Chapter 19

Antioxidants in Fermented Foods

Santa Ram Joshi and Koel Biswas

Contents

19.1 Introduction

The process of food fermentation is practised by human cultures all over the world. It has become a major component of human survival in places where preserved food has become a necessity. The term “fermentation” comes from a Latin word *fermentum* (to ferment). The definition describes fermentation as the process by which chemical changes in an organic substrate occur as a result of the action of microbial enzymes. Fermentation can also be defined as any process for the making of a product by a mass culture of microorganisms. It is one of the oldest and the most economic forms of food preservation which renders benefits from providing bionutrients and minerals to enhancement of flavor and aroma. Extending the shelf life of foods is one of the major objectives of fermentation, with aspects such as wholesomeness, acceptability, and overall quality. Fermented foods make a major contribution to dietary staples in numerous countries across Africa, Asia, and Latin America and small-scale fermentation technologies contribute substantially to food security and nutrition, particularly in regions that are vulnerable to food shortages (FAO 1998).

Fermentation technologies play an important role in ensuring the food security of millions of people around the world, particularly marginalized and vulnerable groups facing shortage or deficiencies in food supplies. Fermented foods are described as palatable and wholesome and are generally appreciated for several attributes: their pleasant flavors, aromas, textures, and improved cooking and processing properties (Holzapfel and Schillinger 2002). These characteristics in fermented foods are enhanced by virtue of the metabolic activities of the enzymes secreted by microorganisms. Traditional skills have been developed for refining fermentation processes (Hammes 1990). Many fermented products despite their many nutritional advantages are often associated with the stigma of being a "poor man's" food.

19.2 Antioxidants

An antioxidant is a molecule that inhibits the oxidation of other molecules. Oxidation of compounds produces free radicals; in turn these radicals can start a chain reaction. When such a chain reaction occurs in a cell, it causes damage to or the death of the cell. It has been reported that oxygen-free radicals and other reactive oxygen species (ROS) may be formed in the human body and in the food system. Antioxidants terminate the chain reactions by removing the free radical intermediates. Oxidative free radicals are byproducts of the normal reactions within our body. These reactions include the generation of calories, degradation of lipids, the catecholamine response under stress, and inflammatory processes (Ikeda and Long 1990). If the balance between oxidative-free radical production and eradication is maintained, the harmful effects of free radicals in the body are minimized. However, if unwanted free radicals are not eradicated efficiently, oxidative stress occurs. Oxidative stress, caused by reactive oxygen or free radicals, has been shown to be associated with the progression of many lifestyle-related diseases such as atherosclerosis, cirrhosis, arthritis, cancer, heart disease, and depression (McCord 2000, Kovacic and Jacintho 2001, Parola and Robino 2001). In order to protect tissues and organs from oxidative damage, the body possesses both enzymatic and nonenzymatic systems. The main enzymes include superoxide dismutase (SOD), glutathione peroxidase (GSH-Px), and catalase (CAT). These enzymes are front line defenders against oxidative damage. In addition to these enzymes, the nonenzymatic mechanism can also protect the body from damages caused by oxidative stress. One of the most common natural antioxidants is vitamin E. It acts as a peroxyl radical scavenger. Recently, investigators and consumers have been showing interest in seeking natural antioxidant components in the diet, which may help to reduce oxidative damage.

19.2.1 Antioxidants and Health

Antioxidants are believed to play an important role in the body's defense system against oxygen-free radicals and other ROS, which also play a significant pathological role in human diseases (Lin and Yang 2007). Natural antioxidants in plants are related to three major groups: carotenoids, vitamins, and phenolics. Phenolic compounds are plant-derived antioxidants that possess metal chelating capabilities and radical scavenging properties. For example, soybean and its products containing phenolic compounds have been shown to possess antioxidant ability. It has been observed that the intake of antioxidants containing soy food is associated with reduced cardiovascular risk resulting from lower blood pressure, and homocysteine. Dietary intake of soybeans and soybean products also decrease risk of cancer, including breast, colon, and prostate cancers. Many studies reported the protective role of certain components of soybean, especially isoflavone, saponin, vitamin C, tocopherol, and phytate against oxidative stress (Diaz-Batalla et al. 2006, Kumar et al. 2009, 2010). It is emphasized that the intake of food-derived antioxidants in the daily diet may reduce oxidative damage and exerts a corresponding beneficial effect on health. Many other antioxidant components have also been found in soybean foods including fermented soybeans, such as isoflavones, tocopherols, phospholipids, chlorogenic acid isomers, caffeic acid, ferulic acid, peptides, amino acids, and melanoidin.

