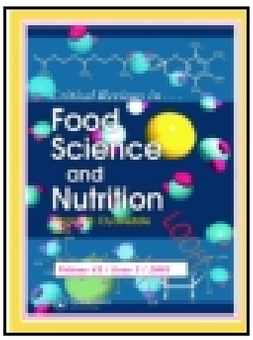

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REVIEW

The function and mechanism of lactic acid bacteria in the reduction of toxic substances in food: a review

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ABSTRACT

N-nitrosamines, heterocyclic amines, polycyclic aromatic hydrocarbons, biogenic amines, and acrylamide are widely distributed and some of the most toxic substances detected in foods. Hence, reduction of these substances has attracted worldwide attention. Lactic acid bacteria (LAB) inoculation has been found to be an effective way to reduce these toxic substances. In this paper, the reduction of toxic substances by LAB and its underlying mechanisms have been described through the review of recent studies. LAB aids this reduction via different mechanisms. First, it can directly decrease these harmful substances through adsorption or degradation. Peptidoglycans on the cell wall of LAB can bind to heterocyclic amines, acrylamide, and polycyclic aromatic hydrocarbons. Second, LAB can indirectly decrease the content of toxic substances by reducing their precursors. Third, antioxidant properties of LAB also contribute to the reduction in toxic substances. Finally, LAB can suppress the growth of amino acid decarboxylase-positive bacteria, thus reducing the accumulation of biogenic amines and *N*-nitrosamines. Therefore, LAB can contribute to the decrease in toxic substances in food and improve food safety. Further research on increasing the reduction efficiency of LAB and deciphering the mechanisms at a molecular level needs to be carried out to obtain the complete picture.

KEYWORDS

Lactic acid bacteria; food safety; *N*-nitrosamines; biogenic amines; polycyclic aromatic hydrocarbons; acrylamide

Introduction

Food contamination is a serious problem affecting food safety and human health, which has attracted extensive attention from consumers (Shoukat 2020). For example, recent studies published by the International Agency for Research on Cancer (IARC) classified the red meats as group II, possibly carcinogenic, and processed meats as group I, carcinogenic to humans (IARC 2015). In the food production process, the use of some additives, such as sodium nitrite and potassium nitrate (Honikel 2008), and processing methods, such as frying and smoking (Flores et al. 2019; Mcafee et al. 2010), may produce certain toxic substances, leading to the occurrence of foodborne diseases. The incidence of foodborne diseases is the second highest among all the disease incidences (Shoukat 2020). Access to safe and healthy food is essential for the healthy living of people (Santini et al. 2018).

It is important to identify compounds that may be harmful to human health present in the raw materials or generated during the production and/or commercialization of food (Flores et al. 2019). These compounds are produced by the interaction of food ingredients when food processing methods such as frying, pickling, baking, fermenting, or heating are used (Barbieri et al. 2019; Barzegar, Kamankesh, and Mohammadi 2019; De Mey et al. 2017; Xiao, Li, Zhou et al. 2018). Among them, *N*-nitrosamines (NAs), polycyclic aromatic hydrocarbons (PAHs), heterocyclic amines (HAs), acrylamide, and biogenic amines (BAs) are the most prominent compounds (Ingenbleek et al. 2019; Lu et al. 2017; Molognoni et al. 2019). These substances are widely studied because of their strong carcinogenicity and widespread presence. Moreover, some of these compounds, such as *N*-dimethylnitrosamine (NDMA), benzo[a]pyrene (BaP), and acrylamide have even been classified as group 2 A carcinogen (IARC 1978), group 1 carcinogen (IARC 2011), and group 2 A carcinogen (IARC 1994), respectively.

As exposure to these toxic substances from diet has been considered a major health problem, different methods have been studied to minimize the content of toxic substances in food. These strategies include using raw materials with low precursor content, radiation effects, changing process conditions (temperature, time, pH, etc.), or adding antioxidants (Choi et al. 2007; Khorshidian et al. 2016; Rahman et al. 2014; Simko 2005). However, these methods have some disadvantages, such as limited scope of application or poor reduction effect (Liao et al. 2019). Recently, studies have found that lactic acid bacteria (LAB) can reduce the content of harmful substances in food. LAB can not only produce enzymes such as biogenic amine oxidase in foods, thereby reducing the possibility of toxic substances in food production (da Silva Sabo et al. 2014), but can also enhance the

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Table 1. Development on functions of LAB in fermented food.

Fermented food	LAB species	Functions	References
Fermented apple juice	*Lactobacillus plantarum* ATCC14917	Antioxidation	Li et al. (2018)
Fermented grape beverage	*Lactobacillus plantarum* *Lactobacillus rhamnosus* *Lactobacillus casei*	Antioxidation	Khanniri et al. (2018)
Yogurt	*Lactobacillus casei* *Lactobacillus delbrueckii*	Antioxidation	Zhang (2011)
Fermented cabbage	*Lactobacillus plantarum*	Antioxidation	Gao, Gao, and Zhu. (2013)
Fermented sausage	*Lactobacillus pentosus*	Inhibit the growth of undesirable bacteria Decrease the content of NDMA and NDEA	Xiao, Li, Zhou et al. (2018)
Smoked pork sausages	*Pediococcus acidilactici* *Pediococcus pentosaceus* *Lactobacillus sakei*	Inhibit the growth of undesirable bacteria Decrease the content of PAHs and BAs	Bartkiene, Bartkevics, Mozuriene et al. (2017)
Fermented silver carp sausage	*Lactobacillus plantarum*	Decrease the content of BAs	Nie, Zhang, and Lin. (2014)
Kimchi	*Lactobacillus sakei* *Lactobacillus curvatus* *Lactobacillus brevis*	Decrease the content of BAs and NDMA	Kim, Kang et al. (2017)
wheat bread	*Pediococcus acidilactici* *Pediococcus pentosaceus* *Lactobacillus sakei*	Decrease the content of acrylamide	Bartkiene et al. (2013a)
Harbin dry sausages	*Lactobacillus pentosus* *Lactobacillus curvatus* *Lactobacillus sakei*	Decrease the content of NAs	Sun et al. (2017)
Harbin dry sausage	*Pediococcus pentosaceus* *Lactobacillus curvatus* *Lactobacillus sakei*	Improve flavor formation	Chen et al. (2016)
Sour meat	*Lactobacillus*	Improve flavor formation	Lv et al. (2019)
Fermented soymilk	*Lactobacillus harbinensis*	Improve organoleptic quality	Zheng et al. (2020)
Stilton cheese	*Lactobacillus plantarum*	Promote the production of fermented aroma	Mugampoza et al. (2019)

