, while hdc gene sequence of both species is not available in the database. In contrast, the sequences of hdc gene in B. licheniformis and B. coagulans (this sequence is completely conserved between the two species) and ldc in B. subtilis have been deposited in the database, while tdc gene sequence is unavailable for the three species of Bacillus. Nevertheless, it has lately been suggested that Bacillus spp. are as significant as Enterococcus spp. for tyramine formation in fermented soybean foods [49]. The deposited genes encoding amino acid decarboxylases of Bacillus spp. and Enterococcus spp., the most important species related to biogenic amine formation in fermented soybean products, are listed in Table 4 (exceptionally, odc-Az encodes an antizyme inhibitor devoid of ornithine decarboxylase activity). All the bacteria and genes mentioned above should be targeted for preventive interventions to reduce biogenic amine formation in fermented soybean foods. Meanwhile, yeasts have been considered to produce only negligible amounts of biogenic amines [50,51]. Fungal distribution to biogenic amine accumulation is remained to be further studied because there appears to be but little literature available dealing with fungal formation of biogenic amines [52].

It is well known that various vasoactive and putrefactive biogenic amines are commonly formed by microbial decarboxylation of amino acids in fermented foods [6,7]. As such, it has been found that soybean fermentation results in an increase in the amount of spermine (and other biogenic amines), but a decrease in that of spermidine [26]. Since spermidine is essential for the growth and development of plants [53,54], this polyamine is abundantly present in soybean and non-fermented soybean foods such as Tofu (a curd product made from soy milk) [26,55,56] and degraded by bacterial enzymes during fermentation [57]. Consequently, fermented soybean foods contain a lower level of spermidine than their raw material, soybean [26,58]. This indicates that development and application of biogenic amine-degrading starter cultures are possible (and necessary) to reduce the contents of biogenic amines in fermented soybean foods. Identifying and understanding the dominant contributors to the formation of biogenic amines may facilitate the development of starter cultures for delaying or avoiding biogenic amine formation in the fermented foods. Taken together, it is clear that distinct and diverse bacterial community and/or capability of producing (and degrading) biogenic amines decisively determine the amounts and diversity of biogenic amines in fermented soybean foods.
Table 4. Genes encoding amino acid decarboxylases in *Bacillus* spp. and *Enterococcus* spp. registered in the NCBI database.

| Species                  | Strain 1               | Source            | Gene for Amino Acid Decarboxylase 2 | No. of Amino Acids | Locus Name | Accession (Version) | Size (bp) |
|--------------------------|------------------------|-------------------|-------------------------------------|--------------------|------------|---------------------|-----------|
| *B. subtilis* subsp. subtilis strain 168 | Isolated strain       | odc-Az            | 331                                 | BACYACA            | L77246.1   | AF12285.1           | 996       |
| *B. licheniformis* / *B. coagulans* A5/ *B. coagulans* SL5 | Isolated strain       | ldc               | 490                                 | AB553282           | AB553282.1 | AB553281            | 1473      |
| *E. faecium* strain 993 | Isolated strains      | odc               | 235                                 | PDLZ01000281       | PDLZ01000281.1| 707                |
| *E. faecium* ATCC 700221 | ATCC                   | ldc               | 191                                 | CP014449.1         | CP014449.1 | 576                |
| *E. faecalis* ATCC 51299 | ATCC                   | ldc               | 611                                 | CP014449.1         | CP014449.1 | 1836               |
| *E. faecalis* ATCC 19433 | Type strain           | ldc               | 194                                 | JSES01000022       | JSES01000022.1| 585               |

1 Genes found in a single strain of each *Bacillus* species have been registered, while those of *Enterococcus* spp. found in multiple strains have been separately assigned to different loci, of which a representative locus is presented in the table; 2 *odc-Az*: 37.0% identity over 119 amino acids to the *E. coli* ornithine decarboxylase antizyme, *odc*: gene for ornithine decarboxylase, *ldc*: gene for lysine decarboxylase, *hdc*: gene for histidine decarboxylase, *tdc*: gene for tyrosine decarboxylase; ATCC: the American Type Culture Collection.

