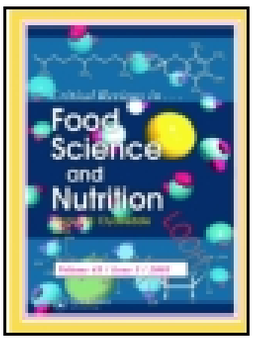

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REVIEW

Recent development in Se-enriched yeast, lactic acid bacteria and bifidobacteria

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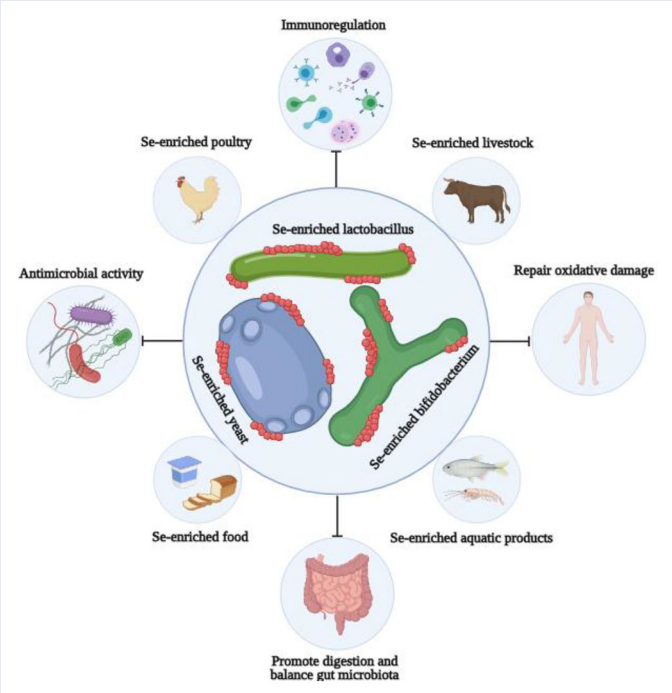
ABSTRACT

Endemic selenium (Se) deficiency is a major worldwide nutritional challenge. Organic Se can be synthesized through physical and chemical methods that are conducive to human absorption, but its high production cost and low output cannot meet the actual demand for Se supplementation. Some microbes are known to convert inorganic Se into organic forms of high nutritional value and Se-enriched probiotics are the main representatives. The aim of the present review is to describe the characteristics of Se-enriched yeast, lactic acid bacteria, bifidobacteria and discuss their Se enrichment mechanisms. Se products metabolized by Se-enriched probiotics have been classified, such as Se nanoparticles (SeNPs) and selenoprotein, and their bioactivities have been assessed. The factors affecting the Se enrichment capacity of probiotics and their application in animal feed, food additives, and functional food production have been summarized. Moreover, a brief summary and the development of Se-enriched probiotics, particularly their potential applications in the field of biomedicine have been provided. In conclusion, Se-enriched probiotics not just have a wide range of applications in the food industry but also have great potential for application in the field of biomedicine in the future.

GRAPHICAL ABSTRACT



KEYWORDS

Bioactivity; Biomedicine; selenium; Se nanoparticles (SeNPs); selenoprotein

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Highlights

- Se-enriched probiotics can meet the body's demand for Se.
- Different types of probiotics have their unique Se enrichment mechanisms.
- Se-enriched probiotics and their Se metabolites have different biological activities.

Introduction

Selenium (Se), as one of the essential trace elements for the human body, is essential for several physiological activities such as body health, metabolism, and immune regulation (Rayman 2012). Unlike other essential trace elements, human Se intake varies greatly around the world, ranging from Se deficiency caused by insufficient intake to Se poisoning due to excessive intake, which is closely related to geographical location (Johnson, Fordyce, and Rayman 2010). The average recommended intake of Se is generally 60 μg/d for men and 53 μg/d for women, whereas, this essential intake is still not up to standard in many regions, especially in developing countries (Rayman 2004, 2008).

In nature, Se exists mainly in the inorganic state, with high toxicity, low biological activity, and difficulty to be absorbed and utilized by the human body. The conversion of inorganic Se to organic form by physical and chemical means can solve this problem. However, most physical and chemical production methods are complex and costly to produce, and there is still a long way to go before they can be used on a large scale (van Overschelde, Guisbiers, and Snyders 2013; Zhai et al. 2017). Enrichment of Se using microorganisms is one of the most promising technologies in the emerging Se industry. This bio-enrichment method uses inorganic Se as a raw material to produce organic Se with high nutrition and low toxicity to meet the needs of the public, especially people in Se-deficient areas. Probiotics are the main object in the research field of Se-enriched microorganisms, including Se-enriched yeast, Se-enriched lactic acid bacteria, and Se-enriched bifidobacteria (Dumont, Vanhaecke, and Cornelis 2006; Pophaly et al. 2014). Se-enriched yeast is the most widely studied Se-enriched beneficial microbe, with strong organic Se conversion ability and high selenoprotein content (Dumont, Vanhaecke, and Cornelis 2006; Kieliszek et al. 2020; Kieliszek and Dourou 2020). Following the Se-enriched yeast, there are more studies on Se-enriched lactic acid bacteria and Se-enriched bifidobacteria. This is mainly because lactic acid bacteria and bifidobacteria have a long history as generally recognized as safe (GRAS) edible bacteria with natural probiotic activity, which are more conducive to the promotion and application in the field of Se-enriched fermented milk, sauerkraut, and other food products (Alzate et al. 2010; Pophaly et al. 2014). These Se-enriched probiotics applied in food can not only provide the gastrointestinal peristalsis, promote digestion and absorption and enhance immunity required by the human body, but also they directly provide abundant organic Se source (mainly selenoprotein), which can finally meet the human body needs from two perspectives of health maintenance and nutrient element supplementation (Asbaghi et al. 2020; Handa et al. 2020; Yi et al. 2020). It is worth noting that Se-enriched probiotics have shown some outstanding excellent properties, such as stronger antimicrobial activity (Yang et al. 2018), thus, these Se-enriched active microbial preparations also have the potential to become novel antimicrobial agents and have great development value in the future biomedical field. This review concludes that the types of Se-enriched probiotics and their Se enrichment mechanism firstly. Secondly, it classifies Se products metabolized by Se-enriched probiotics and assesses their bioactivities. Thirdly, it summarizes the factors affecting the Se enrichment capacity of probiotics and their application in animal feed, food additives, and functional food production. Finally, it provides a brief summary and outlook of research and development of Se-enriched probiotics.

Se-enriched probiotics

Se-enriched yeast

Yeast is a eukaryotic microorganism, widely used in fermented fruit wine, fermented meat products, cereal fermented bread, etc (Rai and Jeyaram 2017). Se-enriched *Saccharomyces Cerevisiaeshi* is the most widely studied yeast, which has a higher efficiency of Se biotransformation compared to other yeasts (Adadi et al. 2019), with protein-bound Se compounds accounting for 60–80% of the overall protein (Bierla et al. 2018). Se-enriched yeast is often mixed with animal feed for livestock breeding to improve meat quality and Se content, including hens (Liu et al. 2021), broilers (Yang et al. 2020), broiler chickens (Tong et al. 2020), sows (Zhang et al. 2020), weaned piglets (Lv et al. 2020), Nellore cattle (Silva et al. 2020), Tibetan sheep (Wang et al. 2019), rainbow trout (Wang et al. 2018), etc. This method of animal-derived Se supplementation has been widely accepted, especially in areas of Se deficiency (e.g., China's Tibet and Europe); besides, co-fermentation of Se-enriched yeast with algae and fungi is also a current research hotspot, including the *marine brown alga Sargassum swartzii* (Vinu et al. 2020), *Chlorella vulgaris* (Vu et al. 2019), *button mushrooms* (Prange et al. 2019), *pleurotus eryngii* (Zhou et al. 2021), but the safety of this group of Se-enriched species needs to be fully assessed. For example, *Spirulina* can enrich Se, but its secreted microcystins (MCs) are potentially harmful (Adadi et al. 2019).

