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Review

Microbial metabolites in fermented food products and their potential benefits

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Abstract

Fermented food products are unique, and their consideration and consumption rates have significantly increased as they have various functional properties which include beneficial health activities to the consumers. Fermented food products contain a plethora of microbial metabolites. Microorganisms are the key factors that determine the characteristics of the food and metabolites produced during fermentation. The major microbial metabolites are enzymes, amino acids, bacteriocins, organic acids, pigments, bioactive compounds (polyphenolics, alkaloids, and antibiotics), and vitamins that enhance the sensorial and nutritional quality of fermented foods. Furthermore, the metabolites possess various probiotic, antioxidant, and antimicrobial activities, and also help control multiple acute and chronic diseases including cancers, cardiovascular diseases, allergies, diabetes, and gastrointestinal disorders. Therefore, the present review elaborates the microbial metabolites of various fermented food products and their functional properties, as well as their impacts on consumers' health.

Introduction

Fermentation is an ancient technique primarily used to preserve food for an extended period, and also to enhance the organoleptic characteristics and functional properties of the food. The term "fermentation" comes from the Latin word meaning "natural decomposition". Fermentation involves the conversion of complex organic substances into simpler compounds catalysed by the actions of microorganisms, which are either naturally occurring or artificially added by inoculation (Steinkraus, 1983). In short, fermentation is a biochemical metabolic process on the organic compounds subjected to various hydrolysis (catabolism) and synthesis (anabolism) processes by the microorganisms (Nigam, 2013). Microbial fermentation is essential to the environment for recycling, and also necessary for human life as it carries lots of primary nutrients. Microorganisms fall in a broad spectrum, with those beneficial for consumers generally considered as suitable microorganisms, while the others are regarded as spoilers and pathogens potentially leading to significant adverse effects such as food spoilage or food poisoning, respectively. Fermented foods may or may not include live microorganisms. Live microorganisms are generally recognised as probiotics which could provide significant health benefits (Fijan, 2014). Fermented dairy products are the primary food type with live organisms. Several food safety organisations have required for a minimum of 10^6 to 10^8 CFU/g to be stated on the label informing that the foodstuff has live cultures.

The collective groups of microorganisms involved in fermentation are bacteria, yeasts, and moulds. *Lactobacillus*, *Acetobacter*, *Saccharomyces*, and *Penicillium* are the prevailing microbial species utilised in food fermentation (Anal, 2019). Among these groups of microorganisms, the majority of the foodstuffs are fermented by yeasts, followed by bacteria, and then moulds. Yeasts have an essential job in the food industry as they produce enzymes that catalyse various biochemical reactions during fermentation, hence the qualities of fermented beverages and bakery products could be increased.

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Factually, almost any sort of raw food material can be fermented. The attributes of that specific fermented food are due to the significant impacts by the source of raw materials as well as by the microorganisms utilised in the fermentation. Furthermore, the fermenting conditions, including the medium, temperature, and type of fermentation, play crucial roles to the outcome of the fermented products. Around the world, fermented products, either alcoholic or non-alcoholic, have a wide range of consumers appreciating the remarkable sensorial attributes these product exhibit (Baschali *et al*., 2017).

Apart from the taste of the fermented foods, recent advancements in identifying the metabolites produced during fermentation have generated broad interest as these can provide several health benefits to the consumers (Behera *et al.*, 2018). The biochemical reactions performed by a living cell are referred to as its metabolism. The microbial cell metabolism includes substrate oxidation and the dissimilation reaction, which break down organic substances in the food and generate energy for growth and maintenance of the cellular steady state (Shimizu, 2013). Enzymes play a crucial role in microbial fermentation, for catabolism of the foodstuffs, and favourable fermentation conditions to the microbial cells. Typically, a microorganism catalyses breakdown of the foodstuffs and produces energy through different metabolic pathways including glycolytic pathways and hexose monophosphate shunt, Entner-Doudoroff pathway (EDP), glyoxylate cycle, tricarboxylic acid cycle, and respiration (Sieuwerts *et al.*, 2008). During these biochemical conversions, the fermentation reactions produce several by-products referred to as microbial metabolites. Generally, humans need naturally occurring metabolites and cellular receptor proteins for their bodily functions. Studies have proven that microbial metabolites have a high potency to control several diseases, and they exhibit various functional properties as well. Therefore, the present review discusses the metabolites produced by microbial fermentation processes.

Microbial metabolites in fermented foods

Fermented foods and beverages are staple foods in human diets. Fermented foods have controlled activity, in which the food is fermented to a particular state, and/or until a required extent of the enzymatic conversion of food components. The major macro- and micronutrients in foodstuffs are the main ingredients that undergo this fermentation-induced conversion. Metabolites are the key indicators for determining the intensity of the fermentation. However, these metabolites vary widely based on sources of food and types of fermentation. This section discusses various microbial metabolites and their types, functions, health benefits, and adverse effects.

Production of amino acids

Amino acids are made of four essential elements namely carbon, hydrogen, oxygen, and nitrogen, and these elements form amine ($–NH_2$) and carboxyl (–COOH) functional groups (α, β, γ, and δ). Amino acids possess specific non-polar, polar, polar acidic, and polar basic characters based on their functional groups. Further, amino acids are classified into three main groups. Essential amino acids (histidine, leucine, isoleucine, lysine, threonine, methionine, phenylalanine, valine, and tryptophan) cannot be produced in the body. Conversely, non-essential amino acids (asparagine, alanine, aspartic acid, glutamic acid, serine, selenocysteine, and pyrrolysine) can be produced by the body, either by chemical transformation of essential amino acids or by hydrolysis of proteins (Wahl and Holzgrabe, 2016). Conditionally essential amino acids (arginine, cysteine, glutamine, glycine, proline, and tyrosine) are vital in the human diet. However, their synthesis is limited under several pathophysiological conditions. Since the creation of monosodium glutamate (MSG) in 1907, the demand to produce amino acid has increased. In addition to industrial applications, amino acids can promote health by regulating essential metabolic pathways for the growth and maintenance of organisms. The global demand for producing amino acids, especially essential amino acids, has dramatically increased due to extensive utilisation in animal feeds, human foods, and pharmaceutical industries (D'Este *et al*., 2018).

An amino acid can be produced in several ways such as by extraction from protein hydrolysate, chemical synthesis, or biological processes (enzymatically catalysed synthesis and fermentation). In particular, fermentation is emerging as the most promising due to the application of new genetic engineering tools (Ikeda, 2003). Several enzymes have been used to catalyse the production of desired amino acids such as hydrolytic enzymes, ammonia lyases, and NAD^+-dependent L-amino acid dehydrogenase (Pollegioni and Servi, 2012).

Microorganisms such as *Escherichia coli*, *Saccharomyces cerevisiae*, *Pseudomonas dacunhae*, and *Crypotococcus lurendii* produce most of these enzymes that catalyse amino acid production. Ramakrishnan *et al.* (2013) reported that the highest yield of amino acid was obtained with the combination of alcalase and neutrase enzymes for a reaction time of 48 h. Aside from their benefits, enzymes are usually expensive and have limited stability, which are the main drawbacks of enzymatically catalysed synthesis. However, fermentation is the most economical and environmentally advantageous process to produce amino acids (Ikeda, 2003).