NAs: *N*-nitrosamines; BAs: biogenic amines; NDMA: *N*-dimethylnitrosamine; NDEA: *N*-nitrosodiethylamine; PAHs: polycyclic aromatic hydrocarbons.

antioxidative potential and the ability to inhibit spoilage bacteria when used in food, even if the food has not been fermented for a long time (Amanatidou et al. 2001; Xiao, Li, Zhou et al. 2018). Our previous studies also found that LAB can significantly reduce the content of NAs in fermented meat products (Shao, Xu et al. 2021; Shao, Zhu et al. 2021; Xiao, Li, Xu et al. 2018; Xiao, Li, Zhou et al. 2018). However, there was no comprehensive overview of these, especially the mechanism of LAB in reducing the toxic compounds. Therefore, this review describes the reduction effect of LAB on toxic substances in food, such as NAs, PHAs, HAs, acrylamide, and BAs, and focuses on the underlying mechanisms. An overview of the function and mechanism of LAB in reducing toxic substances in food would be helpful to promote a safe and green method for food industry to improve food safety. Meanwhile, an improved understanding of the mechanism can guide further studies on deciphering the mechanism at a molecular level. Furthermore, it can also provide a theoretical guidance to clarify the role of LAB in reducing the harmful substances in the process of food digestion.

LAB and their application in food

LAB

LAB is a genus of gram-positive, anaerobic or microaerophilic, non-spore forming, acid resistant cocci and bacilli, which can ferment sugars into lactic acid (Shoukat 2020). LAB are composed of many genera, mainly *Enterococcus*, *Lactococcus*, *Lactobacillus* (the most studied genus up till now), *Streptococcus*, and *weissella* (Vries et al. 2006). Moreover, LAB, a type of probiotic, is considered as "living organisms that, when given in sufficient quantities, are beneficial to the health of the host" (George Kerry et al. 2018). Many studies have shown that LAB play important roles in many health functions, such as reducing lactose intolerance, cholesterol, and incidence rate of atopic diseases, regulating immune system, reducing food allergy, and preventing cancer (Bron, Van Baarlen, and Kleerebezem 2012; Donato et al. 2017; Lebeer, Vanderleyden, and De Keersmaecker 2010; Reis et al. 2017). This is mainly related to the ability of LAB to regulate the function of mucosal barrier, adhere to epithelial cells, produce antimicrobial peptides and bacterins, and interfere with quorum sensing signals (Setbo et al. 2019).

Application of LAB and their roles in food

LAB is widely used and plays an important role in various food products (Table 1). LAB can produce lactic acid during its the growth, thus reducing the pH value of food and inhibiting the growth of some acid-sensitive spoilage bacteria, which contributes to the extension of the shelf life of food (da Silva Sabo et al. 2014). Additionally, some studies have reported that LAB can decrease the reproduction of spoilage bacteria by producing bacteriostatic substances, such as bacteriocins (Cotter, Hill, and Ross 2005; Drider et al. 2006). Moreover, LAB have been proved to possess good antioxidant activity, mainly reflected in the hydroxyl radical scavenging rate, superoxide anion radical scavenging rate, anti-lipid peroxidation rate, and 1,1-Diphenyl-2-Picrylhydrazyl (DPPH) radical scavenging rate, which can

Table 2. Effects of LAB on the reduction of toxic substances in food products.

Food products	Main toxic substances	LAB species	Reduction rate of toxic substances	Ways of reduction	References
Kimchi	NA (NDMA)	*Lactobacillus sakei* *Lactobacillus curvatus* *Lactobacillus brevis*	*L. sakei* (21.7%) *L. curvatus* (23.4%) *L. brevis* (8.8%)	Direct reduction Reduction of it's precursors	Kim, Kang et al. (2017)
Dry fermented sausages	NAs (NDMA, NPYR and NDEA)	*Lactobacillus pentosus*	NDMA (13.08) NDEA (1.89%) NPYR (15.55%)	Direct reduction Improving the quality of microorganisms	Xiao, Li, and Zhou. (2018)
Harbin dry sausages	NAs (NDEA, NDPA, NDPhA, NPIP)	*Lactobacillus pentosus* *Lactobacillus curvatus* *Lactobacillus sakei*	L. curvatus: NDEA (15.2%), NDPA (21.5%), NDphA (15.7%), NPIP (14.6%)	Direct reduction	Sun et al., (2017)
Kimchi	NA (NDMA)	*Leuconostoc carnosum* *Lactobacillus plantarum* *Lactobacillus sakei* *Leuconostoc mesenteroides*	*L. carnosum* (61.8%), *L. plantarum* (77.6%) *L. sakei* (59.2%) *L. mesenteroides* (54.0%)	Direct reduction Reduction of it's precursors	Kim, Kim et al. (2017)
Milk	PHAs	*Lactobacillus bulgaricus*	(3.46%-5.81%)	Physical binding	Abou-Arab et al., 2010
Cooked meat	HAs (Trp-P-2, PhIP, IQ and MeIQx)	*Lactobacillus acidophilus* *Lactobacillus fermentum* *Bifidobacterium longum*	Trp-P-2 (90%-96%) PhIP (>50%) IQ and MeIQx (20%-40%)	Physical binding	Orrhage et al. (1994)
Fermented fish	NA (NDMA)	*Lactobacillus plantarum*	(17.76%)	Direct reduction Reduction of it's precursors	Liao et al. (2019)
Smoked pork sausage	PHAs (BaP and chrysene) BAs	*Pediococcus acidilactici* *Pediococcus pentosaceus* *Lactobacillus sakei*	Bap: (50.63%-56.96%) Chrysene: *L. sakei* (11.83%) BAs: (8.15%-99.65%)	Direct reduction Growth inhibition of amine-positive bacteria	Bartkiene, Bartkevics, Mozuriene et al. (2017)
Wish silage	BA (histamine)	*Lactobacillus sakei* *Lactobacillus curvatus*	(20%-56%)	Degradation	Dapkevicius et al. (2000)
Wine	BAs (histamine, tyramine and putrescine)	*Lactobacillus casei*	Histamine (16%) Tyramine (15%) Putrescine (8%)	Degradation	García-Ruiz et al. (2011)
Bread	Acrylamide	*Lactobacillus brevis* *Lactobacillus plantarum* *Pediococcus pentoseus* *Pediococcus acidilactici*	*P. acidilactici* (84.2%) *L.brevis* (55.6%) *L. plantarum* (49.2%) *P. pentoseus* (39.2%)	Physical binding	Nachi et al. (2018)
Mixed rye bread	Acrylamide	*Lactobacillus. sakei* *Pediococcus pentoseus* *Pediococcus acidilactici*	*L. sakei* (58.2%) *P. acidilactici* (47.6%) *P. pentoseus* (37.8%)	Physical binding	Bartkiene et al. (2013b)