Specifically, Se-enriched yeast, as one ingredient in the animal feed not only brings Se supplementation but also has a direct positive effect on the meat quality of livestock products. Liu et al. (2021) found that the addition of Se-enriched yeast to the diet maintained mitochondrial redox homeostasis in chickens, inhibited reactive oxygen species (ROS)-induced cardiomyocyte apoptosis, and reduced quality loss and oxidative instability in heat-stressed hens. The addition of *Saccharomyces Cerevisiae* and organic Se to pig feed significantly increased the antioxidant capacity and milk fat content of sows, thus improving their reproductive performance and piglet weaning weight (Zhang et al. 2020). Similarly, Lv et al. (2020) found that Se-enriched yeast in

the feed improved nutrient digestibility by inducing lymphocyte activity and antioxidant enzyme expression while inhibiting and down-regulating levels of inflammation and oxidative stress in piglets. Silva et al. (2020) added sodium selenite and Se-enriched yeast to the feed of Nellore cattle and found that the meat Se content of the Se-enriched yeast group was higher than that of the sodium selenite group ($P < 0.001$), while the Se-enriched yeast did not affect the performance, carcass characteristics and quality of Nellore cattle. Wang et al. (2019) found that the addition of Se-enriched yeast was beneficial in improving antioxidant status, digestibility, and nitrogen metabolism of Tibetan sheep. In another study, the supplementation of Se-enriched yeast increased the Se content in lamb muscle compared to inorganic Se (Paiva et al. 2019). In aquaculture, Wang et al. (2018) found that the growth of rainbow trout was highly significantly and positively correlated with the expression levels of four Se-protein genes in the liver and eleven Se-protein genes in the muscle, the addition of Se-enriched yeast in the fish feed was beneficial to the growth of rainbow trout. Se-enriched yeast is also used in poultry breeding. Chickens are often challenged by heavy metal contamination and fungal infections in breeding, and ingestion of Se-enriched yeast seems to solve these problems. Wang et al. (2020) found that Cadmium (Cd) induced oxidative stress in chicken liver and activated the mitogen-activated protein kinase (MAPK) pathway, leading to liver necrosis and damage, while the intake of Se-enriched yeast inhibited oxidative stress and down-regulated its expression, thereby attenuating the damage, likewise, Ge et al. (2021) also found that Se-enriched yeast alleviated Cd-induced cardiac injury in chickens, reduced the destruction of elemental balance and the accumulation of Cd, and weakened Cd-induced inflammatory response through nuclear factor-kappa B/inhibitor of nuclear factor kappa B (NF-κB/IκB) signaling pathway. Mycotoxin contamination is also a serious problem in the breeding process. For ochratoxin A (OTA)-induced cecum injury in broilers, Se-enriched yeast inhibited NF-κB expression and increased the expression levels of tight junction-related genes Claudin-1, Occludin, and zonula occludens-1 (ZO-1) through regulating toll-like receptor 4/myeloid differentiation factor 88 (TLR4/MYD88) signaling pathway, which ultimately antagonized OTA-induced intestinal barrier damage (Yang et al. 2020). Similar results emerged from the study of Tong et al. (2020) who found that Se-enriched yeast significantly reduced the level of oxidative stress in broilers (significant increase in superoxide dismutase activity, total antioxidant capacity, and total glutathione content). A recent study has shown that Se-enriched yeast can help protect chickens from avian influenza virus attacks by enhancing the effectiveness of vaccines, suggesting that Se-enriched yeast also has adjuvant antiviral activity in poultry (Shojadoost et al. 2020). At present, Se-enriched yeast is mostly used in the feed of the livestock industry, whose ultimate purpose is to improve the quality of meat products and provide organic Se that is conducive to human absorption.

Se-enriched lactic acid bacteria and bifidobacteria

In addition to fungi, some bacteria also can enrich Se (Shang et al. 2021). Following the Se-enriched yeast, the research on Se-enriched lactic acid bacteria and Se-enriched bifidobacteria have also become a hot spot (Dawood et al. 2020; Yi et al. 2020). This type of edible bacteria is widely trusted by the public and it generally provides a good taste and tasty food experience while acting as a probiotic in fermented foods, suitable for all ages (De Filippis, Pasolli, and Ercolini 2020). From the perspective of human nutrition and body health maintenance, these bacteria are also expected to serve as a carrier of Se enrichment, and eventually, it promotes human health through Se supplementation and probiotics. Compared with yeast, lactic acid bacteria and bifidobacteria are much smaller and have less protein content and corresponding converted organic Se, however, lactic acid bacteria and bifidobacteria have their inherent advantages, which are not only reflected in the wide application of these probiotics in fermented foods, but also as the main representative products of most live bacterial preparations in health care products. In terms of physiological properties, the growth and metabolic activities of lactic acid bacteria and bifidobacteria, including the appropriate growth temperature and pH, are closer to those of the human body. The number of bacteria per unit volume can reach an ideal high density, so it can ensure a high survival rate in the harsh environment of the digestive tract. These bacteria are more likely to colonize the intestine than yeast and play an important role in maintaining intestinal flora and intestinal homeostasis (De Filippis, Pasolli, and Ercolini 2020). Presently, in the field of functional food development, the research on Se-enriched yogurt and Se-enriched beverage is intense. Palomo et al. (2014) found that selenocysteine content increased and chaperones content decreased in Se-enriched fermented yogurt compared to common fermented yogurt, suggesting that Se affects the expression level of chaperones, thus reducing the influence of stress factors on lactobacillus. Xu, Bao, et al. (2019) added 1% Se-enriched *Streptococcus thermophilus* as the starter during juice fermentation and found that the final Se content of the juice was 13 times higher than the control. Wang et al. (2021) found that co-fermentation of Se-enriched *Lactobacillus plantarum* (Lp-Se) with *pleurotus eryngii* significantly increased the Se content, total phenol content, and antioxidant activity of *pleurotus eryngii*; the lactic acid/acetic acid ratio was significantly higher. During the fermentation process, the level of umami substances such as 1-octen-3-ol was increased, which ultimately improved the overall quality of *pleurotus eryngii*. Dawood et al. (2020) added Se-enriched *Streptococcus thermophilus* and Se-enriched *Lactobacillus delbrueckii* subsp. *bulgaricus* in tilapia feed effectively improved the growth, oxidative status, and expression levels of immune-related genes in tilapia. While meeting the needs of the human body for organic Se, much and more research is turning to the field of disease prevention and treatment, and Se-enriched lactic acid bacteria and bifidobacteria have shown some potential. Yi et al. (2020) administered Se-enriched *Bifidobacterium longum* (SeBL) and