The production of amino acids through fermentation utilises the phenomenon that a microorganism converts complex organic substances into simpler compounds by the action of intrinsic organic catalysts generated by the microorganisms (Steinkraus, 1983). Fermentation produces only the L-form amino acids; so, further purification steps are not needed. It can be done at mild operation conditions to prevent product degradation, and its maintenance cost is low as compared to an extraction process (Ugimoto, 2010). The most common microorganisms used to produce a broad spectrum of amino acids are *Corynebacterium glutamicum* and *Escherichia coli* (Ikeda, 2003). High yields of lysine and glutamic acid (up to 50% w/w) have been obtained using genetically modified *C. glutamicum* which is also the pioneer microorganism in producing essential amino acids, particularly L-lysine, L-valine, L-isoleucine, L-threonine, L-aspartic acid, and L-alanine for commercial purposes (Ivanov *et al.*, 2013). *C. glutamicum* utilises glucose, sucrose, fructose, ribose, mannose, or maltose as carbon source (D'Este *et al.*, 2018). Inhibition studies have demonstrated that growth decreases at glucose concentration above 50 g L^{-1} with L-glutamic acid concentration of 12 g L^{-1}. *E. coli* has been modified to enable the production of aromatic amines such as L-tryptophan, L-phenylalanine, and L-tyrosine. Glucose, sucrose, mannose, xylose, arabinose, galactose, and fructose could be used as the substrate for fermentation (Noor *et al.*, 2013). To maximise the performance of microorganisms in fermentation, in particular the yield, fermentative carbon source, and production of microbial metabolites, several biotechniques have been applied such as amplification of rate-limiting enzymatic pathway, amplification of the first enzyme after a branch point, cloning of a gene encoding an enzyme, introduction of functional or energetic enzymes through gene coding to replace the normal enzyme, and amplification of first enzyme leading from central metabolism to increase carbon flow in the pathway (D'Este *et al.*, 2018). Metabolic engineering strategies involve point mutation in the gene of enzymes and microorganisms relevant to targeted production of a particular amino acid. Microbial cells are producers of valuable amino acids from inexpensive raw materials (Figure 1).

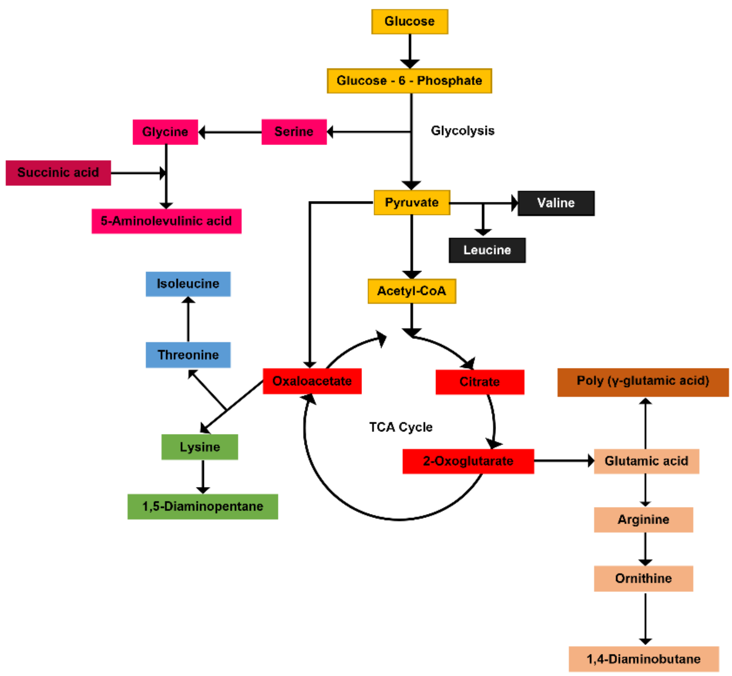

Figure 1. Amino acid production from glucose in the metabolic pathway of a microorganism during fermentation. Adapted from Hirasawa and Shimizu (2016).

The key step in fermentation is inoculum preparation, which impacts productivity and yield. Furthermore, the oxygen transfer rate (OTR) also influences productivity. It was found that increasing OTR led to 45% higher production of L-phenylalanine, whereas a lower OTR favoured L-tryptophan production (D'Este *et al*., 2018). Process temperature needs to be carefully chosen based on the target compounds to be produced. L-glutamic acid production increases at 41°C on using *C. glutamicum* strain, whereas *Bacillus methanolicus* produces L-lysine and L-glutamate at maximum temperature of 50°C (Brautaset *et al.*, 2007).

The production of an amino acid via fermentation strictly depends on the selection of raw materials and microorganisms used. For example, sulfur-containing amino acids like methionine and cysteine were obtained from fermented soybean products and biologically active taurine, found in salt-fermented shrimp paste, respectively. Raw material mostly used to produce amino acids are grains, sugars, molasses, yeasts, fruits, and other biological materials, particularly paraffin and synthetic nutrients, including ammonium chloride, ammonium nitrate, and potassium phosphate (Hill and Stewart, 2019). A microorganism has specific mechanisms to regulate the quantities of enzymes required to obtain the amino acid, and once a specific amino acid is produced, the enzyme is inactivated (Robinson, 2015). Once produced by fermentation, amino acids are generally purified with extraction. Physical or mechanical techniques are used by applying heat or maceration. However, in chemical methods, petroleum solvents, ammonia, strong acid and/or base treatments, and ion-exchange methods have been used to obtain the final product, which was mostly crystalline in nature (Sanjukta and Rai, 2016).

Amino acids generated through fermentation enrich the taste and flavour of the fermented foods. Amino acids produced by fermentation enhance the primary tastes of sweet (lysine, alanine, glycine, serine, and threonine), bitter (phenylalanine, arginine, tyrosine, leucine, valine, histidine, methionine, and isoleucine), umami, and sour (glutamic and aspartic acids) in fermented foods (Rabie *et al.*, 2009). Amino acids are utilised as biochemical substances in numerous industrial applications like in animal feed additives (lysine, methionine, and threonine), flavour enhancers (aspartic acid, serine, and monosodium glutamate), antioxidants (cysteine, L-tryptophan, and L-histidine), sweeteners (aspartame developed from aspartic acid and phenylalanine), and ingredients in pharmaceutical and cosmetic products (Friedman and Levin, 2012). Consuming amino acid-rich food is not only good for growth of the animal, but it also improves the quality of the meat and meat products. Amino acid incorporated in feed and food provides multi-level benefits such as improvement in digestibility, increased glucose tolerance, inhibition of pathogenic bacteria and toxin formation, degradation of plant toxins (cyanogenic glycosides), and reduction in antinutritional factors such as proteinase-inhibitors, phytic acid, urease, and oxalic acids (Stewart, 2017).

Production of enzymes

Enzymes are proteinaceous by nature, and act as biological catalysts in all living systems. Enzymes in food industries are applied in the manufacturing of wine, cheese, bread, beer, and vinegar since ancient times. Apart from the food industries, enzymes are also used in detergents, textiles, and paper industries. Microbial enzymes are cost-effective because of their easy production and better stability as compared to those from plant and animal origins. A known producer of enzymes of industrial interest is the genus *Bacillus* that contributes approximately 50% of the total enzyme production (Schallmey *et al.*, 2004). Enzymes catalyse hydrolysis, and are produced by a wide range of microorganisms. Commercially important hydrolyser enzymes (amylase, protease, and lipases) are derived from *Bacillus* species such as *B. licheniformis*, *B. stearothermophilus*, and *B. amyloliquefaciens* (Teodoro and Martins, 2000). Apart from *Bacillus* spp., mould strains such as *Aspergillus niger* and *A. oryzae* are also widely used to derive industrially relevant enzymes. Among hydrolysers, enzymes, in particular α- and β-amylase, have received special attention due to their tolerance for elevated temperatures (Konsoula and Liakopoulou-Kyriakides, 2007). The production of enzymes by thermophilic microorganisms shows a great advantage in reducing the risk of contamination when operated at an elevated temperature.