NAs: *N*-nitrosamines; NDMA: *N*-dimethylnitrosamine; NDEA: *N*-nitrosodiethylamine; NPYR: *N*-nitrosopirrolidine; NDPA: *N*-nitrosodi-n-propylanime; NDphA: *N*-nitrosodiphenylamine; NPIP: *N*-nitrosopiperidine; PAHs: polycyclic aromatic hydrocarbons; HAs: heterocyclic amines; Trp-P-2: 1-methyl-5H-pyrido[4,3-b]indol-3-amine; PhIP: 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine; IQ: 2-amino-3-methylimidazo[4,5-f]quinoline; MeIQx: 2-Amino-3,8-dimethylimidazo[4,5-f]quinoxaline; BaP: benzo[a]pyrene; BAs: biogenic amines.

decrease the risk of accumulation of reactive oxygen species (Kullisaar et al. 2002; Lin and Chang 2000; Zhang 2011). Recently, some studies have found that LAB can also decrease the content of toxic substances in food, such as NAs and PAHs (Bartkiene, Bartkevics, Mozuriene et al. 2017; Xiao, Li, Zhou et al. 2018), which has attracted many researchers' attention.

Decrease of toxic substances in food by LAB

NAs

Formation of NAs in food

NAs have been hotly debated in the scientific community because of their carcinogenicity, mutagenicity, and teratogenicity to humans (Chung, Lee, and Sung 2002). NDMA, *N*-nitrosodiethylamine (NDEA), *N*-nitrosopiperidine (NPIP), and *N*-nitrosopirrolidine (NPYR) are the most common carcinogens found in food (Sallan et al. 2020), among which NDMA and NDEA have the strongest carcinogenicity and are defined as class 2A carcinogens by IARC (IARC 1978).

NAs are formed during the reaction of nitrous reagents, such as dinitrogen trioxide (N_2O_3) and nitrosonium cation (NO^+) with secondary amines (Honikel 2008). The nitrite reagents are mainly produced by the reduction of nitrite and nitrate added to food. Lv et al. (2007) inferred that the reaction between dimethylamine (DMA) and nitrous acid (HNO_2) to generate NDMA is based on the active intermediate N_2O_3 formed by two molecules of HNO_2 and then nitrosation with DMA. The NAs formed by the reaction of the nitrite reagents with the primary amines are very unstable and can be immediately degraded to alcohol and nitrogen, while the tertiary amines will not react with the nitrite reagents (Bryan et al. 2012). In addition, BAs, such as

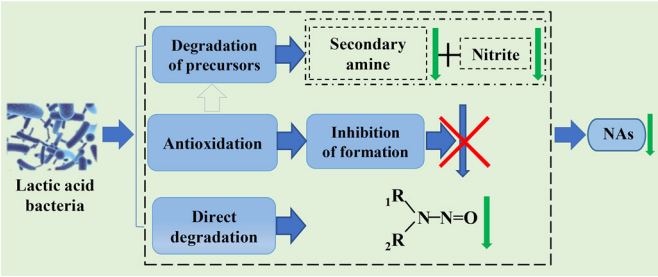

Figure 1. Mechanism of reduction of NAs in food by LAB (based on Shao, Xu et al. 2021). NAs: *N*-nitrosamines. Solid arrow: confirmed ways. Dotted arrow: proposed ways.

putrescine and cadaverine, are also precursors to NAs (Drabik-Markiewicz et al. 2011). The formation of NAs in food is influenced by many factors, such as temperature, pH, protein oxidation, and non-heme iron content (De Mey et al. 2017; Sun, Meng, and Ma 2014). Furthermore, the addition of some spices, such as black pepper in food also affects the content of NAs, due to the presence of its precursors, such as pyrrolidine and piperine in black pepper (Flores et al. 2019).

Function and mechanism of reducing NAs in food by LAB

LAB is widely found in fermented foods and plays an important role in food flavor and quality (Kim, Kang et al. 2017). In the recent years, some studies have found that LAB has the ability to decrease NAs in food (Table 2). In a study by Sun et al. (2017), the influence of three LAB strains (*Lactobacillus pentosus*, *Lactobacillus curvatus*, and *Lactobacillus sakei*) on the reduction of NAs and the quality characteristics of Harbin dry sausage were studied. Four kinds of NAs were detected in dry sausage: NDEA, *N*-nitrosodi-n-propylanime (NDPA), *N*-nitrosodiphenylamine (NDPhA), and NPIP. *L. curvatus* has strongly reduces the production of all the four kinds of NAs, while *L. pentosus* only has reduces the production of NDPA and NDPhA.

The way of reducing NAs by LAB has always been a research direction. According to the past research, there are many methods by which LAB decreases NAs in food (Fig. 1). LAB may directly decrease the content of NAs by adsorption or metabolism, which is one of the important methods. Nowak, Kuberski, and Libudzisz (2014) inoculated four LAB strains (*Lactobacillus rhamnosus* LOCK 0900, *L. rhamnosus* LOCK 0908, *Lactobacillus casei* LOCK 0919, and *Lactobacillus brevis* 0945) under different culture conditions (24 h in MRS, 168 h in modified MRS N, and 168 h in phosphate buffer) to study their mechanisms behind the reduction in NDMA and the effect of different concentrations of NDMA on the growth and survival rate of these strains. In addition, this study also examined the effect of membrane extracts of strains and culture supernatants on the reduction of NDMA. The results showed that the reduction rate of four strains in NDMA was up to 50%, among which *L. brevis* had the best effect, and the survival rate of strains was not affected by the concentration of NDMA. In addition, the authors found that both the culture supernatants and membrane extracts of the four strains could reduce the content of NDMA. This suggests that the four strains may decrease NDMA content by adsorption or metabolism. Subsequently, our laboratory studied the mechanism of reduction of NDMA and NDEA by *L. pentosus* R3 in Mann-Rogosa-Sharp (MRS) broth and *L. pentosus* R3 exhibited good reduction efficiency, with a rate of 22.05% for NDMA and 23.31% for NDEA. NDMA and NDEA were not detected in the whole cell extracts of *L. pentosus* R3, which indicated that the mode of reducing NAs might be metabolism (Xiao, Li, Xu et al. 2018). This result is consistent with that of Grill, Crociani, and Ballongue (1995) who reported that the metabolism of NDMA, NPIP, and NPYR by B*ifidobacterium longum* bb536 in vitro may be due to the role of intracellular enzymes. In addition, this study also showed that the surface protein on the cell wall of the strain was responsible for the reduction of NAs. However, further studies are required on the characterization of the surface proteins and molecular evidence for the reduction reaction.