6. Control Strategies for Reducing Biogenic Amines in Fermented Soybean Foods

Regarding intervention measures that reduce biogenic amine formation in fermented soybean foods, to date, only a few reports are available in literature as follows: the use of irradiation [59], addition of nicotinic acid as a tyrosine decarboxylase inhibitor [43], and use of *Bacillus* starter cultures [60–63]. However, when extended to other fermented foods, a review of the relevant literature reveals that several types of intervention methods have been developed and used to reduce biogenic amine contents in the foods (mainly fermented sausage and cheese), which involve chemical intervention, such as the use of food additives and natural antimicrobial compounds [43,64–67], physical intervention, such as the use of irradiation [59,68], high hydrostatic pressure [69,70] and modified atmosphere packaging [71,72], and biological intervention, particularly such as the use of starter cultures [60–63,73–76]. The biological intervention methods also involve the control or adjustment of intrinsic and extrinsic factors, such as alterations of temperature, pH, a_w, and Eh, which have been well reviewed in literature [77–79].

Up to this day, thousands of additives have been used to extend shelf life of foods because of their antimicrobials, antioxidants, and antibrowning properties. Natural additives have lately been of great interest in food industry due to consumers’ health concerns [80]. Apart from being used as food preservatives, numerous food additives and natural antimicrobial compounds, including glycine [64], nicotinic acid [43], potassium sorbate, sodium benzoate [67], sodium chloride [64,66], clove [65–67], garlic [65], etc., have been found to be effective in suppressing bacterial ability to produce biogenic amines in foods. Among the compounds, nicotinic acid is only one compound proven to practically inhibit the formation of biogenic amines (particularly tyramine) in a fermented soybean food, viz., Cheonggukjiang [43]. In the report, the addition of nicotinic acid at concentrations of 0.15% and 0.20% resulted in significant reductions, by approximately 70% and 83%, respectively, compared to the control, of tyramine content in the treated Cheonggukjiang samples after 24 h of fermentation. In addition, it is worth noting that even though a successful reduction of biogenic amines in a food product can be achieved by the addition of any of a variety of compounds, some of the additives may cause organoleptic alterations, such as an atypical taste and flavor, in the final food product, especially in the case of fermented soybean foods [5,49]. Therefore, sensory evaluation should be incorporated.
as an integral part of a program investigating effective inhibitors of biogenic amine formation in fermented soybean foods.

Besides the chemical intervention measures described above, a variety of physical intervention processes have been developed and applied for food preservation, which involve not only well-known classical processes, for instance, heating, refrigeration, and freezing, but also emerging novel processes such as microwave heating, ohmic heating and pulsed electric fields developed during the past 25 to 35 years [81]. Among the physical intervention methods, irradiation, high hydrostatic pressure and modified atmosphere packaging have been relatively recently reported to successfully inhibit biogenic amine formation in fermented foods, which have been achieved mostly by reducing microbial population, for instance, lactic acid bacteria, closely related to the fermentation of foods [59,69–72]. Despite the technological progress that has been made, as for fermented soybean foods, there has been only a single report describing biogenic amine reduction in the food treated by one of the physical intervention processes. In the report, γ-irradiation of raw materials with doses of 5, 10, and 15 kGy significantly reduced the contents of histamine, putrescine, tryptamine and spermidine by approximately 20–50% (but not tyramine, β-phenylethylamine, cadaverine, spermine and agmatine) in the final product of a fermented soybean food, viz., probably Doenjang [59]. However, it needs here to be noted that the irradiation even with the lowest dose resulted in an immediate and significant decrease in the numbers of Bacillus spp. and lactic acid bacteria, known as dominant bacteria in the food, by up to about 3 log CFU/g and 2 log CFU/g, respectively. As is well known, many of the physical intervention processes prevent the growth of fermenting microorganisms, as well as of biogenic amine-producing microorganisms, which may in turn not only delay fermentation, but also lead to abnormal fermentation caused by undesirable microorganisms resistant to the treatments [82]. Thus, introducing the processes would be somewhat challenging in the case of fermented soybean foods, considering the presence of fermenting and/or beneficial bioactive microorganisms in the foods.