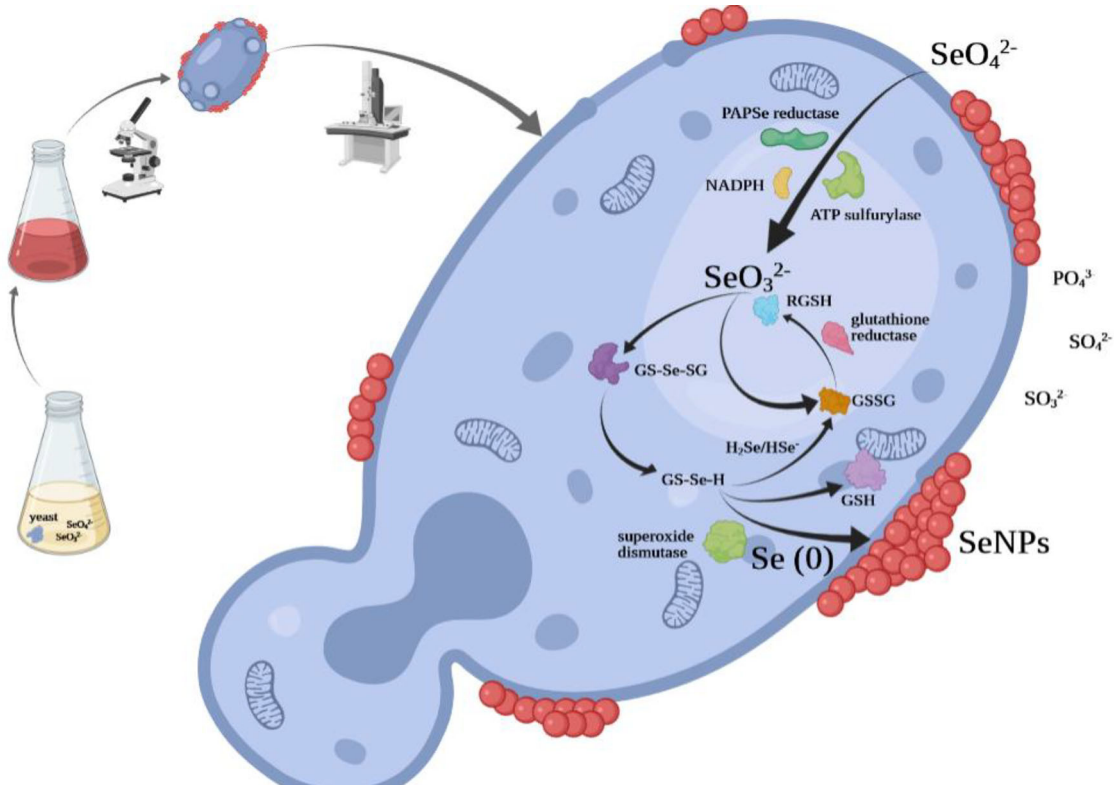

Figure 1. Se metabolism by yeast cells. GSH, glutathione; RGSH, reduced glutathione; GSSG, oxidized glutathione; GS-Se-SG, selenodiglutathione; GS-Se-H, glutathionylselenol; Se (0), elemental selenium; SeNPs, selenium nanoparticles. Created with BioRender.com.

Bifidobacterium longum (BL) to mice with liver injury, respectively, and found that both SeBL and BL inhibited lipid accumulation in mouse hepatocytes; in addition, SeBL also inhibited the oxidative stress activity of mouse hepatocytes by decreasing hepatic malondialdehyde (MDA) levels and increasing superoxide dismutase (SOD) activity. Overall, SeBL has a stronger protective effect than BL. Guo et al. (2013) combined extracellular polysaccharide (EPS) of *Lactococcus lactis* subspecies with $SeCl_2O$ to form Se-exopolysaccharide (Se-EPS) and found that Se-EPS had strong antioxidant activity both in vitro and in vivo. Both EPS and Se-EPS increased the phagocytic capacity of macrophages, spleen and thymus indices, and hemolytic complement activity (HC50), in general, Se-EPS showed stronger immunomodulatory activity than EPS. Yang et al. (2018) found that Se-enriched *Lactobacillus bulgaricus* and Se-enriched *Streptococcus thermophilus* showed stronger antagonistic effects against *Salmonella typhimurium*, *Escherichia coli*, *Staphylococcus aureus*, and *Listeria monocytogenes* than the strains without Se.

Accumulation and metabolism mechanism of selenium

The process of microbial Se enrichment is complicated. According to the enrichment site of Se, it can be divided into extracellular and intracellular (Figure 1). Yeast as a eukaryotic cell culture model has been widely used in various studies (Rai, Pandey, and Sahoo 2019). In terms of the extracellular environment, phosphodiester and sulfide bridges, mannose phosphate residues, negatively charged phosphate groups, carboxyl and hydroxyl groups on the yeast cell wall are all negatively charged functional groups that play a decisive role in the enrichment of extracellular inorganic Se (Klis et al. 2002; Kordialik-Bogacka 2011). The hydrophobicity of the cell wall surface determines the strength of biosorption, which depends mainly on the content of polysaccharides, proteins, and lipids in the yeast cell wall (Kordialik-Bogacka 2011). Polysaccharides in the cell wall, such as mannans, dextran, and chitin, weaken the permeability of exogenous inorganic Se to the interior of yeast cells while exerting adsorption capacity, with mannans being particularly prominent (Kieliszek et al. 2015). Previous studies have shown that the polysaccharide-bound Se content increases with increasing Se concentration in the culture medium (Kieliszek et al. 2015). In terms of the intracellular environment, the intracellular accumulation process of Se depends mainly on the active intracellular transport, which can overcome the impermeability of the cell membrane to Se ions. During the culture process, the different types of sugar in the medium determine the difference in the yeast Se enrichment mechanisms, which in turn determine the yeast Se enrichment content (Kieliszek et al. 2015). In the case of Se-enriched *S. cerevisiae*, it has two Se transport systems, one high affinity, and the other low affinity. Both transport systems are dependent on glucose in the culture medium, and glucose significantly increases the rate of Se uptake by yeast cells (Gharieb and Gadd 2004; Rosen and Liu 2009). It should be noted that phosphate ions, sulfate ions and exogenous amino acids in the culture medium also inhibited or promoted the Se-enrichment capacity of *S. cerevisiae* (Lazard et al. 2010). Lazard et al. (2010) found that at

low phosphate concentrations, the phosphate Pho84p and Pho89p transporters determined the binding degree of *S. cerevisiae* to selenite ions, whereas when *S. cerevisiae* was at high phosphate concentrations, the Se transporter was gradually replaced by the phosphate Pho87p, Pho90p, and Pho91p transporters (low-affinity transporters). Besides, Se concentration and Se species also affect the process of Se enrichment in yeast cells. It has been shown that yeast have better bio-enrichment properties in a culture medium containing organic Se (Perez-Corona et al. 2011). At present, the mechanism of yeast Se enrichment has been elucidated and can be summarized into four steps, first, selenate (VI) is converted to selenite (IV) by adenosine triphosphate (ATP) sulfidase, 3′-phosphoadenylyl selenate (PAPSe) reductase, and thioredoxin reductase (NADPH); second, selenite (IV) reacts with reducing glutathione (GSH) to form selenium-glutathione (GS-Se-SG) and oxidized glutathione (GSSG), the latter is then converted to reducing glutathione (GSH) by glutathione reductase; third, GS-Se-SG is transformed into glutathione selenol (GS-Se-H) in yeast cells, which is further transformed into hydrogen selenide (H_2Se/HSe^-) to form GSSG; finally, GS-Se-H is converted to elemental Se (0) and GSH, catalyzed by superoxide dismutase.