In addition to the direct decrease, LAB can also indirectly decrease the content of NAs in food by precursor reduction and antioxidation. A study reported that the contents of NDMA, sodium nitrite, BAs, and DMA can be significantly decreased by inoculating LAB strains (*L. sakei, L. curvatus, and L. brevis*) into kimchi, which indicated that LAB can also indirectly decrease the content of NDMA by reducing its precursors (Kim, Kang, et al. 2017). Kim, Kim et al. (2017) inoculated four other LAB species (*Leuconostoc carnosum, Leuconostoc mesenteroides, L. plantarum, and L. sakei*) into kimchi and found that these strains could decrease the content of NDMA by inhibiting its formation up to 50% in addition to directly reducing the precursor. Similar results were reported by Liao et al. (2019) who found that *L. plantarum* significantly decreased the levels of NDMA and its precursors (trimethylamine, DMA, and nitrite) in the fermentation process of traditional Chinese fermented fish.

Oxidation is also an important factor affecting the formation of NAs. Lipid oxidation may promote the occurrence of protein oxidation (Kikugawa, Kato, and Hayasaka 1991), which may produce some amines to promote the formation of NAs (Herrmann, Granby, and Duedahl-Olesen 2015). In addition, non-heme iron has been found in many foods, which can promote nitrosation through a "metal assisted mechanism" (Gok 2012). Furthermore, non-heme iron is a precursor of the reactive oxygen radicals that promote the oxidation of lipids and proteins (Oueslati et al. 2016). Therefore, the antioxidant activity of LAB may also be a potential way to decrease NAs. In our previous study, it was found that when LAB significantly decreased the content of NAs in fermented sausage, the total volatile basic nitrogen and carbonyl content also significantly decreased, indicating that inhibiting protein oxidation may be a way for LAB to decrease the NA content (Xiao, Li, Zhou et al. 2018). Similar study conducted by Sun et al. (2017) also reported that LAB can inhibit the oxidation of lipids and proteins in fermented sausage, which may contribute to the reduction of NAs. In addition, LAB have Fe^{2+}, hydroxyl radical, and DPPH radical scavenging abilities (Amanatidou et al. 2001;

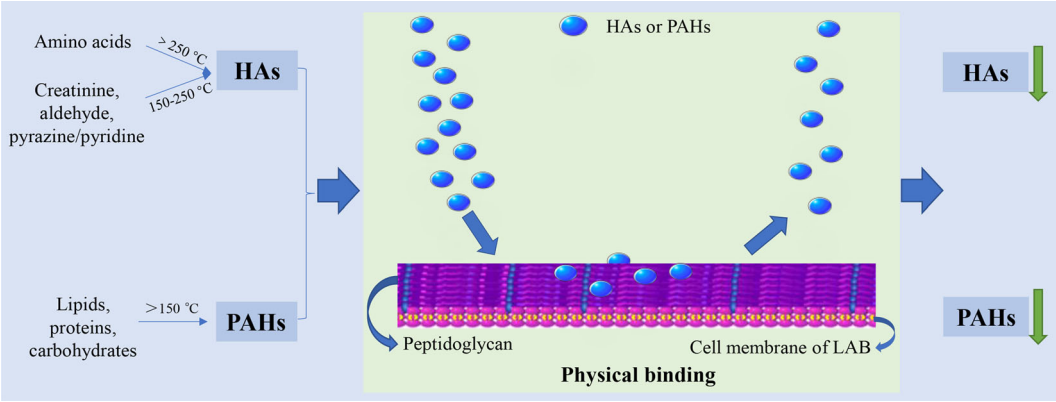

Figure 2. Formation of HAs and PAHs in food and the mechanism of their reduction by LAB. HAs: heterocyclic amines; PAHs: polycyclic aromatic hydrocarbons.

Gao, Gao, and Zhu 2013; Zhang 2011). However, the mechanisms of antioxidation and reduction of NAs by LAB need to be further clarified.

HAs

Formation of HAs in food

HAs were first discovered by Nagao et al. (1977) in a study about smoke from roasted and grilled fish. The main source of human exposure to HAs is cooked meat and fish. The high temperatures used in cooking (boiling, frying, and roasting), can easily lead to the conversion of amino acids in meat and fish into the chemical HAs (Zamora, Alcon, and Hidalgo 2013). Among the known HAs, eight species are classified as probably (2 A) or potentially (2B) carcinogenic (IARC 1993), which have shown strong genotoxicity, mutagenicity, and carcinogenicity in animal experiments, and they are probably also related to human cancer etiology (Meurillon and Engel 2016). Thus, reduction of HA content in foods is of utmost importance.