Furthermore, lesser viscosity and excellent solubility of the substrate could be obtained at elevated temperatures, which increase the product yield due to favourable conditions (de Souza Vandenberghe *et al*., 2016). Protease enzymes have prime applications in food, textile, pharmaceutical, and detergent industries, and represent approximately 30% of the global enzyme market. Production of enzymes can be increased in a fermented product by adopting specific microorganisms and an optimal medium for microbial growth (Nascimento *et al.*, 2011). Enzymes like lipase have gained considerable interest in industrial applications due to their high stability, no requirement for cofactors, and broad substrate specificity (Teodoro and Martins, 2000). Metabolites produced by microorganisms during fermentation are given in Table 1.

Table 1. Metabolites produced by various microorganisms during fermentation.

Metabolite	Microorganism	Fermentation substrate	Reference
L-arginine	*Corynebacterium glutamicum*	Sucrose	Park *et al.* (2014)
L-asparagine	*Pseudomonas fluorescens*	M9 agar medium	Badoei-Dalfard (2016)
L-cysteine	*Pantoea ananatis*	Luria-Bertani broth	Takumi *et al.* (2017)
L-histidine	*Corynebacterium glutamicum*	Molasses (15%)	Kulis-Horn *et al.* (2014)
L-leucine	*Corynebacterium glutamicum*	CGXIIG growth medium	Feng *et al.* (2018)
L-lysine	*Bacillus methanolicus*	SOBsuc medium	Nærdal *et al.* (2017)
L-tryptophan	*Escherichia coli*	Seed fermenter	Liu *et al.* (2017)
L-tyrosine	*Brevibacterium lactofermentum*	Processed Iranian cane and beet molasses	Sadeghiyan-Rizi *et al.* (2014)
L-valine	*Corynebacterium glutamicum*	Brain heart infusion broth	Zhang *et al.* (2018)
L-phenylalanine	*Aspergillus oryzae*	Potato dextrose agar	Ali and Haq (2010)
DL-methionine	*Corynebacterium glutamicum*	Glucose, urea, and molasses-based media	Ali *et al.* (2018)
Amylase	*Bacillus subtilis*	Sugarcane bagasse hydrolysate	Rajagopalan and Krishnan (2008)
Cellulase	*Aspergillus niger*	Apple pomace	Dhillon *et al.* (2012)
Beta-glucanase	*Trichoderma viride*	Oatmeal and peptone	Yang *et al.* (2015)
Invertase	*Saccharomyces cerevisiae*	Red carrot residue	Rashad and Nooman (2009)
Lactase	*Lactobacillus acidophilus*	Fermented ragi	Akolkar *et al.* (2005)
Xylose	*Streptomyces murinus*	Luria-Bertani broth	Sarmiento *et al.* (2015)
Protease	*Aspergillus niger*	Skerman's basal mineral salt media (BSM)	Atalah *et al.* (2019)
Peptidase	*Debaryomyces hansenii*	Fermented sausage	Bolumar *et al.* (2008)
Vitamin B_1	*Bacillus subtilis*	Cashew apple	Kaprasob *et al.* (2018)
Vitamin B_2	Propionibacteria	Whey-based liquid medium (WBM)	Deptula *et al.* (2017)
Vitamin B_3	*Lactobacillus* Sp., *Leuconostoc mesenteroides*, *Bifidobacterium longum*	Cashew apple juice	Kaprasob *et al.* (2018)
Vitamin B_6	*Bacillus subtilis*, *Escherichia coli*	Minimal medium with yeast extract	Rosenberg *et al.* (2017)
Vitamin B_{12}	Propionic acid bacteria	Glycerol and glucose	Pophaly *et al.* (2012)
Vitamin C	*Bacillus thuringiensis*	L-sorbose limiting medium	Yang *et al.* (2013)
Vitamin K	*Lactococcus*, *Lactobacillus*, *Enterococcus*	GM17 media	O'Connor *et al.* (2007)

The hydrolyser enzymes produced by microorganisms provide considerable financial benefits to the food industries in improving the taste and texture of various foodstuffs. Microbial enzymes are highly consistent and easy to modify and optimise for better performance (Gurung *et al*., 2013). Recent studies have found that microbial enzymes, especially the fibrinolytic enzymes, show promising effects in the health industries (Singh *et al*., 2016). Fibrin is an insoluble aggregate that is formed by the cleavage of fibrinogen in the blood by thrombin during wound recovery. Usually, the blood may solubilise the fibrin by an enzymatic action of plasmin once the wound heals. However, abnormal accumulation of fibrin in the blood vessels may lead to severe impairment of bodily functions, especially the cardiovascular system (Rafieian-Kopaei *et al.*, 2014).

Cardiovascular diseases are life-threatening and globally prevalent. The clotting of blood in blood vessels (intravascular thrombosis) is the primary cause of heart diseases. They can be treated by the administration of plasminogen activators, which are urokinase, streptokinase, and tissue plasminogen activator (Adivitiya and Khasa, 2017). This fibrolytic therapy is expensive, has a short half-life after intravenous administration, and may also cause side effects such as gastrointestinal bleeding, allergic reactions, and resistance to repercussion. The fibrinolytic enzymes can be found in fermented foods, though studies on their characteristics and applications are still in developing stages. Several studies have reported that fibrinolytic enzymes in fermented foods are mainly produced by *Bacillus* spp. The fibrinolytic enzymes and their origin in fermented foods are given in Table 2. The extracellular fibrinolytic enzymes produced by microbial fermentation have two possible mechanisms which are hydrolysis of fibrin, and the inhibitory effect of thrombin. Wei *et al.* (2011) reported that the fibrinolytic enzymes from chickpea fermented by *B. amyloliquefaciens* showed noticeable effects when produced in a solid-state fermentation. Stephani *et al.* (2017) reported that *Stenotrophomonas* sp. isolated from soybean *tofu* drugs were able to produce fibrinolytic enzymes. The fibrinolytic activity of this extracted enzyme was similar to a commercially obtained fibrinolytic enzyme (lumbrokinase).

Table 2. Fibrinolytic enzymes from different food sources.

Food source	**Fibrinolytic enzyme**	**Reference**
Natto	Nattokinase	Sumi *et al*. (1987)
Tofuyo	Soybean milk coagulating enzyme (SMCE)	Fujita *et al.* (1993)
Shiokara	Katsuwokinase	Sumi *et al.* (1995)
Chungkook-jang	Alkaline serine protease	Kim and Kim (1999)
Kimchi	*Bacillus* protease	Noh *et al.* (1999)
Fermented shrimp paste	Neutral metalloprotease	Wong and Mine (2004)
Indonesian fermented *tofu*	*Stenotrophomonas*	Stephani *et al.* (2017)
Rice *koji*	Serine protease	Shirasaka *et al.* (2012)
Fermented red bean	Serine protease	Chang *et al*. (2012)

Production of vitamins

Vitamins are organic food substances, and also considered essential nutrients to keep the body running smoothly. Vitamins have no caloric value, and are not energy sources, but play a crucial role in the utilisation of nutrients by facilitating the metabolic processes (Patel *et al.*, 2013). Living organisms, especially humans, receive vitamins from external sources because the internal system is unable to produce them. A regular supply of vitamins is needed, and in case of excess depletion or insufficient quantity, acute and chronic diseases may emerge. Vitamins are abundantly produced in plants and animal sources, and majority of the water-soluble vitamins are obtained from plants, while majority of the fat-soluble vitamins are obtained from fat-rich sources.