Unlike Se-enriched yeast, lactic acid bacteria and bifidobacteria are not traditional model microorganisms, and their Se enrichment mechanism remains obscure. Numerous studies have shown that bacteria accumulate and transform selenite and selenate by a variety of mechanisms (Avazeri et al. 1997; Basaglia et al. 2007). A general idea of the overall process of Se enrichment in bacteria through the studies of some Se-enriched bacteria such as *Thauera selenatis*, *Escherichia coli*, *Bacillus mycoides*, and *Stenotrophomonas maltophilia*. Firstly, selenate or selenite is transported into the bacterial cell, probably through sulfate permeases (Aguilar-Barajas et al. 2011); also, a nonspecific and inefficient anion transport system can transport sulfate, selenate, and selenite, but the relevant transporters have not been identified (Aguilar-Barajas et al. 2011), *E. coli* can also use sulfate permease for intracellular transport of selenite (Rosen and Liu 2009). Secondly, the reduction of these Se oxyanions in bacterial cells, one of which is by dissimilation of selenate and selenite, resulting in Se^0, catalyzed by anaerobic microorganisms in anaerobic sediments (Oremland et al. 2004). Oremland et al. (2004) found that *Sulfurospirillum barnesii*, *Bacillus selenitireducens*, and *Selenihalanaerobacter shriftii* could transform selenate or selenite into extracellular stable and homogeneous Se^0 spherical particles (diameter 300 nm) with monoclinic crystalline structures; Se^0 also was intracellularly enriched with nitrate as an electron acceptor, forming extracellular selenium nanoparticles (SeNPs) with the reduction effect of first growing cells. In fact, there have been many controversies about the mechanism of selenite reduction in bacterial cells. Intracellular thiol compounds and glutathione play an important role in selenite reduction (Debieux et al. 2011; Ridley et al. 2006; Turner, Weiner, and Taylor 1998). Kessi and Hanselmann (2004) found that selenite and thiol groups exhibit high reactivity in the reduction process by *Rhodospirillum rubrum* and *Escherichia coli*, and this was accompanied by the production of Se-digluthathione intermediate, which is followed by the production of Se^0, selenodisulphides (RS-Se-SR) was an important product during the reduction process, and glutathione (GSH) plays an important role in the reaction (Harrison, Ceri, and Turner 2007). In general, selenite can be reduced to Se^0 by bacterial nitrate/nitrite reductase and sulfhydryl groups of peptides or proteins. Multiple mechanisms may be involved in the reduction process and need further investigation. Thirdly, a portion of Se^0 is transported outside the cell through the cell membrane for further transformation of SeNPs, which occurs only in the context of intracellular reduction and extracellular assembly. Finally, the assembly of SeNPs. Considerable research has been done at this stage, but it is not entirely clear how exactly SeNPs are assembled. It has been suggested that the process of bacterial transformation and assembly of SeNPs might involve the Ostwald ripening mechanism (Lampis et al. 2014; Zhang et al. 2011) and that these small particles of original size SeNPs can aggregate to produce larger size SeNPs (Kessi and Hanselmann 2004). Overall, there are four main steps to determine the mechanism of bacterial Se enrichment (Figure 2). (1) selenate and selenite are transported into the cell under the action of sulfate permeability enzyme, (2) then anaerobic microorganisms in the anaerobic matrix produce Se^0 through the dissimilation (respiration) of selenate and selenite. After that, (3) Se^0 nuclei are sent out of the cell; finally, (4) these elemental Se^0 are equipped as SeNPs. Of these, step 2 and step 4 are always exist, and the presence of step 1 and step 3 depends on the location of step 2 and step 4, namely intracellular, periplasmic or extracellular.

Species of selenium transformed by probiotics

Selenium nanoparticles

Selenium nanoparticles (SeNPs) are one of the most significant phenotypic characteristics of Se-enriched probiotics. Under the scanning electron microscope, numerous nanomorphal spheres are visible on the cell surface of Se-enriched bacteria, while the biomass of Se-enriched bacteria is visible as red or light red to the naked eye. This is also a direct manifestation of the macroscopic effect of the accumulation of many nano-sized spheres. SeNPs are involved in the synthesis of various antioxidant proteins, such as glutathione peroxidase (Sakr, Korany, and Katti 2018), and thus have antagonistic effects on many diseases caused by oxidative stress, such as arthritis, tumors, and cardio-brain diseases (Malhotra et al. 2016; Yang, Li, et al. 2017). In the treatment of metabolic diseases, SeNPs alleviated and treated streptozotocin (STZ)-induced diabetic rats, reduced blood sugar, increased insulin levels in the pancreas and plasma, and restored damaged pancreatic tissue (El-Borady et al. 2020). SeNPs have better antioxidant and antitumor activity compared to other forms of Se (Li and Xu 2020). Especially in the field of tumor therapy, SeNPs have a dual synergistic effect of providing therapeutic vectors and enhancing anticancer activity, showing good tumor prevention and

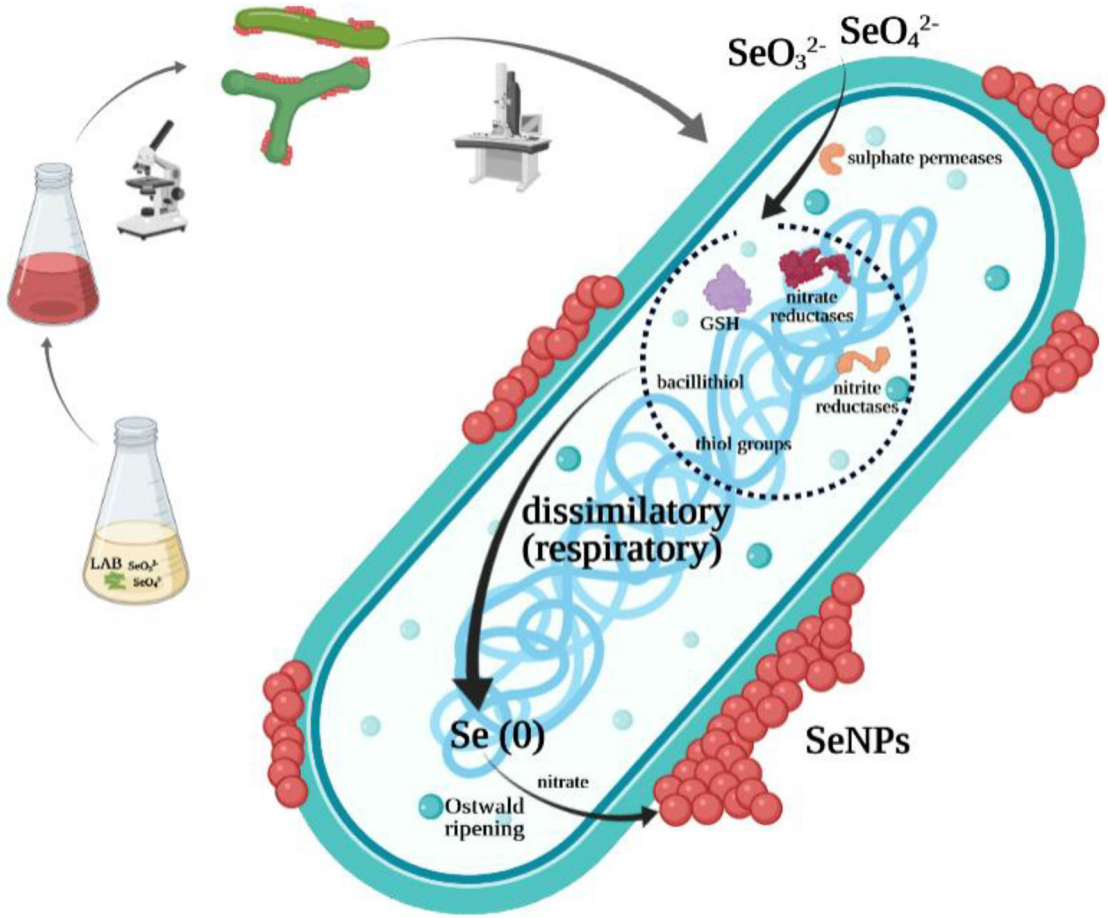

Figure 2. Se metabolism by bacterial cells. GSH, glutathione; Se (0), elemental selenium; SeNPs, selenium nanoparticles. Created with BioRender.com.