So far, more than 30 kinds of HAs have been reported (Puangsombat, Jirapakkul, and Smith 2011). They are classified into two distinct families, the pyrolytic HAs and the amino imidazo azaarenes (AIAs). As the name indicates, pyrolytic HAs are mainly formed at high temperatures (generally more than 250 °C) (Skog, Johansson, and Jägerstad 1998) by amino acid precursors, such as glutamate, ornithine, tryptophan, or phenylalanine, and also by the pyrolysis of casein and soybean globulin. At high temperatures, reactive radicals as well as deamination and decarboxylation products are produced by these substances, and some reactions may occur leading to the formation of pyrolytic HAs (Murkovic 2004). Totsuka et al. (1999) observed that high-temperature cooked foods contained 2.39–795 ng/g of norharman and 0.62–377 ng/g of harman, and emphasized the difference in the amount of HA precursors in different meats. AIAs are produced by Maillard reaction at ordinary cooking temperatures (150–200 °C). They can be produced by a variety of precursors, because their skeleton is formed by stroke degradation products in the Maillard reaction between the amino acids and hexoses (Milic, Djilas, and Canadanovicbrunet 1993). In addition, the formation of different AIAs in the presence of creatinine, sugar, and amino acids depends on the types of sugars and amino acids (Skog, Johansson, and Jägerstad 1998). However, early studies using C^{14} labeled reactions have demonstrated that 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP), a high-content compound in AIAs, can be formed from phenylalanine and creatinine with phenylacetaldehyde as an intermediate, even in the absence of glucose (Shioya et al. 1987). This result was subsequently confirmed by Zamora, Alcon, and Hidalgo (2013) who found that phenylacetaldehyde can be generated from different pathways, some of which do not require reducing sugars, and may be related to reactive carbonyls produced by free amino acids. Therefore, the mechanism of HA formation is still obscure and needs further study.

Function and mechanism of reducing HAs in food by LAB

LAB is a beneficial bacterium, which is widely used in foods. In recent years, researchers have found that LAB can decrease the content of HAs in food (Table 2), which has aroused people's interest. Moreover, many studies have shown that LAB mainly decrease the HA content by adsorption (Figure 2). The binding ability of cells, cell fractions and cell wall skeleton (CWS) of *Lactobacillus acidophilus* IFO 13951 and *Bifidobacterium bifidum* IFO 14252 to 3-Amino-1,4-dimethyl-5H-pyrido[4,3-b]indole (Trp-P-1) and 1-methyl-5H-pyrido[4,3-b]indol-3-amine (Trp-P-2) was studied. The reducing abilities of cells and CWS in Trp-P-1 and Trp-P-2 were significantly higher than those of the cell fractions. After the cells and cell walls were treated with lysozyme and α-amylase, the ability of reducing Trp-P-1 and Trp-P-2 was higher than that of the untreated group. Peptidoglycan in the cell wall was found to be the main component binding HAs (Zhang and Ohta 1991). Another study reported the binding ability of seven LAB strains to four HAs (2-Amino-3,8-dimethylimidazo[4,5-f]quinoxaline (MeIQx), 2-amino-3-methylimidazo[4,5-f]quinoline (IQ), Trp-P-2 and PhIP) in cooked protein-rich food. The binding abilities of different strains were slightly different, but their binding efficiencies to different HAs were significantly different. These strains almost completely binds Trp-P-2 and adsorbs about 50% PhIP, which has poor binding ability for IQ and MeIQx (Orrhage et al. 1994). Similar results have been reported in Stidl et al. (2008) who studied the ability

of eight LAB strains to reduce five HAs (2-amino-9H-pyrido[2,3-b]indole (AαC), PhIP, IQ, MeIQx, and 2-amino-3,4,8-trimethylimidazo[4,5-f]quinoxaline (DiMeIQx)) in cooked meat and found that *Lactobacillus helveticus* and *Sterptococcus thermophilus* had the highest clearance capacity. Moreover, they also found that different kinds of HAs had significantly different rates of reduction, the ranking order of detoxification being AαC > DiMeIQx > MeIQx > IQ > PhIP. In addition, many studies have reported the factors that affect the reduction of HAs by LAB. Inoculation concentration, pH, and inoculation time have been found to have an impact on the reduction effect (Faridnia et al. 2010; Nowak and Libudzisz 2009; Zsivkovits et al. 2003). However, whether LAB can decrease the content of HAs by other ways, such as by reducing precursors or inhibiting formation, needs further research in the future.

PAHs

Formation of PAHs in food

PAHs are a general term for a class of hydrocarbons. Their molecules contain two or more benzene rings, which are distributed in a linear, angular, or clustered fashion (Cook, Hewett, and Hieger 1933). PAHs have strong carcinogenic, teratogenic, and mutagenic effects, which can easily lead to skin cancer, vascular cancer, and other diseases (Armstrong et al. 2004). Among them, BaP is the most toxic and the first environmental chemical carcinogen found, and it is widely distributed and stable, accounting for 1%–20% of all the carcinogenic PAHs (Simko 2002). Of late, PAHs have been detected in different kinds of foods. Highly polluted food mainly includes meat and fish products, particularly after smoking and roasting processes. In addition, a large number of PAHs have been found in oil and grain (Chen and Chen 2001; Rozentāle et al. 2015).

The mechanism of PAH formation was first studied by Badger and Moritz (1959) who made a hypothesis about BaP formation for the first time. They hypothesized that the organic compounds are first cracked under the conditions of high temperature and anoxia to produce hydrocarbon-free radicals which combine to form acetylene. The acetylene is then polymerized to produce vinyl acetylene or 1,3-butadiene, cyclized to form phenylbenzene, further combined to form butylbenzene and tetrahydronaphthalene to finally form BaP. Later, Davies and Wilmshurst (1960) studied the pyrolysis reaction of starch in anaerobic condition, and found that BaP content was 17 μg/kg when the pyrolysis temperature was 650 °C. In the study of carbohydrates and fatty acids, it was also found that a large number of PAHs can be produced under high temperatures (Howard and Fazio 1969). Recent studies have found that PAHs are mainly formed by fat oxidation, protein decomposition, amino acid polymerization, and Maillard reaction of the food products at high temperature, and the main precursors of PAHs include amino acids, creatine, creatinine, and glucose (Mcgrath, Chan, and Hajaligol 2003; Park et al. 2017).

Function and mechanism of reducing PAHs in food by LAB

Recently, the reduction of PAHs by LAB in food has gained increasing attention because it is natural and thus, more acceptable to consumers than the physical and chemical methods (Król et al. 2017). The surface treatment of cold smoked sausage with LAB before and after smoking can significantly decrease the content of PAHs in the sausage (Bartkiene, Bartkevics, Mozuriene et al. 2017). Many researchers have studied the mechanism by which LAB reduce PAHs, and reported that physical adsorption is the main method used by LAB to decrease PAHs (Figure 2).