The use of starter cultures has been suggested to be a successful way to enhance not only the quality and safety, but also the healthy functions, of fermented foods, causing less adverse organoleptic and unhealthy alterations [83–85]. Thus, with that a variety of microorganisms have been compared and screened for the ability to degrade biogenic amines and/or inability to produce biogenic amines in fermented foods, not only at the level of genus, species, or both, but also at the level of individual strain [73–76]. As for the fermentation of soybean, Bacillus strains have been steadily proposed as starter cultures to improve the sensory quality, but not the safety of fermented soybean foods [86,87]. On the contrary, less attention has been given to starter cultures for preventing or reducing biogenic amine formation in fermented soybean foods. As mentioned above, Bacillus spp. have been known as fermenting (or contaminating) microorganisms responsible for biogenic amine formation in different types of fermented soybean foods. Therefore, it is imperative to screen proper starter cultures (particularly Bacillus starter culture) with no or less ability to produce biogenic amines for the production of fermented soybean foods [62]. With respect to this, there have been a few reports in literature in which Doenjang and Cheonggukjang samples prepared with B. subtilis and B. licheniformis starter cultures, respectively, with low abilities to produce biogenic amines (the data on individual strains were not presented in the reports) contained lower levels of biogenic amines than those of previous studies [61,62]. Alternatively, the use of starter cultures that can degrade biogenic amines may facilitate the reduction of biogenic amines in fermented soybean foods [77]. At present, only two reports of biogenic amine-degrading starter cultures for the production of fermented soybean foods are available in literature as described below. In one study, B. subtilis and B. amyloliquefaciens strains which had been isolated from traditionally fermented soybean products degraded significant amounts of histamine (up to 71% of its initial concentration by B. amyloliquefaciens), tyramine (up to 70% by B. amyloliquefaciens), putrescine (up to 92% by B. subtilis) and cadaverine (up to 93% by B. subtilis) in cooked soybean after 10 days of fermentation [60]. In another study, B. subtilis and B. amyloliquefaciens strains which had been isolated from commercial fermented soybean products degraded 30–40% of tyramine in a phosphate buffer and probably thereby reduced tyramine content by 40–65% in the final
product of Cheonggukjang, as compared to the control [63]. In addition, B. subtilis and B. idriensis strains isolated from a traditional fermented soybean food have been reported to be not only capable of degrading of, but also incapable of producing histamine and tyramine in vitro (but not applied to practical fermentation of soybean in the study) [88]. Consequently, it is feasible to screen Bacillus strains capable of degrading and/or incapable (or less capable) of producing biogenic amines, which would, in turn, make it possible to use them as starter cultures for reducing biogenic amine contents in fermented soybean foods. In the meantime, it is also necessary to fully identify and characterize Bacillus genes involved in the formation and degradation of biogenic amines, which would be helpful not only in selecting starter culture candidates but also in providing strategies to efficiently regulate the expression of these genes encoding relevant enzymes. Such molecular genetic studies would be further needed for better understanding of mechanisms by which intervention methods influencing intrinsic and extrinsic factors and/or microbial growth inhibit biogenic amine formation, at the level of gene. It is noteworthy that in addition to the aforementioned Bacillus starter cultures, strains of E. faecium and L. plantarum have also been proposed as starter cultures for fermented soybean foods because of their abilities to produce bacteriocin or to degrade biogenic amines, respectively [46,89]. Considering that the species are present as contaminants at relatively low levels in fermented soybean foods, as described above, further research is required prior to practical application to the fermentation of soybean in food industry.