Vitamins are relatively unstable, and can be affected by several factors such as heat, light, air, food components, and food processing conditions. The supply of vitamins is not sufficient only from the natural sources. Chemical synthesis is an effective way to increase vitamin availability, but it is energy-intensive with higher costs of production. A recent study reported that fermentation could have a crucial role in the commercial production of water-soluble vitamins. Fermented foods generally have higher vitamin contents than their raw counterparts. Tempeh is fermented soybean cakes that have a higher content of vitamin B complex than unfermented soy products

(Walther *et al.*, 2013). Fermentation of foodstuff by microbial action can improve the bioavailability of vitamins such as biotin, folate, riboflavin, pantothenic acid, pyridoxamine, pyridoxine, pyridoxal, and thiamine (Marco *et al*., 2017). *Tarhana* is a fermented, dried soup powder, prepared by lactic acid bacteria such as *Lactobacillus bulgaricus* and *Streptococcus thermophilus* (Daglioğlu, 2000). This fermented product has an acidic sour taste, and serves as a good source of essential proteins, vitamins, and minerals.

Submerged fermentation (SMF; which involves a liquid nutrient medium) and solid-state fermentation (SSF; which is performed on a solid substrate) are the two main fermentation methods (Saxena and Singh, 2011). Vitamin contents in the fermented product rely on raw material, microbial strains, and substrate conditions applied during fermentation. Fermentation with *Lactobacillus* decreases the content of vitamin B_1, whereas fermentation with a yeast increases its level (Hucker *et al*., 2014).

Different forms of vitamins can be derived from various microorganisms. Notably, *Bacillus subtilis* has a considerable potential to produce a wide range of vitamins on a large scale. Vitamins possess diverse biochemical functions; vitamin D functions as a hormone, vitamin E functions as an antioxidant, vitamin A functions as a mediator and regulator of cell signalling, and vitamin B complex functions as precursors of coenzymes (Bolumar *et al.*, 2008). Vitamins are predominantly functioning as coenzymes, which act as catalysts and substrates in metabolism (Park *et al*., 2014).

Vitamins that are produced by fermentation are found to have broad applications including as food additives, health supplements, and therapeutic agents (Singh *et al.*, 2016). The combination methods such as chemical and microbial processes on producing vitamins are widely applied on a commercial scale. Furthermore, improved fermentation technologies such as medium optimisation, mutation, screening, genetic engineering, and biocatalysts can be used to improve the production of vitamins (Binod *et al*., 2010). Though the production of vitamins is feasible through fermentation, until now, only very few vitamins including folate, and vitamins K, A, B_2, B_6, B_{12}, and C are widely produced on a commercial scale (Wang *et al.*, 2018). Other types of vitamins have not been produced commercially due to the difficulties in raw material utilisation as a fermentable source. Typically, majority of vitamins can be obtained from foods and food ingredients, and studies have found that vitamins synthesised in fermentation could have increased concentrations, thus making them readily available for human metabolic systems.

Production of organic acids

Organic acids are widely distributed in nature, and have received considerable attention in industrial applications as food additives, and in pharmaceuticals and cosmetics. Since ancient times, organic acids have been used to preserve food. By penetrating the cell wall, they disturb the normal function of pH-sensitive strains such as *Salmonella* spp., *Clostridia* spp., *E. coli*, *Listeria monocytogenes,* and *Campylobacter* spp. (Suiryanrayna and Ramana, 2015). Organic acid is utilised as platform chemical in various industrial applications, including foods, beverages, pharmaceuticals, textiles, detergents, solvents, petrochemicals, dyes, and adhesives (Singh *et al.*, 2016). Organic acid exhibit redox potential and have pKa value in the range of 3 (carboxylic acid) to 9 (phenolic acid). They vary widely in molecular weight, from relatively small compounds such as citric acid, to much bigger humic compounds with enormous numbers of carboxylic and phenolic acids. Fermentation is widely utilised in producing various organic acids over conventional methods due to the high purity, selectivity, cost-effectiveness, and eco-friendly nature (Sauer *et al*., 2008). At present, α-ketoglutaric acid, citric acid, lactic acid, gluconic acid, acetic acid, and itaconic acid are widely produced, and propionic, succinic, and pyruvic acids are also reported to be produced by fermentation (Yang *et al*., 2013).

Organic acid production by microbial fermentation is a promising approach for the production of biodegradable polymers, and potentially could replace petroleum-based or synthetic chemicals. Organic acids could normally be obtained in one particular form by fermentation, and can then be converted into various substances via chemical conversions. For example, succinic acid produced from the fermentation of wheat by *Acinobacillus succinogenes* could further be converted into tetrahydrofuran, 1,4-diaminobutane, succindiamide, 1,4-butaediol, succinonitrile, dimethyl succinate, N-methyl-pyrrolidone, and 2-pyrrolidone (Sauer *et al*., 2008). An essential multifunctional organic acid, the α-ketogenic acid, is formed in the TCA cycle, and a major contributor in amino acid and protein metabolisms. Several reports claim that α-ketogenic acid can be produced by fermentation, and especially by bacterial fermentation. Bacterial species such as *Arthrobacter paraffineus*, *Bacillus mesentericus*, *B. megaterium*, *B. natto*, *Bacterium succinicum*, *Pseudomonas fluorescens*, and *Corynebacterium glutamicum*, and yeast species such as *Candida rugosa*, *C. catenulata*, *Torulopsis glabrata*, *Pichia dispora*, *P. besseyi*, and *Yarrowia lipolytica* are utilised to produce α-ketogenic acid (Khan *et al.*, 2017).

Citric acid is the pure form of tricarboxylic acid, and a biodegradable and eco-friendly chemical that is widely used in food industries as acidulant, antioxidant, preservative, and flavour enhancer. Citric acid can be produced by various bacteria, moulds, and yeasts. Among them, *Aspergillus niger* through SMF was reported for the commercial production of citric acid (Chen and Nielsen, 2016). Furthermore, other species such as *Candida catenulata*, *C. guilliermondii*, *C. tropicalis*, and *Yarrowia lipolytica* are also used for citric acid production (Kubicek and Karaffa, 2001).

Fumaric acid, also referred to as fumarate, or 2-butenedioic acid, or *trans*-1,2-ethylenecarboxylic acid, is a naturally occurring organic acid with low solubility. Fumaric acid is a minor metabolite from microbial fermentation as compared to other organic acids, and was first produced through fermentation using *Rhizopus* spp. *Circinella*, *Mucor*, *Cunninghamella*, *Saccharomyces cerevisiae*, *Aspergillus niger*, and *A. flavus* could also produce fumarate in fermentation (Carta *et al*., 1999).