Zhao et al. (2013) studied the binding ability of fifteen LAB strains to BaP and found that *L. plantarum* CICC 22135 and *L. pentosus* CICC 23163 exhibited the best binding efficiencies, reaching 64.36% and 66.73%, respectively. The binding process is affected by pH, culture time, and temperature, but the live and dead cells of these strains had no significant effect on the reduction of BaP. This showed that the main mechanism of reducing BaP by LAB is physical adsorption. Zhao et al. (2013) pointed out that the peptidoglycan on the cell wall was the main binding site of BaP, and the peptidoglycan with complete structure was needed for binding BaP. It was also found that the effect of heat-killed LAB cells on BaP reduction was not significantly different from that of the living cells. Similar results were also observed in a study by Qi et al. (2011). They studied the ability of *L. plantarum* 121 and *L. pentosus* ML32 to bind to BaP, and found that the reduction rates of BaP were 56% and 65%, respectively, and there was no significant difference in the reduction ability after thermal death. *Bifidobacterium lactis* Bb-12 has a very high BaP clearing capacity of about 71.5%, but the number of living cells is not high. This study confirmed once again that the physical binding of LAB is related to the removal of BaP (Lo et al. 2004). In view of the diversity of PAHs, the reduction effects and mechanism of LAB on other PAHs should be further clarified. In addition, the molecular biological mechanism by which LAB reduce PAHs needs to be further studied.

BAs

Formation of BAs in food

BAs are low molecular weight nitrogen compounds with biological activity (Maijala, Nurmi, and Fischer 1995). Low concentration of BAs has certain benefits to human body, such as maintaining normal physiological activities of cells and maintaining the stability of biofilm. However, high concentrations of BAs have toxic effects, resulting in the damage of human nervous and cardiovascular systems (Drabik-Markiewicz et al. 2011). Therefore, a wide range of studies on BAs have been conducted.

BAs are widely found in food, especially in fermented meat products. This is because BAs are mainly produced by the action of amino acid decarboxylase secreted by microorganisms or by amination and transamination of aldehydes and ketones (Maijala, Nurmi, and Fischer 1995). Also, the large number of amino acid decarboxylase positive bacteria

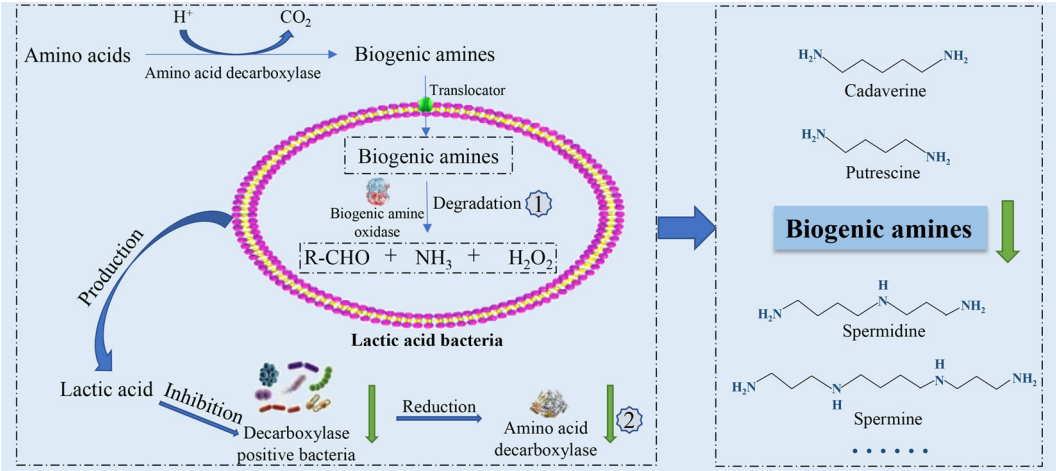

Figure 3. Two ways of reducing biogenic amines by LAB in food.

in fermented meat products, such as *Enterobacter* and *Micrococcus*, promote the accumulation of BAs (Muscat et al. 2009; Rodriguez-Jerez et al. 1994). It is generally believed that the presence of precursors of BAs (amino acids), amino acid decarboxylase-positive bacteria, and favorable conditions for decarboxylation are the necessary conditions for the formation of BAs in food products (Lorenzo et al. 2007). The common BAs in fermented food are histamine, cadaverine, putrescine, and tyramine, among which histamine and tyramine are considered to be the most harmful to the human body, while cadaverine and putrescine are reported to enhance the toxicity of histamine and tyramine (Hernández-Jover et al. 1997). In addition, cadaverine and putrescine can react with nitrite to form NAs (Kim, Kang et al. 2017). Latorre-Moratalla et al. (2008) found that the main BA in the European traditional fermented sausage was tyramine, followed by putrescine and cadaverine, and the content of tyramine was up to 473.43 mg/kg.

In addition, some researchers found that the content of BAs in food is diverse. The content of BAs in dry fermented sausage is the highest after 30 days of ripening, and only about half of that after 70 days. In addition, different BAs showed different trends, among which tyramine, cadaverine, tryptamine, and putrescine showed a downward trend in the process of ripening, the content of amphetamine showed a wave-type change, spermine first decreased and then increased, and spermidine always showed a downward trend (Roseiro et al. 2006). Gardini et al. (2002) found that except spermine, the content of all the other BAs in fermented sausage increased.

Function and mechanism of reducing BAs in food by LAB

The content of BAs in food mainly depends on the ratio of amino acid decarboxylase, biogenic amine oxidase, and biogenic amine dehydrogenase. Amine oxidase can oxidize and deaminate BAs to ammonia, aldehyde, and hydrogen peroxide, and amine dehydrogenase dehydrogenates BAs to produce aldehydes (Tapingkae et al. 2010; Zaman et al. 2011). Therefore, screening LAB with amine oxidase activity is an effective way to control the formation of BAs in food (Figure 3). Many studies have reported that some LAB strains possess amine oxidase activity. Dapkevicius et al. (2000) found that *L. sakei* isolated from fish sauce had significant histamine oxidase activity and could degrade histamine effectively. Similarly, Kalae, Spieka, and Kfizek (2000) also reported that some LAB strains in kimchi have amine oxidase activity. LAB in red wine were also found to have amine oxidase activity, which significantly decreased the content of putrescine, tyramine, and cadaverine (García-Ruiz et al. 2011). However, there are only a few studies on amine dehydrogenase activity in LAB strains.