Aside from the use of starter cultures, the production of biogenic amines has been known to be dependent on intrinsic and extrinsic factors of foods [77–79]. Furthermore, the factors may provide combined effects, especially in connection with technology applied, viz., the chemical and physical intervention measures described above [90]. As of now, however, the alterations of temperature, pH, a_w, and Eh (as another important, but classical, biological intervention strategy), seem to be less preferable for studies on the reduction of biogenic amines in fermented soybean foods than other alternatives, considering that there are no relevant reports available, which might be because of the need to consider strict demands of consumers and governments on unique sensory properties and manufacturing processes of fermented soybean foods. Nonetheless, it is expected that the changes of the intrinsic and extrinsic factors within narrow ranges would be applicable, depending on the types of fermented soybean foods, if organoleptic evaluation is preceded. The intrinsic and extrinsic factors influencing biogenic amine formation in foods have been well reviewed in a recent article [8]. Biogenic amine reduction strategies, including chemical, physical and biological intervention methods, are summarized in Table 5.

| Parameter Categories     | Highly Effective Strategies                                                                 |
|--------------------------|---------------------------------------------------------------------------------------------|
| Chemical intervention    | Nicotinic acid [43], glycine [64], garlic [65], clove [65], clove and sodium chloride [66], clove with potassium sorbate and sodium benzoate [67] |
| Physical intervention    | Irradiation [59,68], high hydrostatic pressure [69,70], modified atmospheric packaging and temperature [71,72] |
| Biological intervention  | Lactic acid bacteria [84], Lactobacillus sake + Pediococcus pentosaceus + Staphylococcus carnosus + S. xylosus [73], S. carnosus [74], S. xylosus [74–76], L. plantarum [89], Bacillus subtilis [60,63,88], B. amyloliquefaciens [60,63], B. licheniformis [62], B. idriensis [88], B. subtilis + Aspergillus oryzae + Mucor racemosus [61] |
| Intrinsic and extrinsic factors | Temperature, pH, a_w, Eh [77–79]                                                         |

Table 5. Biogenic amine reduction strategies for food products.

7. Conclusions

The presence of histamine in fish is of concern in many countries due to its toxic potential and implications. Accordingly, there are specific legislations regarding the histamine content in fish and
fish products in US, EU, and other countries. In contrast, the significance of biogenic amines in fermented soybean foods has been overlooked despite the presence not only of abundant precursor amino acids of biogenic amines in soybean, but also of microorganisms capable of producing biogenic amines during the fermentation of soybean. Fortunately, the studies published to date indicate that the amounts of biogenic amines in most fermented soybean food products are within the safe levels for human consumption. However, it should be pointed out that the contents of vasoactive biogenic amines in certain types and/or batches of fermented soybean food products are greater than toxic levels. Nonetheless, lack of both legislation and guidelines on the contents of biogenic amines in fermented soybean food products may lead to serious (or unnecessary) concerns about the safety of the fermented foods. Therefore, it is required to establish guidance levels of biogenic amines in fermented soybean food products based on information about the national daily intake of the fermented foods per person and the amounts of biogenic amines in different types of fermented soybean foods commonly consumed in each country.

Meanwhile, many efforts have been made to reduce biogenic amines in various fermented foods, particularly fermented sausage and cheese, whereas less attention has given to biogenic amines in fermented soybean foods. Consequently, there is at present a little information available regarding intervention methods to reduce biogenic amines in fermented soybean foods. Although empirical data on controlling biogenic amines in fermented soybean foods are not much in literature, several reports have suggested that the use of starter cultures capable of degrading and/or incapable of producing biogenic amines is a preferable way to biocontrol biogenic amines in fermented soybean foods because it probably causes less adverse organoleptic and unhealthy alterations as well as little changes in bacterial communities in the foods. Alterations of intrinsic and extrinsic factors, such as temperature, pH, aw, and Eh, in fermentation and manufacturing processes are also needed to be taken into consideration when biocontrol strategy is employed. With a successful reduction of biogenic amines in addition to significant health benefits, consumers may place a much higher value on fermented soybean foods.

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