Gluconic acid is also known as polyhydroxycarboxylic acid, and found in a wide range of organisms. Gluconic acid is non-toxic, soft, and non-volatile organic acid, with a wide range of applications in the food and pharmaceutical industries. Gluconates are salts of gluconic acid, formed in a neutral (pH) aqueous solution. Gluconic acid can be produced by three different ways that are electrolytic addition of oxygen to glucose solution, chemical oxidation of glucose with a hypochlorite solution, and lastly, by fermentation (Sumitra *et al.*, 2006). A wide range of microorganisms can produce gluconic acid such as fungal (*Aspergillus*, *Gliocladium*, *Penicillium*, *Scopulariopsis*, and *Gonatobotrys*) and bacterial (*Acetobacter methanolicus*, *Pseudomonas fluorescens*, *Gluconobacter oxydans*, *Moraxella*, *Pullularia*, *Tetracoccus*, *Enterobacter*, and *Scopulariopsis*) species that play an essential role in converting inexpensive carbohydrate to valuable gluconic acids (Ramachandran *et al*., 2006). Conversion of glucose into gluconic acid by *Aspergillus niger* is depicted in Figure 2.

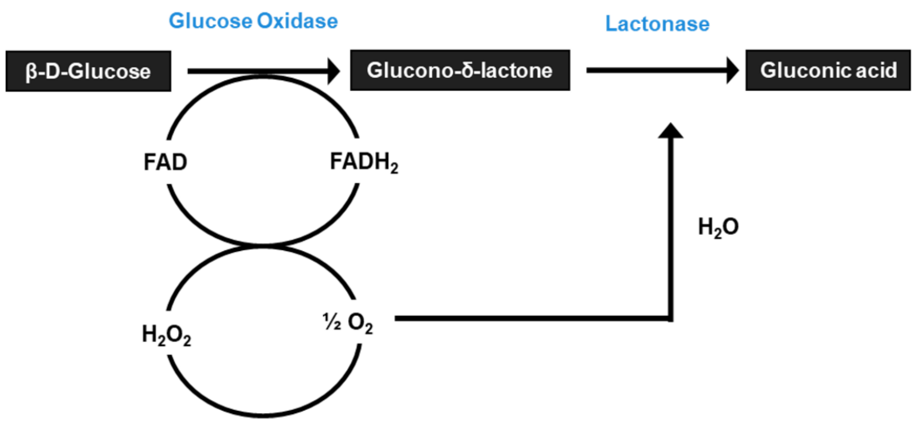

Figure 2. Conversion of glucose into gluconic acid by *Aspergillus niger*. Adapted from Sumitra *et al.* (2006).

Lactic acid is a commodity chemical, and possesses a wide range of applications in food, pharmaceutical, cosmetic, and leather industries (Chen and Nielsen, 2016). Lactic acid is dominant by its amount among the organic acids produced during fermentation. Strain selection is important for high production capacity and high optical purity of lactic acid. Lactic acid bacteria (LAB) are preferred over fungi in the production of lactic acid due to the high acid tolerance and yield. D- or L-lactic acid is produced by *Lactobacillus* strain. LABs are grouped into two classes based on the end product of fermentation. Homofermentative LAB have aldolase enzyme, and produce maximal yield of lactic acid as the major end product. This class is of interest for large scale production of lactic acid, whereas heterofermentative LAB use alternative pentose monophosphate pathway, and convert pentose sugar to lactic acid and by-products (acetic acid) (Abdel-Rahman *et al*., 2013). *Enterococcus mundtii* QU 25 and engineered *Lactobacillus plantarum* were recently reported to convert pentose to lactic acid homofermentatively. Various techniques were introduced to improve the production and optical purity of lactic acid such as deletion of a by-product producing gene, strain improvement, and development of bacterial strains by chemically defined media. In contrast, several bacterial (*Escherichia*, *Bacillus*, *Kluyveromyces*) and yeast (*Saccharomyces*) species are also involved in the efficient production of lactic acid (Ghaffar *et al.*, 2014).

Production of bacteriocins

Biopreservation is a natural means of preservation by microorganisms or their products. Bacteriocins are the antimicrobial low molecular weight peptides synthesised by the bacterial proteins during fermentation. Bacteriocins are ribosomally-synthesised antimicrobial peptides (AMP) of 20 - 60 amino acid length, with the ability to inhibit both food spoilage and pathogenic bacteria (Walsh *et al*., 2015). Generally, bacteriocins are effective in inhibiting pathogenic bacteria such as *Bacillus cereus*, *Clostridium botulinum*, *Staphylococcus aureus*, and *Listeria monocytogenes*. Gram-positive, Gram-negative, and archaea bacteria are known producers of bacteriocins. Among these microorganisms, lactic acid bacteria are known to be potential producers of antimicrobial substances like organic acids, hydrogen peroxide, bacteriocin, and others (Todorov *et al*., 2012).

Nisin, an antimicrobial substance produced by *Lactococcus lactis* subsp. *lactis*, was first reported in 1993, and later named NISIN (Group N *Streptococcus* Inhibitory Substance IN). Nisin is a long cyclic polypeptide that has 34 amino acids with a molecular mass of 3,500 Da. Food and Drug Administration (FDA) granted "generally regarded as safe" (GRAS) status to the antimicrobial peptide nisin for various applications in the food industry. Nisin is now used in over 50 countries as a natural biopreservative (Kamarajan *et al.*, 2015).

Bacteriocins are classified based on the source microorganism, amino acid composition, type of post-translational modifications, and size. Further classification of bacteriocins is based on the antibacterial activities, heterogeneity, biomedical, and food applications. Bacteriocins produced by Gram-positive bacteria are classified into 12 groups based on biochemical and genetic characteristics. Bacteriocins produced by Gram-negative bacteria are divided into two categories, which are colicins and microcins. Colicins can be classified into three classes based on their mode of action. Microcins are classified into two classes, I and II (with the subclasses IIa and IIb) (Yang *et al.*, 2014). Bacteriocins produced by archaeal members are halocins and sulfolobicins. *Halobacteria* are responsible for the production of halocins, and these are typically classified based on their size (3.4 to 35 kDa), whereas sulfolobicins are produced by members of *Sulfolobus islandicus*, and these are narrow spectrum bacteriocins. Antimicrobial peptides like nisin and pediocin respectively produced by *Lactococcus lactis* and *Pediococcus acidilactici* have been found to inhibit the germination of *C. botulinum* and growth of *L. monocytogenes* in a variety of ready-to-eat food products (Mazzotta *et al*., 1997).

The production of bacteriocins is intrinsically highly regulated: instead of producing a large number of bacteriocins, the bacteriocin producers prevent intruders from settling down by regulating the formation of a biofilm via inhibition of quorum sensing with low-level production. The maximum bacteriocin production can be found during the late exponential and early stationary growth phases (Karthikeyan *et al*., 2013). Bacteriocins exhibit a variety of regulatory functions, primarily in human health and food applications. One of the vital functions of bacteriocins is as an antimicrobial agent, especially bactericidal. Bacteriocins bind to the cell wall components, which are lipid or surface molecular binding sites, via specific and/or non-specific receptors. Once bound to the receptor, then the bacteriocin facilitates pore formation as well as direct cell lysis, which results in cell death via dissipation of the proton motive force of bacterial systems. The primary inhibitory mechanisms of bacteriocin are cell permeabilisation and pore formation on target bacteria (Moll *et al.*,1999).