treatment functions (Li and Xu 2020; Liu et al. 2012), and their anticancer mechanisms mainly include cell cycle arrest, antioxidation, apoptosis, and interruption of the cell signaling pathway (Huang et al. 2013; Luo et al. 2012). Besides, SeNPs specialize in fighting bacteria and fungi (Dutta, Nenavathu, and Talukdar 2014; Mojtaba Shakibaie, Mohazab, and Mousavi 2015). In terms of particle size, SeNPs have high degradability, low toxicity, and can be gradually removed by the human body, which is expected to become a new nutritional supplement (Sakr, Korany, and Katti 2018). The size of nanoparticles plays an important role in cellular processing, and therefore, the size of nanoparticles also determines the extent of their retention and removal in vivo and the specific mode of action (Chaudhary, Umar, and Mehta 2014). In general, nanoparticles smaller than 10 nm are quickly removed from the body through the kidney, particles with a particle size of 10–150 nm are isolated in the bone marrow, particles larger than 200 nm participate in the splenic space, and particles smaller than 500 nm can remain in the body for a long time and eventually be eliminated through the slow clearance of the liver, particles larger than 500 nm can be removed by macrophages and monocytes of the reticuloendothelial system (RES) (Sakr, Korany, and Katti 2018). In animal experiments, the median lethal dose (LD50) of SeNPs for mice was 113 mg Se/kg and 15 mg Se/kg for sodium selenite (Li and Xu 2020). Wang, Zhang, and Yu (2007) found that the LD50 of selenomethionine in mice was 92.1 mg Se/kg, and the LD50 of SeNPs was 25.6 mg Se/kg. In terms of bioavailability and toxicity, SeNPs are highly biocompatible and biodegradable in vivo, with lower toxicity than sodium selenite and some selenoproteins.

SeNPs are also common products of other Se-enriched microorganisms, including bacteria, fungi, and molds (Bierla et al. 2018; Hu et al. 2019; Tugarova and Kamnev 2017). Microbially synthesized SeNPs are different from those of physicochemical methods in that microbially synthesized SeNPs generally contain proteins related to the assembly and stability of SeNPs (Debieux et al. 2011). It should be noted that the particle size of the SeNPs transformed by different microorganisms varies greatly. Table 1 gives some information on the SeNPs produced by Se-enriched probiotics. Yeast, lactic acid bacteria, and bifidobacteria produce SeNPs of different particle sizes, varying widely from a few nm to several hundred nm, by adsorption, reduction, and metabolism of inorganic Se (selenate or selenite). This phenomenon may be closely related to the role of different enzymes in the process of dissimilation reduction of different microorganisms (Oremland et al. 2004). However, there is still a lack of comprehensive investigations on the SeNPs generated by Se-enriched microorganisms, and particle size heterogeneity is one of them. SeNPs derived from Se-enriched yeast, lactic acid bacteria, and bifidobacteria have demonstrated outstanding biological activities in several

Table 1. Characteristics of SeNPs produced by probiotics.

Microorganism	Precursor	SeNPs bioactivity	Size	References
Saccharomyces cerevisiae MTCC 36	Na_2SeO_3	Significant antimicrobial activity against *Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumonia*, *Salmonella typhimurium*, *Staphylococcus aureus*, and *Bacillus subtilis*	30–100 nm	(Hariharan et al. 2012)
Candida utilis ATCC 9950	Na_2SeO_3	Antioxidant activity	20–30 nm	(Kieliszek et al. 2020)
Saccharomyces cerevisiae	Na_2SeO_3	Antioxidants or antimicrobial agents	4–250 nm	(Alvarez-Fernandez Garcia et al. 2020)
Yarrowia lipolytica NCIM 3589	Na_2SeO_3	Protect Artemia salina against *Vibrio harveyi* infections	30–60 nm	(Hamza et al. 2017)
Saccharomyces cerevisiae	Na_2SeO_3	Antioxidant activity	75–709 nm	(Faramarzi, Anzabi, and Jafarizadeh-Malmiri 2020)
Magnusiomyces ingens LH-F1	SeO_2	Inhibit *Arthrobacter* sp. W1 (Gram positive)	70–90 nm	(Lian et al. 2019)
Lactobacillus acidophilus NCDC 15	Na_2SeO_3	N/A	15–50 nm	(Visha et al. 2015)
Lactobacillus acidophilus	Na_2SeO_3	Against five different sensitive and resistant bacterial strains (*Escherichia coli*, *Staphylococcus aureus*, *Bacillus subtilis*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*); significantly degrade bacterial biofilm	2–15 nm	(Alam et al. 2019)
Lactobacillus acidophilus CRL 636 *Lactobacillus bulgaricus* CRL 656 *Lactobacillus reuteri* CRL 1101	Na_2SeO_3	N/A	176 ± 13 nm 160 ± 24 nm 130 ± 23 nm	(Moreno-Martin et al. 2017)
Lactobacillus plantarum ATCC 8014	SeO_2	Induce an efficient immune response through the elevation of the pro-inflammatory cytokines IFN-γ, TNF-α, and IL-2 levels and increase NK cell activity.	$<$250 nm	(Yazdi et al. 2012)
Lactobacillus casei *Bifidobacterium sp.* *Lactobacillus acidophilus*	$NaHSeO_3$	N/A	50–500 nm 400–500 nm 50–500 nm	(Sasidharan and Balakrishnaraja 2014)
Lactobacillus bulgaricus	Na_2SeO_3	Elevate the contents of essential elements including P, Mg, Mn, Zn, Ca, and total amino acids	$\leq$180 nm	(Xia, Chen, and Liang 2007)
Lactobacillus brevis	SeO_2	Cause more efficient immune responses in vivo and reduced the liver metastasis in metastatic form of mouse breast cancer	N/A	(Yazdi et al. 2013)
Lactobacillus casei ATCC 393	Na_2SeO_3	Possess significant antioxidant and anticancer activities in vitro; can protect the intestinal barrier function against oxidative damage via Nrf2-mediated signaling pathway; an increase of ROS reduced ATP and MMP, and maintain intestinal epithelial permeability in NCM460 cells challenged by H_2O_2; Protective effects on intestinal barrier dysfunction caused by enterotoxigenic *Escherichia coli* K88	50–80 nm	(Qiao et al. 2020; Xu, Qiao et al. 2018; Xu, Qiao, Ma, Yan et al. 2019; Xu, Guo, et al. 2018; Xu, Bao, et al. 2019)
Lactococcus lactis NZ9000	Na_2SeO_3	protect intestinal epithelial cells against H_2O_2 and ETEC K88-caused injury and maintains the intestinal epithelial barrier integrity by exerting antioxidative and anti-inflammatory activities	38–152 nm	(Xu, Qiao, Ma, Guo et al. 2019; Xu, Bao, et al. 2019)
Lactobacillus acidophilus CRL 636 *Lactobacillus reuteri* CRL 1101	Na_2SeO_3	Se-enriched *L. reuteri* CRL 1101 exert strong resistant in the presence of bile salts	25–370 nm	(Pescuma et al. 2017)
Lactococcus lactis CRL 2011 *Lactobacillus brevis* CRL 2051 *Lactobacillus plantarum* CRL 2030	Na_2SeO_3	N/A	125–155 nm 56–66 nm 58–70 nm	(Martinez et al. 2020)
Lactobacillus acidophilus Lactobacillus plantarum Lactobacillus rhamnosus	Na_2SeO_3	exhibit a significant antimicrobial activity against pathogenic fungi	20–150 nm	(Rajasree and Gayathri 2015)