Inhibition of amino acid decarboxylase-positive bacteria growth is also an important way for LAB to inhibit the accumulation of BAs in food (Figure 3). LAB as biological preservatives contribute to inhibit the growth of foodborne pathogens, thereby reducing the production of BAs (Özogul & Hamed, 2018). Sun et al. (2016) inoculated *L. plantarum* in Harbin fermented sausage, found that the strain could grow well and inhibit the survival of decarboxylase positive bacteria, thus significantly reducing the content of six kinds of BAs (cadaverine, putrescine, tryptamine, 2-phenylethylamine, histamine, and tyramine) in sausage. Lu et al. (2015) found that *L. sakei* can significantly inhibit the growth of some spoilage bacteria, such as *Enterobacteriaceae* and *Pseudomonas*, which promote the formation of BAs in the traditional Chinese sausage production process. During the fermentation of kimchi (Kim, Kang, et al. 2017), red wine (Capozzi et al. 2012), and fish (Liao et al. 2019), LAB were also found to have the same ability to inhibit the formation of BAs. This is mainly because LAB produces lactic acid during food fermentation, making the pH drop rapidly, which inhibits the growth of some decarboxylase-positive bacteria and the activity of amino acid decarboxylase, thus reducing the production of BAs (Bovercid, Izquierdopulido, and Vidalcarou 1999). In addition, recent studies also found that the cell-free supernatant of LAB can also reduce the content of some BAs, which may be because some antibacterial substances and organic acids in the supernatant inhibit the growth of unwanted strains (Kuley et al., 2018; Özogul et al., 2015; Özogul et al., 2017; Toy, Özogul, and Özogul 2015). The addition of cell-free supernatant of LAB is also

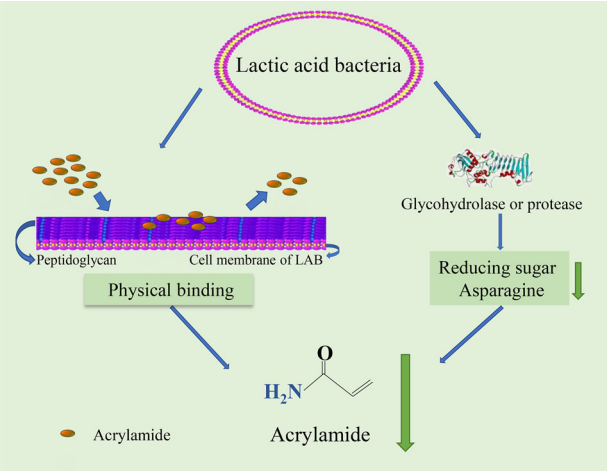

Figure 4. Mechanism of reduction of acrylamide by LAB in food.

considered as a method to reduce the content of BAs in food production.

Unfortunately, certain LAB strains have been found to exhibit amino acid decarboxylase activity, which can promote the production of BAs (Lonvaudfunel 2001). Additionally, some LAB strains can increase the formation of BAs especially when combined with other microorganisms (Özogul & Hamed, 2018). Furthermore, some LAB strains may have both amino acid decarboxylase and biogenic amine oxidase activities, which results in the simultaneous production and reduction of BAs. Therefore, the use of molecular biology means to regulate the expression of enzymes related to the production or degradation of BAs will be the focus of future research.

Acrylamide

Formation of acrylamide in food

Acrylamide, an unsaturated amide, has strong carcinogenicity and mutagenicity (Dearfield 1995). In addition, acrylamide can also cause neurological damage in humans. Therefore, it has been classified as Group 2 A carcinogen (probable human carcinogen) by the IARC (IARC 1994). Acrylamide has attracted worldwide attention since its detection in hot processed foods in 2002 (Mottram, Wedzicha, and Dodson 2002). Later, acrylamide was also detected in other food products, such as potato chips, bread, and coffee (Anese et al. 2009).

In recent years, the formation mechanism of acrylamide in food has been studied by many researchers. The asparagine pathway is important for the formation of acrylamide in foods (Mottram, Wedzicha, and Dodson 2002) and refers to the formation of acrylamide by dehydration condensation at the initial stage of the Maillard reaction between asparagine and glycosyl compounds (reducing sugars). In this way, asparagine can form acrylamide by directly dicarboxylic and deamination under heating conditions, but the amount of acrylamide formed is extremely low, and large amounts of acrylamide can be formed in the presence of asparagine and carbonyl compounds (Yaylayan, Wnorowski, and Perez Locas 2003). Moreover, Stadler et al. (2002) and Zyzak et al. (2003) found that asparagine was the main source of acrylamide formation, which was confirmed through labeled isotope experiments. In fact, some researchers have also found another pathway which produces acrylamide without the presence of asparagine. This process is dominated by acrolein and acrylic acid, which have similar chemical structures to acrylamide and are recognized as the precursors of acrylamide (Zhang et al. 2009). Ehling, Hengel, and Shibamoto (2005) found that lipids produce trocar acrylic acid through hydrolysis and oxidation reactions at high temperature, and then acrylic acid reacts with amino compounds to form acrylamide. Monosaccharides decompose into many small molecular substances (such as formaldehyde and acetaldehyde) during the heating process, which form acrylic acid, and then produce acrylamide (Vattem and Shetty 2003).

Function and mechanism of reducing acrylamide in food by LAB

Measures to decrease acrylamide have been studied due to its widespread presence in foods and high toxicity to humans. Methods such as suitable raw material selection or changing process parameters are not encouraged because of their poor effect on reducing acrylamide or the serious damage they could cause to sensory quality (Xu, Oruna-Concha, and Elmore 2016). In the recent years, LAB have been found to have a increased ability to reduce acrylamide in food (Table. 2). Nachi et al. (2018) found that LAB significantly decreased the acrylamide content in wheat bread. Similar results were also found in mixed rye bread (Bartkiene, Bartkevics, Pugajeva et al. 2017) and fermented potato chips (Baardseth et al. 2006).