Bacteriocins usually stimulate the efflux of amino acids and cations from the cell membrane and vesicles, thus causing the loss of proton motive force, interfering with the cellular biosynthesis, and collapsing the membrane potential, which eventually lead to cell death. Bacteriocin-producing cultures are predominantly used as starter cultures, and they contribute to fermentation and preservation, thereby serving both in flavour development and food safety simultaneously. Bacteriocin is a cost-effective biopreservative, and has less regulatory control than conventional pure peptides (Johnson *et al.*, 2018). Bacteriocin consumption through fermented foods does not require any special legislation approval. However, the strain must be studied clearly for a suitable food environment in which it can grow and produce harmless bacteriocins. Bacteriocins are bioactive substances possessing potential therapeutic effects in the human system, to treat both multi-drug resistant and chronic bacterial infections. Bacteriocin resistance of a microorganism can be overcome by using a combination of different bacteriocins and antimicrobial compounds (Algburi *et al.*, 2017). The action of bacteriocins is against both Gram-positive and Gram-negative bacteria, and they are beneficial even at a low concentration. Bioengineering at specific amino acid residues can be done to increase the potency of bacteriocins against food spoilage and pathogenic bacteria (Mathur *et al*., 2018).

While there are several bacteriocins produced, nisin and pediocins PA-1 from LAB are the only sources currently used in the food industry. Bacteriocins are used as preservative agents to control *Clostridium botulinum*, *L. monocytogenes*, *B. cereus*, *E. coli*, *S. aureus*, and *Alicyclobacillus acidoterrestris* in various foodstuffs, including dairy, meat, vegetable, and fish (Singh, 2018). Subtilin, lichenicidin, cinnamycin, actagardine, epidermin, lacticin, carnobateriocin, piscicolin, divergicin, mutacin, mundticin, mesenterocin, enterocin, sakacin, leucocin, curvain, enterocin, lysostaphin, duramycin, brevinine, ruminococcin, curvaticin, and columbicin are some other bacteriocins produced by microorganisms during fermentation.

Production of pigments

Pigments are colours that rely on the reflection or scattering of light, and mostly obtained from fruits, vegetables, roots, minerals, plants, algae, and microorganisms: these are known as bio-colours or natural pigments. Microbial pigments are found beneficial among the natural pigments owing to their stability, availability due to lack of seasonal variations, cost-effectiveness, and high yield through strain improvement (Dufossé *et al*., 2005). Natural pigments are divided into three groups, which are carotenoids, flavonoids (anthocyanin), and tetrapyrroles (chlorophylls and phycobiliproteins). Microorganisms produce pigments at a low cost and rapidly, which motivates research on them. The microorganisms used for pigment production must be non-pathogenic and non-toxic. Pigments produced from microorganisms are ideal for broad application as they can use a wide range of carbon and nitrogen sources, and are highly tolerant to pH, temperature, and minerals (Babitha, 2009). Recent advancements in the genetic sector help improve pigment production by tuning the genetic nature of microorganisms. There is a wide range of pigments that have been commercially produced by different microorganisms.

Bacteria such as *Achromobacter*, *Bacillus*, *Brevibacterium*, *Cornebacterium michigannise*, *Pseudomonas*, *Rhodococcus maris*, and *Streptomyces* are responsible for producing pigments (orange, red, yellow, blue, and brown). Moulds can also produce a wide range of pigments (Joshi *et al.*, 2003). *Aspergillus glaucus*, *Blakeslea trispora*, *Helminthosporium catenarium*, *H. gramineum*, *H. cynodontis*, *H. avenae*, *H. catenarin*, *Monascus purpureus*, *Penicillium cyclopium*, and *P. nalgeovense* are reported widely for producing pigments (orange, red, cream, bronze, maroon, and yellow). *Cryptococcus* sp., *Phaffia rhodozyma*, *Rhodotorula*, and *Yarrowia lipolytica* are the yeast species that produce pigments such as yellow, orange, red, and brown (Venkatachalam *et al.,* 2018). Algae, specifically *Dunaliella salina*, produce red pigments. These microorganisms can be isolated and cultured from various environmental sources such as water bodies, soils, insects, and animals. Among these, *Monascus* spp. produce azaphilone pigment with various colours such as yellow (ankaflavins and monascin), orange (rubropunctatin and monascorubin), and red (rubropuntamine and monascorubramine). In addition to that, microorganisms like *Aspergillus* and *Penicillium* have also been widely utilised in production of natural pigments (Pattanagul *et al*., 2007).

Pigments like β-carotene and astaxanthin from fungal cultures are used as precursors of vitamin A, and as single-cell proteins for aquaculture animals. The pigment produced by *Monascus* strains (monascarubromine) is widely used in food industries to colour meat, fish, creams, and ketchups to replace synthetic alternatives (Hamano and Kilikan, 2006). Furthermore, the pigments isolated from microorganisms have various bio-pharmacological activities including antioxidant, antimicrobial, anticancer, and anti-inflammatory effects. For example, prodigiosin is a pigment produced by the Gram-negative bacterium *Serratia marcescens*, and possesses antibacterial, antiprotozoal, antifungal, cytotoxic, and anti-inflammatory properties (Gulani *et al*., 2012). Yeast- and mould-derived pigments can be used as food additives to enhance the immune response, and to inhibit cholesterol synthesis, and are also reported as biologically safe. Food-grade natural colourants derived from microorganisms during fermentation process are shown in Table 3 (Caro *et al.*, 2012).

Table 3. Natural colourants derived from microorganisms during fermentation.

E-number	Natural colourant	Microorganism	Colour	Reference
E-101	Riboflavin	*Bacillus subtilis*	Yellow	Caro *et al.* (2012)
E-160a	Beta-carotene	*Blakeslea trispora*	Orange-yellow	
E-160a	Beta-carotene	*Dunaliella salina*	Orange-yellow	
E-160d	Lycopene	*Blakeslea trispora*	Yellow to red	
E-161j	Astaxanthin	*Haematococcus pluvialis*	Yellow to red	
E-161g	Canthaxanthin	*Haematococcus lacustris*	Orange to red	

Production of bioactive compounds

Bioactive compounds occur naturally in plants as well as in foodstuffs, and are considered extra nutritional constituents present in small quantities, mainly including secondary metabolites such as alkaloids, pigments, antibiotics, and polyphenols (Nigam, 2009). Bioactive compounds are the group of molecules that possess biological activity in humans when they are consumed. Bio-availability and bio-accessibility of bioactive compounds in humans are not based on the concentration, but on source of food, molecular size, solubility, and various chemical interactions with the metabolic process in human. Bioactive compounds can have beneficial health effects including decrease in cardiovascular diseases, cancers, and diabetes, and also possess activities like antimicrobial, anti-mutagenic, antioxidant, anti-allergenic, and anti-inflammatory activity (Martins *et al.*, 2011). However, the bio-availability and bio-accessibility of these compounds play crucial roles in the beneficial effects. Phytosome and nano-carriers are recent technologies to increase bioavailability, but are too expensive to commercialise. Furthermore, bioactive compounds can be extracted from natural sources. Usually, solid-liquid extraction in heat-reflux systems is widely used to extract bioactive compounds from natural sources. However, other techniques include the use of supercritical fluids, high pressure processes, microwave-assisted extraction, and ultrasound-assisted extraction. During fermentation, bioactive compounds are produced as secondary metabolites by microorganisms with high quality, enhanced activity, and reduced toxicity (Nigam, 2009). Previous studies have reported that fermentation plays a significant role in providing human body access to these bioactive compounds in a more agreeable way than in unfermented food forms.