in vitro and in vivo experiments, including antioxidant and antibacterial activities, and new evidence also suggests that Se-enriched probiotics and their SeNPs have excellent performance in immune regulation, tumor and inflammation response (Xu, Guo, et al. 2018). Notably, whether the prominent bioactivity of SeNPs produced by these Se-enriched probiotics is directly related to their particle size or their underlying regularity has not been revealed. Huang et al. (2003) mixed different concentrations of bovine serum albumin with sodium selenite to produce SeNPs of three sizes: large, medium, and small. By testing the free radical scavenging rate of these SeNPs, it was found that the smaller the diameter, the higher the scavenging rate, that is, the scavenging rate of SeNPs on free radicals is size-dependent. Whether this characteristic pattern also exists in SeNPs produced by Se-enriched probiotics is still unknown, which needs further investigation. Antimicrobial activity is one of the most studied characteristics of Se-enriched probiotics, which is closely related to SeNPs. In some studies, Se-enriched probiotics have shown stronger antimicrobial activity than non-Se-enriched strains, which may also be due to the role of SeNPs (Yang et al. 2018).

Other selenium speciation

In addition to the large amounts of SeNPs secreted on the outer surface of the cells, there are also hundreds of selenocompounds in Se-enriched probiotic intracellular, and their biological properties and concentration ratios are different, mainly influenced by the test method (Bierla et al. 2018; Gilbert-Lopez et al. 2017; Tugarova and Kamnev 2017). There are five highly active Se metabolite precursors in Se-enriched yeast, which have low molecular weights, including selenocysteine (SeCys), selenohomocysteine (SeHCys), selenoglutathione (SeGlu), methylselenol (CH_3SeH), selenoadenosine (Bierla et al. 2012). SeCys is the core substance of 25 common and very important selenoproteins (Kryukov et al. 2003). Under certain conditions, the selenoprotein formed by the insertion of SeCys is mainly specified by the UGA codon in the mRNA (Kryukov et al. 2003), when the supply of Se is insufficient, the body preferentially synthesize this type of selenoprotein (Reeves and Hoffmann 2009). Single nucleotide polymorphisms (SNPs) in selenoprotein genes have important effects on disease risk and mortality and are critical for human health (Rayman 2009). In addition, selenoproteins include a series of antioxidant enzymes such as glutathione peroxidase, glutathione reductase, thioredoxin reductase, and glutathione S-transferase, the activities of which are significantly increased in Se-enriched yeast (Kieliszek et al. 2020). Selenomethionine (SeMet) is considered to be another very important basic selenoprotein in Se-enriched yeast, which can be nonspecific binding to body proteins to replace methionine. And it has high bioavailability and is the most easily absorbed selenoprotein (Rayman 2008). Several studies have shown that SeMet can account for more than 90% of the total Se content in yeast cells (Gharieb and Gadd 2004; Rayman 2012; Schrauzer 2000; Tapiero, Townsend, and Tew 2003), but individual differences exist. For example, the proportion of SeMet in Se-enriched *Saccharomyces Cerevisiae* was over 60% (Bierla et al. 2018), while the proportion of SeMet in Se-enriched *Candida Utilis* ATCC 9950 was only 10% (Kieliszek et al. 2020). Biological activity tests have shown that SeMet had antioxidant properties and it improved immunity and stimulated DNA repair enzyme activity (Laffon et al. 2010). In the process of Se enrichment in yeast, inorganic Se enters yeast cells and undergoes a series of physicochemical reactions to produce hydrogen selenide (Kieliszek et al. 2015), which is metabolized under the action of homocysteine synthase to form selenohomocysteine (SeHCys). In the presence of homocysteine methyltransferase, SeHCys can be further converted to selenocystathionine or SeMet. SeMet can be transformed into the oxidized form of Se-adenosylselenomethionine (SeAM) by S-adenozylomethionine synthase under aerobic conditions, and further methylated to form adenosyl homo-seleno cysteine (SeAHCys) and being released. These compounds can be reformed (SeHCys) under hydrolysis. Also, SeMet can be converted to SeCys catalyzed by the cystathionine γ-lyase enzyme, and then SeCys can be converted to seleno-methyl selenocysteine (SeMeCys) and S-adenosilhomo-selenocysteine by reaction with S-adenosylmethionine (SAM) in the presence of selenomethyltransferase (SMT), Se-methylselenocysteine can be converted to γ-glutamyl-se-methyl cysteine; next, SeCys are integrated into yeast intracellular proteins via a specific Sec-tRNA^{Sec} complex. In addition, there are other Se compounds in Se-enriched yeast cells, such as selenocystationine, Se-methylselenocysteine, and γ-glutamyl-Se-methylselenocysteine, among which Se-methylselenocysteine and γ-glutamyl-Se-methylselenocysteine have anticancer activity, especially for human and animals. Se-methylselenocysteine and γ-glutamyl-Se-methylselenocysteine can be converted to methylselenol which has strong anticancer activity (CH_3SeH) (Rayman 2008; Schrauzer 2000).

In Se-enriched lactic acid bacteria and bifidobacteria, SeCys and SeMet are important representatives of selenoproteins (Castañeda-Ovando et al. 2019; Lee et al. 2019; Pescuma et al. 2017), especially SeCys is also the main selenoprotein in Se-enriched yogurt (Palomo et al. 2014). Similar to Se-enriched yeast, the contents of SeCys and SeMet in different Se-enriched lactic acid bacteria also differed. Pescuma et al. (2017) added inorganic Se to the medium of *Lactobacillus acidophilus* CRL636 and *Lactobacillus reuteri* CRL1101 and found that SeCys and SeMet were formed in the cells of both strains, among which, CRL1101 having significantly higher levels of SeCys and SeMet than CRL636. Zhang et al. (2009) found that SeMet was the major selenoprotein in Se-enriched *Bifidobacterium animalis* 01. Gomez-Gomez et al. (2019) identified selenoproteins (mainly SeCys) related enzymes, including cystathione beta-lyase, thioredoxine reductase, and NAD/FAD oxidoreductase, which are highly expressed in Se-enriched *Lactobacillus reuteri* CRL 1101 to protect the host from oxidative damage. Xia, Chen, and Liang (2007) found that after being enriched with Se, the total amount of essential elements P, Mg, Mn, Zn, Ca, and amino acids were significantly increased in *Lactobacillus bulgaricus* cells. However, data on Se species in Se-enriched lactic acid bacteria and bifidobacteria cells are scarce, and the biological activities of related selenoproteins need to be further explored and functionally verified.