Many reports have reported that the mechanism by which LAB reduces acrylamide content is via direct adsorption (Figure 4). Serranonino et al. (2015) studied the interaction between teichoic acids and acrylamide on the cell walls of fourteen LAB strains. The results showed that teichoic acids may be related to binding of acrylamide. The binding degree of acrylamide to bacterial cell wall is inversely proportional to the content of glucose, D-alanine or phosphoric acid. Hydrogen bonds may be formed between carbonyl oxygen and the amino group between adjacent acrylamide and D-alanine directly attached to the position D-4(L-2) of ribitol. This explained the ability of LAB to decrease the bioavailability of acrylamide through physical binding. In addition, Zhang et al. (2017) studied the binding ability of four LAB strains (*L. plantarum* 1.0065, *L. casei* ATCC393, *L. acidophilus* LADS1.0307, and *S. thermophilus* KLDS1.0316) to acrylamide. The results showed that the binding capacity of bacterial peptidoglycan to acrylamide was 33.65%–87%. *L. plantarum* 1.0065 has the highest binding capacity and the highest carbohydrate content in its peptidoglycan structure, which is positively related to the ability of peptidoglycan to bind acrylamide. In addition, the binding capacity was positively correlated with alanine, aspartic acid, glutamic acid, and lysine levels. Alanine has the highest content of peptidoglycan and amino acids, and hence has a significant effect on the binding of acrylamide. Similar results have been found in the study of Shen et al.

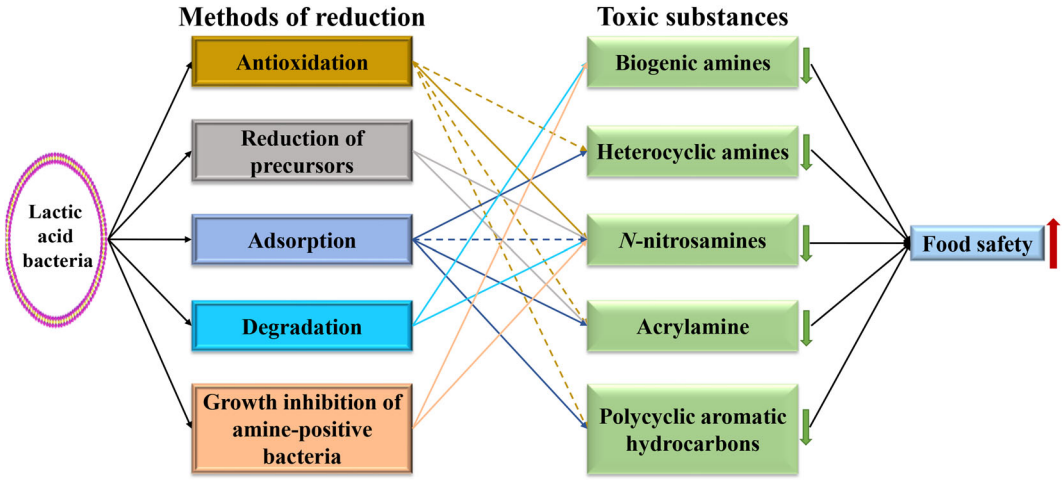

Figure 5. Overview of the mechanism of reduction of toxic substances by LAB in food. Solid line: confirmed methods. Dotted line: proposed methods.

(2019) which reported that increasing cell wall roughness can improve the adsorption capacity of the strain to acrylamide. The hydrophobicity of the strain is related to the adsorption of acrylamide. The main functional groups of acrylamide adsorbed to LAB were C=O, C–O, and N–H groups, which indicated that peptidoglycan and cell wall protein were the main components of the LAB strains which adsorbed acrylamide.

LAB can also control the formation of acrylamide by reducing its precursors, such as asparagine and reducing sugar (Figure 4). In mixed rye bread, LAB significantly decreased the content of acrylamide, which may be related to the low starch hydrolase activity and high protein hydrolase activity of the tested strains (Bartkiene et al. 2013b). However, different results were observed in another study by Bartkiene et al. (2013a). LAB significantly decreased the content of acrylamide in wheat bread, where the process depended on the pH and activity of amylase. The acrylamide content was inversely proportional to the activity of amylase, but was not related to the activity of proteolytic enzyme. Baardseth et al. (2006) found that the content of acrylamide in potato chips fermented by LAB decreased by 48%–94% after frying, and reported that the raw material sugars might be fermented into lactic acid by LAB, thus reducing the content of precursors in raw materials. Recently, it has been found that LAB species also have an asparaginase gene (Amer et al. 2013). Aishwarya et al. (2019) cloned the asparaginase gene from *L. casei* ATCC 393 and *Lactobacillus reuteri* DSM20016, and were expressed in *Escherichia coli*. However, the research on application of asparaginase in LAB strains is still limited, and more studies are also needed to clarify its effectiveness.

Future challenges and trends

The mechanism of LAB in reducing the harmful substances has not been completely clear till now and should be further studied not only in the food sytem, but also in the process of food digestion. Many antioxidants, such as sodium ascorbate and tea polyphenols, can decrease the content of HAs, PAHs, and acrylamide by reducing the production of free radicals or inhibiting the Maillard reaction. The antioxidative activity exhibited by LAB strains can also contribute to the reduction of these harmful substances. For future studies, focus should be on the reduction effects and mechanism behind the reduction of these substances by LAB antioxidants. In addition, most of the current studies have been conducted in food systems, and more in vivo experiments are needed to clarify the role of LAB in the digestion process. Furthermore, studies on how LAB can reduce toxic substances from the perspective of molecular biology and studies on improving the reduction efficiency of LAB need to be explored.

Conclusions

This article reviewed the function and mechanism of LAB in reducing NAs, HAs, PAHs, BAs, and acrylamide in food. As shown in Figure 5, LAB can directly decrease these toxic substances by binding or degradation. For example, peptidoglycans on the cell wall of LAB can bind to HAs, acrylamide, and PAHs. LAB can indirectly decrease the content of toxic substances by reducing their precursors. The reduction of secondary amines and nitrites contribute to the decrease in the content of NAs. In addition, the decrease of asparagine and reducing sugar also had a significant effect on the decrease of acrylamide. The antioxidant properties of LAB also contribute to the reduction of toxic substances. LAB can inhibit the growth of spoilage bacteria, which are amino acid decarboxylase-positive, to control the accumulation of toxic substances, such as BAs and NAs. Additionally, the reduction of toxic substances by LAB in food can be affected by many factors, such as pH, temperature, and the type of bacterial strains. The review of the function and mechanism of LAB in reducing toxic substances in food can help the food industry to promote the application of LAB in reducing the harm and enhancing food safety and the health of consumers.

Disclosure statement

No potential conflict of interest was reported by the authors.

Author contributions

Xuefei Shao identified and interpreted the literature sources and drafted the manuscript. Baocai Xu and Conggui Chen collected relevant research and review papers. Peijun Li and Huiting Luo completed proof-reading and final editing of the manuscript.

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