Polyphenols are the secondary metabolic compounds produced in plants via the shikimic acid pathway, but their level and type varies widely depending on the plants, genetic factors, and environmental conditions (Kris-Etherton *et al*., 2002). Phenolics are categorised as free phenolic and bound phenolic types. Free phenolic compounds are found in the plant vacuoles, whereas bound phenolic compounds are linked to cell wall integrals, which are cellulose, hemicellulose, lignin, pectin, and protein. Polyphenols are considered natural antioxidants, with structure comprising at least one C6 aromatic ring, a benzene ring with at least one but possibly more hydroxyl groups, synthesised from phenylalanine by the phenylalanine ammonia-lyase. Lee *et al*. (2008) reported that *koji* produced from fermentation of beans using different food-grade filamentous fungi (*Aspergillus* sp. and *Rhizopus* sp.) had enhanced antioxidant properties. The reason might be increased phenol and anthocyanin contents. Polyphenolics include phenolic acids (hydroxy-benzoic acids and hydroxy-trans-cinnamic acids), coumarins, flavonoids (flavones, flavonols, flavanones, flavanolols, flavanols, and anthocyanidins), isoflavonoids, lignans, stilbenes, and phenolic polymers (proanthocyanidins and hydrolyzable tanins) (Craft *et al*., 2012). Fermentation not only extracts the phenolics but also converts them into different metabolites, which have various bioactivities. During fermentation, microorganisms increasingly produce various enzymes including cellulolytic, ligninolytic, and pectinolytic enzymes (Martins *et al*., 2011). These enzymes lyse the cell walls, thus releasing phenolic compounds that undergo further conversion processes, including glycosylation, deglycosylation, methylation, glucuronidation, and sulphate conjugation. Enzymatic conversion of the flavonoids during fermentation is a self-protecting activity by the microorganisms because a high level of flavonoids could be toxic to the microorganisms. Therefore, these polyphenols are turned into various metabolites. In a similar way, soybean fermented with *Bacillus pumilus* had significantly increased flavanols and gallic acid, with decreased amounts of isoflavone glycosides, malonylglyosides, and flavanol gallates. This was caused by bacterial ß-glucosidase and esterase activities (Cho *et al*., 2009).

de Beer *et al*. (2015) studied the fermentation of rooibos at different temperatures (30 - 40°C) which effectively degraded aspalathin and nothofagin, and formed flavanones. Rocchetti *et al*. (2019) observed the fermentation of quinoa and buckwheat with *Lactobacillus paracasei* and *Pediococcus pentosaceus*, and found increased total phenolics and antioxidant activities from the unfermented state. In another study, defatted wheat germ fermented with *Bacillus substiles* had an increased level of free phenolics. However, this decreased the level of bound phenolics due to the strong interactions of bound phenolics with protein: consequently, more free phenolics were released (Liu *et al*., 2017). Shin *et al*. (2019) reported that the solid-state fermentation of black rice bran using *Aspergillus awamori* and *A. oryzae* had increased the extractability of phenolic acid components. Malolactic fermentation of black chokeberry and sea buckthorn juice using *L. plantarum* showed decreased phenolic acid content. However, the flavonols and anthocyanins in the chokeberry remained unaffected. Sadh *et al*. (2018) reported that peanut cake fermented with *A. awamori* at 30°C for 144 h had significantly improved phenolic and antioxidant properties. Wang *et al*. (2013) reported that rice straw fermented with *Pichia stipitis* had increased phenolic acids.

Alkaloids are naturally occurring organic nitrogen-containing bases that possess diverse physiological effects on humans and animals. They are bitter-tasting compounds that are produced substantially by the plants, animals, and microorganisms (Dembitsky *et al*., 2015). Alkaloids are divided into two types, which are heterocyclic alkaloids (pyrrole, indole, and quinolone) and non-heterocyclic alkaloids (phenylethylamine, tropolone, and steroidal). Indole structure can be found in a wide range of fermented food products. It has strong binding affinity properties for many receptors, and possesses a wide range of pharmacological properties, which include antipsychotic, antihypertensive, antitumor, antimicrobial, antiparasitic, and antimalarial activity. In food fermentation, indole production is considered an adverse effect as it causes 'plastic-like' off-flavour formation, especially in wine (Arevalo-Villena *et al*., 2010). Indole alkaloids can be produced in fermented foods by *Saccharomyces bayanus*, *S. cerevisiae*, *Lactobacillus lindneri*, *Hanseniaspora uvarum*, *Oenococcus oeni*, *Candida stellate*, *Kluyveromyces thermoloterans*, *Pediococcus parvulus*, and *P. cerevisiae.* Pyrrole is a colourless volatile alkaloid that is synthesised by the cyclisation of 1,4-dicarbonyl compounds with abundant ammonia and/or primary amines. It has antibacterial, anti-inflammatory, antioxidant, anticholesterol, antitumour, and immune suppressant activities. Pyrrole production in fermented food is achieved by microbial degradation of indole by various microorganisms including bacteria and fungi, under aerobic fermentation conditions. *Cupriavidus* sp. has the ability to convert indole into pyrrole. Under aerobic conditions, indole is degraded by oxidation, followed by the heterocyclic ring cleavage, which produces pyrrole (Arora *et al*., 2015).

Health benefits of microbial metabolites

Fermentation involves the breakdown of carbohydrates into end products such as organic acids, alcohols, carbohydrates, and several antimicrobial metabolites that enhance the shelf life of food products by inhibiting spoilage and/or pathogenic microorganisms. Fermentation promotes the growth of beneficial bacteria collectively known as probiotics. Probiotics modify the gut microbiota, thus improving digestion and enhancing immune response, in addition to anti-carcinogenic and hypocholestrolemic effects (Widyastuti and Febrisiantosa, 2014). Fermentation enhances the digestibility of proteins and carbohydrates, and also improves the bioavailability of vitamins and minerals. The metabolites from food fermentation have shown positive effects against various diseases. However, their full beneficial effects on human health are not well known (Field *et al*., 2007). Fermented foods exhibit health benefits, particularly reducing blood cholesterol, increasing immunity, prevention from pathogens, and control of various diseases including carcinogenesis, osteoporosis, diabetes, obesity, allergies, and atherosclerosis. During fermentation, various bioactive metabolites are developed by the microorganisms, and the types of metabolites produced depend on the raw materials and strains of microorganism utilised (Aguilar-Toalá *et al*., 2017). For example, microbial fermentation by bacteria could produce bioactive peptides that are proven non-pharmacological compounds with significant health effects. The valyl-prolyl proline and isoleucyl-prolyl-proline are the main bioactive peptides produced in fermented foods which could reduce hypertension.

Extracellular polysaccharides (EPSs) are natural high molecular weight polysaccharides, and biologically produced through various microbial fermentation processes. *Acetobacter* spp., *Azotobacter* spp., *Mucor* spp., *Agrobacterium* spp., *Leuconostoc* spp., *Aspergillus* spp., and *Alcaligenes* spp. can produce EPSs. EPSs can control the cholesterol in the blood by binding with it directly, thus reducing cholesterol absorption in the body, and promoting the release of bile acids (Nampoothiri *et al*., 2017).

Bacteriocins are the antimicrobial peptides synthesised in ribosome by the bacteria during fermentation. Bacteriocins are considered as GRAS, and can be used as preservatives in a wide range of foods to control the onset of pathogens. Nisin, mersacidin, labyrinthopeptin, subtilosin, entrocine A, caseicin, and helveticin J are a few examples of the many large molecules and stable bacteriocins produced during fermentation (Field *et al.*, 2007). LAB is the essential fermenting bacterial family that produces a large number of bacteriocins. Bacteriocins from LAB control cardiovascular diseases, and also exhibit antimicrobial, antimutagenic, antioxidant, and antihaemolytic properties (Aguilar-Toala *et al.*, 2017).