Factors affecting the selenium-enrichment capacity of probiotics

Effect of inorganic selenium concentration on the growth

There is no doubt that the type of Se (e.g., Na_2SeO_3 and Na_2SeO_4) and the concentration of Se in the external culture environment have an absolute influence on the Se enrichment process and the final Se content during the preparation of Se-enriched probiotics. Kieliszek and Dourou (2020) found that 10 mg/L of Na_2SeO_3 in the culture medium had negative effects on the yield and the total lipid accumulation of two *Yarrowia lipolytica* strains, and significantly altered yeast cells morphology and the intracellular lipid droplets sizes and distributions, which may be caused by selenite stress conditions, thus, causing metabolic disorder in yeast cells and affecting the quality, lipid content, and morphology of yeast cells, however, the high

concentrations of Se inhibited yeast growth and caused oxidative stress (Kieliszek et al. 2019). Another study found that sodium selenite at different concentrations (10, 20, 40, 60 mg/L) inhibited the growth of *Saccharomyces cerevisiae* MYA-2200 and *Candida utilis* ATCC 9950, whereas *Candida utilis* ATCC 9950 was highly resistant at 10 mg/L of Na_2SeO_3, and it could reach the highest biomass yield (Kieliszek, Błażejak, and Płaczek 2016), but with increasing Na_2SeO_3 concentration (over 30 mg/L), the growth of *Candida utilis* ATCC 9950 was significantly inhibited (Kieliszek et al. 2020). Zhang et al. (2019) found that 15 mg/L Na_2SeO_3 inhibited the growth of *Candida utilis* CCTCC M 209298, but increased the intracellular glutathione biosynthesis and exocytosis levels. Golubev and Golubev (2002) found that the degree of tolerance to inorganic Se varied considerably among yeasts. Genera such as *Candida Maltosa*, *Hanseniaspora Valbyensis*, *Kluyveromyces Marxianus*, *Yarrowia Lipolytica*, *Cryptococcus Curvatus*, *Cryptococcus Humicola* were more resistant to high concentrations of Na_2SeO_4 (0.1 mol/L), on the contrary, genera such as *Dekkera*, *Schizosaccharomyces*, *Bullera*, *Cryptococcus*, and *Holtermannia* showed poor Se tolerance. The same phenomenon was observed in Se-enriched lactic acid bacteria and bifidobacteria. Palomo-Siguero et al. (2016) found that *Lactobacillus bulgaricus* LB-12 grew normally in medium containing 1 mg/L Na_2SeO_3, but was significantly inhibited when the concentration reached 10 mg/L. Zhang et al. (2009) found that the concentration of Na_2SeO_3 over 10 mg/L significantly inhibited the growth of *Bifidobacterium animalis* 01. Xu, Bao, et al. (2019) tested the Se tolerance (0–20 μg/mL Na_2SeO_3) of *Lactobacillus plantarum*, *Streptococcus thermophilus*, and *Bifidobacterium breve*, and found that *L. plantarum* growth was inhibited at any concentration of Na_2SeO_3. *S. thermophilus* grew well at the concentration of 0 to 16 μg/mL after 12 h of fermentation, but began to be inhibited after more than 16 μg/mL. After 18 h of fermentation, *B. breve* grew well at concentrations ranging from 0 to 8 μg/mL, but its growth began to be inhibited when the concentration exceeded 8 μg/mL. However, some probiotics are more resistant to Se. In the study of Mörschbächer et al. (2018), Na_2SeO_3 concentrations of 30 or 60 mg/L did not affect the growth of several Lactobacillus strains. Pusztahelyi et al. (2015) found that Se-resistant *Lactococcus lactis* ssp. *lactis* R703, *Bifidobacterium animalis* ssp. *lactis* BB12, *Lactobacillus casei* 431 were able to tolerate high concentrations of $NaHSeO_3$, especially BB12, this strain still grew well at 1000 mg/L $NaHSeO_3$. It should be seen that the concentration of inorganic Se in the culture medium directly affects the growth and biomass accumulation of probiotics, and these factors ultimately affect the amount and rate of Se enrichment of strains.

Other factors

When the concentration of sodium selenite was 20 mg/L and the culture temperature was 28 °C, the Se content of *C. utilis* ATCC 9950 biomass increased and then decreased with the initial pH value, and it reached the peak at pH = 5; meanwhile, the sulfate and phosphate anions in the culture medium significantly weakened the Se enrichment capacity of *C. utilis* ATCC 9950, but carbonate and biocele anions did not affect (Kieliszek et al. 2018). Xu et al. (2020) found in a single-factor experiment that sodium chloride concentration below 8% significantly enhanced the Se-enrichment capacity of *Lactobacillus rhamnosus* ATCC 53103, while the total Se-enrichment content of *L. rhamnosus* ATCC 53103 decreased significantly when the sodium chloride concentration was higher than 8%; the pH test was further carried out and it was found that the total Se enrichment content increased with the increase of pH value. The Se content of the strain reached a peak when the pH reached 6, and then began to decrease as the pH continued to rise; in the temperature test, the total Se content of this strain reached its peak at 37 °C with the increase of temperature, and then began to decrease; finally, under the optimal conditions (8% salt concentration, culture at pH 6.5 and 37 °C), this strain achieved the optimal Se enrichment rate of 65.35%. Yang, Li, et al. (2017) tested the Se enrichment rates of *Lactobacillus delbrueckii* ssp. *bulgaricus* (Lb) and *Streptococcus thermophilus* (St) under different culture conditions and the results of the single-factor experiment showed that the Se enrichment rates of both strains were the highest when the initial pH reached 6. In the inoculation dose test, 8% Lb and 6% St reached the maximum Se enrichment rate. In the temperature test, the maximum Se enrichment rates were achieved at 35 °C and 40 °C for Lb and St, respectively. Finally, under the optimized conditions, the Se enrichment rates of Lb (6.73% inoculum doses, culture at pH 5.96 and 33.24 °C) and St (6% inoculum doses, culture at pH 6.37 and 40 °C) reached 94.34% and 97.05%, respectively. Overall, the Se concentration in the culture environment, the biomass of the bacteria, and the types of strains are the key factors that determine the Se enrichment content and the enrichment rate during the process of Se enrichment of probiotics. Factors such as temperature, pH, incubation time and inoculum amount also affect the final results. In the process of preparing Se-enriched probiotics, more considerations should be given from the dual perspectives of Se enrichment and Se enrichment rate, and the ultimate goal should be clarified, and then various influencing factors should be optimized and regulated to obtain the desired product.

Characteristics and application of selenium-enriched probiotics

Se-enriched yeast, Se-enriched lactic acid bacteria, and Se-enriched bifidobacteria can provide the essential Se element for the human body, which is the biggest feature and application value of Se-enriched probiotics. Compared with physical and chemical methods to produce Se, this biological Se enrichment method can produce more organic Se, which is conducive to the digestion and absorption of the human body, with high safety and high nutritional value, and as a food additive or dietary supplements, it is suitable for the promotion and application of Se deficiency areas. However,

the probiotics themselves can produce some characteristic changes during the Se enrichment process, and these changes endue the Se-enriched probiotics more functional properties compared with the ordinary probiotics, not only as Se supplements but also with more functional food possibilities in functional food, health care products and medicine fields.

Se-enriched probiotics showed good resistance in a harsh environment. Martinez et al. found that there was no difference in the growth of Se-enriched or non-Se-enriched *Lactobacillus brevis* CRL 2051 and *Fructobacillus tropaeoli* CRL 2034 in fruit juice milk (FJM) beverage (Martinez et al. 2019). Shakibaie et al. (2017) isolated a Se-enriched *Lactobacillus brevis* LSe from the traditional Iranian dairy product Spar. This strain was able to tolerate high concentrations of sodium selenite (3.16 mM), with no significant differences in survival rate under a low pH environment at different periods. In addition, the adhesion ability of LSe to Caco-2 cells was similar to that of the control strain *Lactobacillus plantarum*, indicating that Se enrichment does not affect some inherent biological activities of probiotics. Saini and Tomar (2017) found that *Lactobacillus fermentum* NCDC77 (S8) and *Lactobacillus fermentum* (S23) had a high Se enrichment capacity and were more resistant to low pH and bile. In addition, these Se-enriched strains had good adhesion and self-polymerization properties, and low resistance to antibiotics. Pescuma et al. (2017) found that the growth rate of Se-enriched *Lactobacillus reuteri* CRL1101 was slightly lower than that of non-Se-enriched strains, but their bile salt tolerance was enhanced and intracellular selenoprotein content was significantly increased. Notably, Se-enriched probiotics have excellent antioxidant activity (Guo, Guo, and Liu 2020; Yang, Li, et al. 2017), not just due to SeNPs have strong antioxidant properties but part of the main reason is that bacteria inside the cells of antioxidant enzymes such as glutathione peroxidase and glutathione reductase, and thioredoxin reductase activity improved significantly (Kieliszek et al. 2020). Guo, Guo, and Liu (2020) found that Se-enriched peptides in Se-enriched yeast had high antioxidant activity, significantly reducing MDA levels in the liver and serum of mice, and enhancing the glutathione peroxidase (GPx) activity. In addition, these Se-enriched peptides applied to the dorsal skin of mice effectively alleviated ultraviolet B (UVB) radiation-induced skin damage and oxidative stress by increasing GPx, catalase activity, and glutathione content in the skin or serum. The application of antimicrobial activity, including antibacterial, fungus, etc., Se-enriched probiotics exhibited antagonistic activity against a variety of pathogenic microorganisms (Yang et al. 2018) and more effective compared to the non-Se-enriched parental strains, which may result from the influence of SeNPs or specific selenoproteins, or a combination of both. In addition, the enrichment process of Se may also affect the activity of probiotics metabolites, including extracellular polysaccharides, bacteriocins, antimicrobial peptides, organic acids, and other substances. However, the underlying reasons need to be further explored and revealed.

Although the overall characteristics of Se-enriched probiotics have not been fully understood, at least in animals, Se-enriched probiotics have shown good effects. As a feed additive, Se-enriched probiotics have demonstrated the desired Se-supplementing effects and other highly effective biological activities, and importantly, their safety has been widely recognized. On the one hand, Se-enriched probiotics can increase the content of organic Se in animal products, on the other hand, they can exert positive biological activities on the animal body itself, including antibacterial, fungi, antivirus, antioxidant, immune regulation, etc (Dawood et al. 2020; Lee et al. 2019; Liu et al. 2021; Lv et al. 2020), and this has brought great convenience to animal husbandry and poultry breeding and saved the cost of disease prevention. In the food industry, Se-enriched probiotics are often used as food additives or starters to co-ferment with a variety of foods to produce functional Se-enriched foods, thus achieving the purpose of Se supplementation (Bierla et al. 2018; Xu, Bao, et al. 2019; Zhou et al. 2021). In addition, specific Se-enriched probiotics can also strongly antagonize a variety of food-borne pathogenic microorganisms (Yang et al. 2018), thus avoiding microbial contamination and prolonging the shelf life of food. It is expected that Se-enriched probiotics are also beginning to show great potential in the medical field. Especially in the field of cancer treatment, SeNPs and some selenoproteins be effective in disease prevention and treatment (Li and Xu 2020; Sakr, Korany, and Katti 2018). In tumor radiation therapy, selenoproteins play an important role in radiation-induced ROS damage, DNA damage repair, and cytokine control; a continued Se supplementation significantly improved the patient's physical condition and reduced the adverse effects of radiotherapy without compromising the efficacy (Handa et al. 2020). Interestingly, probiotics showed similar beneficial effects on some toxicity associated with radiation therapy, helping to mitigate damage while improving overall efficacy (Mego et al. 2013). Recent clinical data found that specific probiotics combined with immune checkpoint blockade (ICB) performed well in tumor immunotherapy (Lee et al. 2021; Si et al. 2021). While these data are encouraging, there is limited evidence to support the use of probiotics as adjuncts to anti-cancer therapies, and further confirmation of their true role and actual effectiveness is needed. Theoretically, Se-enriched probiotics have various functions such as SeNPs, selenoproteins, and probiotics. In clinical disease prevention and treatment, one plus one may be more than two (Se and probiotics). At present, only a small amount of in vitro and animal experiments confirmed the Se-enriched probiotics have prominent biological activity, providing higher bioavailability of organic Se along with other activities. However, the actual effect and the mechanism of action of Se-enriched probiotics in the medical field needs to be verified by more basic research and clinical and preclinical trials.

Conclusions

Endemic Se deficiency is a worldwide nutritional problem and Se supplementation is a top priority. The rise of Se-enriched probiotics first needs to achieve this goal.

Compared with traditional physical and chemical methods, the biological Se-enriched method is safer and more economical. It is known that many organisms are capable of enriching inorganic Se and transforming it to organic forms, in addition to several recognized probiotics mentioned in this review, including *Bacillus subtilis* (Shang et al. 2021), *Escherichia coli* (Moreno-Martin et al. 2021), *Staphylococcus aureus* (Moreno-Martin et al. 2021), *Trichoderma harzianum* (Hu et al. 2019), *Chlorella vulgaris* (Vu et al. 2019). However, probiotics have inherent advantages over other microorganisms, including recognized safety, a long history of consumption, high public acceptance, and promotion of human gastrointestinal motility. Therefore, probiotics are most suitable as Se-enriched carriers. At present, Se-enriched probiotics have made great achievements in the field of food and health products. With the increasingly prominent role of Se-enriched probiotics in antiviral, antibacterial, antioxidant, antitumor and immunomodulation, these Se-enriched probiotics will also have a great potential in the future medical field.

However, there are still some key issues that need to be addressed for Se-enriched probiotics. In terms of the key points and difficulties in the preparation of Se-enriched probiotics, the balance between Se enrichment rate, Se enrichment amount, and probiotics activity needs to be clarified. In the future development of functional foods, nutraceuticals, or adjuvant pharmaceutical preparations, Se-enriched probiotics should not only be satisfied with a single supplement of Se, but it should also be considered to bring more biological functions, and the activity and life cycle of probiotics are the basis to ensure their biological functions. High concentrations of inorganic Se may lead to a shift in the Se enrichment process of probiotics from physiological enrichment to pathological enrichment, and thereby these strains may be destroyed and inactivated when high levels of Se enrichment or Se enrichment are obtained. Therefore, it is of greater significance to prepare Se-enriched probiotics under the premise of ensuring both Se-enriched amount and the survival rate of probiotics. In terms of supplementing with high-value organic Se, the selenoproteins produced by Se-enriched probiotics should be refined and specified in order to target the production of more needed and nutritionally valuable Se compounds, such as by adding serine to the culture medium, which can lead to more selenocysteine production by *Streptococcus thermophilus* (Castañeda-Ovando et al. 2019), and the biological function of each selenoprotein needs further validation. In terms of potential applications in the biomedical field, the medicinal activity of Se-enriched probiotics should be gradually overtaken from pre-clinical exploratory studies to the clinic to verify their real efficacy.

In summary, Se-enriched probiotics have been proven to have outstanding efficacy and great application value in animal feed, food as well as health products. Meanwhile, the great potential value of Se-enriched probiotics in biopharmaceuticals deserves further comprehensive exploration and development.

Disclosure statement

The authors declare no conflict of interest.

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