Lactobacillus spp. tend to increase the level of propionic acids, lactic acids, acetic acids, and citric acids, and also produce lipolytic, glycolytic, and proteolytic enzymes, which could express several health benefits. Fermented foods from *Bifidobacterium* spp. exhibit hypocholesterolemic activities by binding with cholesterol and triglycerides in the intestine (Bourrie *et al*., 2016). Consumption of fermented foods increases the levels of water-soluble vitamins, especially vitamins B_1, B_2, B_7, B_9, and B_{12} in the human body (Patel *et al*., 2013). *Lactococcus* spp. can synthesise conjugated linolenic acid, which shows anticarcinogenic, anti-atherosclerosis, anti-inflammatory, antidiabetic, anti-osteoporosis, anti-adipogenic, and hypotensive activities (Yang *et al*., 2014). Yogurt is a fermented dairy product produced by *Lactobacillus* spp. containing high proteins, vitamin B_2, vitamin $B1_2$, calcium, magnesium, and zinc, as compared to unfermented milk (Wang *et al*., 2013).

Adverse effects

Fermented foods are considered safe and suitable for a wide range of consumers. However, their spoilage may cause mild to severe responses, depending on food type and the extent of spoilage. Abnormal fermentation conditions in temperature, fermentation time, or the use of unsterile equipment and spaces may cause the fermented food to spoil, thus becoming unsafe to consume. Fermented foods are high in probiotic content, and the most common adverse effect of fermented food is bloating or flatulence. However, the symptoms may be severe when consumed with fibre-rich foods. The application of a bacterial strain before its proper identification has led to negative impacts, thus causing negative perceptions regarding functional foods. The main side effects of fermented foods are unpleasant digestion, headache, increased histamine level, and allergic reactions. For a majority of the population, probiotics and other forms of fermented foods are safe, and minor side effects can disappear rapidly. However, improper fermentation conditions may lead to developing biological hazards caused by various pathogenic bacteria. Bacterial strains such as lactobacilli and bifidobacteria are rarely associated with adverse effects because of having no genes associated with pathogenicity (Gawai and Prajapati, 2017). However, still researchers are concerned about resistance to host innate defence mechanisms to be considered in terms of safety aspect. Furthermore, enterococci are reported to have virulence factors such as DNAse, gelatinase, haemolysin, or presence of structural genes. Research in this particular area still needs further *in vivo* and genomic assessments of risk factors through animal model studies. Antibiotic resistance that can be developed by the exchange of antibiotic resistance markers between pathogens and food microorganisms is another major risk associated with functional foods (Schmid *et al.*, 2006). Antibiotic resistance can be exchanged by plasmid-mediated gene transfer and a starter culture like *Lactobacillus* could also act as a source. Therefore, the strain should be systematically monitored for resistance before application. Typically, fermented food products may contain biogenic amino acids, mycotoxins, foodborne pathogenic bacteria, and degraded organic acids when the production has failed. Biogenic amines (histamine, tyramine, agmatine, cadaverine, putrescine, spermine, and spermidine) are produced in the food by spoilage microorganisms that break down amino acids and convert them into biogenic amines, by the activities of amino acid decarboxylase and/or by the amination and transamination of aldehydes and ketones. The consumption of toxic biogenic amines in food may induce severe migraine, headache, insomnia, depression, diarrhoea, and others. Biogenic amine production is reported to be strain-dependent. *Enterococcus faecium* strain leads to biogenic amine (tyramine) accumulation in red wine during malolactic fermentation, whereas *Enterococcus faecalis* was responsible for biogenic amine production in fermented soybean. Histamine and tyramine were the major biogenic amines produced in high levels by microorganisms through the activity of amino acid decarboxylases. High amounts of these amines lead to a flushed face, sweating, rash, burning taste in mouth, diarrhoea, and cramps with severe respiratory distress (Gawai and Prajapati, 2017). Medina-Pradas and Arroyo-Lopez (2015) reported that fermented olives have high levels of putrescine, cadaverine and tyramine with *Lactobacillus plantarum*, *Pediococcus* spp. and *Leuconostoc mesenteroides*. Şanlier *et al.* (2019) stated that fermented vegetables and soy products have high contents of histamine, tyramine, cadaverine, putrescine, and tryptamine due to the metabolites of *Lactobacillus plantarum*, *Rhizopus oligosporus*, and *Trichosporon beiglii*.

Mycotoxins are the toxic secondary metabolites of certain mould species. Mycotoxins are mutagenic, teratogenic, and carcinogenic, and consumption may cause various side effects (skin irritation, immunosuppression, neurotoxicity, depression, dizziness, eye irritation, fatigue, headache, hearing loss, muscle weakness, skin rashes, vision changes, *etc.*) to the consumers. *Penicillium*, *Aspergillus*, *Cladosporium*, *Alternaria*, *Fusarium*, and *Stachybotrys* are the common mould species that produce mycotoxins in foods and crop commodities. Pascari *et al.* (2018) found various mycotoxins which were transferred from the malt to boiled wort, and the temperature did not cause any changes to these mycotoxins. Bauer *et al.* (2016) found several mycotoxins including ergot alkaloids, alternariol, deoxynivalenol, and zearalenone in beer. Bacteria, yeasts, moulds, and enzymes are used in a novel way to remove various mycotoxins by binding or biodegradation. Further, degradation of organic acids during fermentation is another significant issue. Microorganisms such as *Lactobacillus buchneri* could convert lactic acid into acetic acid, thus causing off-odour in fermented olives. *Propionibacterium* and *Pectinatus* spp. can convert lactic acid into propionic acid in whey, thus causing taste changes (Lucena-Padros *et al.*, 2014). Fermentation of foodstuff under abnormal conditions may also give N-nitroso compounds and genotoxins, which can lead to cancers. Ethyl carbamate (Group 2A carcinogen) or 3-MCPD (3-monochloropropane-1,2-diol) and 1,3-DCP (1,3-dichloropropan-2-ol) (Group 2B carcinogen) are found in soy sauce produced through improper fermentation conditions (Crews *et al.*, 2000). Fermentation of seafood deserves extra attention due to an invasion by nematode worms in the raw seafood materials, and these can be effectively inactivated by salting, freezing, or irradiation treatments (Zhang *et al.*, 2014). As previously mentioned, lactic acid in many fermented vegetables could act as a biopreservative, inhibiting most pathogenic and spoilage microorganisms. However, it could also be converted to various other organic acids by different microorganisms, thus adversely affecting the shelf-life and stability of fermented foods.

Conclusion

Fermentation was traditionally aimed to balance the food availability and food preservation. It is an eco-friendly alternative for production and extraction of metabolites from natural sources. Fermented foods possess unique nutritional values that enhance the health through metabolites produced during fermentation. Interaction and bioactive compound production add novel flavours to fermented foods. Moreover, this area has great potential to expand in the near future due to the rising consumer desire for healthy foods. Many scientific studies have also reported the sustainable and promising opportunities of fermentation. Microbial metabolites possess numerous applications in both medical and nutrition industries. However, majority of commercial metabolite production is from various pathogenic microorganisms, and only very few GRAS microorganisms are utilised. Abundant levels of various metabolites are produced during fermentation, but still many of them are not well-studied and reported. The real challenge is to find safer metabolites generated in food fermentation. Therefore, the present review could provide the knowledge on the beneficial effects of microbial metabolites produced during fermentation.

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