Owing to the risks of consuming synthetic antioxidants, research studies of natural products containing antioxidant activity have increased, with the aim of replacing synthetic antioxidants or applying associations that reduce their toxic effects (Aungulu et al. 2007, Mendiola et al. 2010). Among the several classes of naturally occurring antioxidant substances, phenolic compounds have drawn particular attention because they inhibit lipid peroxidation (Kristinova et al. 2009) and lipo-oxygenation *in vivo* that is mainly due to the reducing properties of chemical structures that enable neutralization or sequestration of free radicals, as well as the chelation of transition metals, thus avoiding the phase of inhibiting the spread of oxidative processes. Vegetable tissues are good sources of these compounds, often containing simple phenols, phenolic acids (derived from benzoic and cinnamic acid), coumarin, flavonoids, stilbenes, condensed and hydrolyzable tannins, lignins, and lignans (Melo and Guerra 2002, Moon and Shibamoto 2009).

Among the sources of phenolic compounds, rice (*Oryza sativa*) should be highlighted because it is one of the most produced and consumed cereals in the world and plays an important role in the diet–health relationship, and contains distinct phenolic compounds, tocopherols, tocotrienols, and g-oryzanol mainly associated with the pericarp (Iqbal et al. 2005). Another example of a natural source of antioxidants is *Terminalia chebula,* a native plant to India. The dried ripe fruit of *Terminalia chebula* is used in the Indian systems of medicine such as Ayurveda and Siddha. It is a well-known ayurvedic rasayana which possesses adaptogenic properties (Rege et al. 1999). The active principal constituents of *Terminalia chebula* are gallic acid, ellagic acid, tannic acid, ethyl gallate, chebulagic acid, chebulinic acid, corilagin, beta-sitosterol, terchebulin, caffeic acid, mannitol, anthraquinones, ethanedioic acid, terpinene, terpinenol, and so on (Saleem et al. 2002, Kim et al. 2006, Xie et al. 2006).

Since antioxidative peptides can protect the human body from free radicals and slow the progression of many chronic diseases in addition to providing nutritional value, there has been a significant increase in interest in such antioxidants (Rajapakse et al. 2005, GokturkBaydar et al. 2007). Several traditional fermented soybean foods, including *miso*, *natto*, *tempe, sufu*, and *douchi*, possess many advantageous properties such as free radical scavenging activity and reducing power and ion-chelating abilities (Santiago et al. 1992, Berghofer et al. 1998, Gibbs et al. 2004). *Miso* has been used as a traditional daily seasoning for several centuries in Japan. It is also used to reduce plasma cholesterol levels (Horii et al. 1990), colonic aberrant crypt foci (Ohara et al. 2002), cerebrovascular disease (Kanazawa et al. 1995), and hypertension (Kanda et al. 1999).

In Indonesia, the fungus used for the preparation of *miso* belongs to a genus other than *Aspergillus* (Sastraatmadja et al. 2002). *Aspergillus* spp. has been used as starter organisms for the preparation of *koji* for thousands of years. They are typically used in the fermentation industry to produce enzymes (Bennett and Klich 1992), organic acids (Raper and Fenell 1965), vitamins (Bennett 1985), soy sauce, *miso*, and *sake* (Hesseltine 1981), and antibiotics (Kozakiewicz 1989). The acceptability, nutritional value, and functionality of the resulting hydrolyzate, such as antioxidant activity, proliferation of both human hybridoma and mouse macrophage cells after 1 h of hydrolysis by *Aspergillus oryzae*, and LAB fermentation have been reported to be improved.

Lactobacillus species are probably the most important bacteria in the food industry. They are widely used as starter cultures and have been reported to play significant roles in the production of fermented food. *Lactobacillus* species are generally recognized as safe (GRAS) and have been reported to have beneficial health properties, as a result of which they are also finding increasing use as probiotics in other health-related applications. An array of beneficial activities such as immunomodulatory, antiallergenic, antimicrobial, antihypertensive, and antitumourigenic effects have been reported (Ishida-Fujii et al. 2007). *Lactobacillus* sp. has also been shown to possess antioxidant activities (Kapila et al. 2006).

19.3 Oxidative Stress

Oxidative stress results when the oxidant/antioxidant ratios tilt in favor of oxidant factors, and it is involved in the aging process and also causes inflammation (Madamanchi et al. 2005). Free radicals attack cellular components leading to oxidation of lipids, proteins, and DNA, thus causing structural and functional changes to these molecules. Oxidation of food constituents is also a key event in food spoilage. This may reduce the nutritional value and safety of food by producing undesirable flavors and toxic substances. The global interest in harnessing the beneficial properties of microbes and their metabolites for human health make it important to explore potential uses of indigenous food grade lactobacilli in the development of functional foods and probiotics. Research has found that *Lactobacillus fermentum* is a superior microbial producer of ferulic acid. Ferulic acid is a naturally found phenolic acid and is a potent antioxidant which is able to neutralize free radicals, such as ROS. ROS have been implicated in DNA damage, cancer, and accelerated cell aging. Recent studies suggest that FA has antitumor activity against breast cancer (Kampa et al. 2003), liver cancer (Lee et al. 2005), and is effective in preventing cancer induced by exposure to various carcinogenic compounds such as benzopyrene (Lesca 1983) and 4-nitroquinoline 1-oxide (Tanaka et al. 1993).

19.4 Naturally Occurring Antioxidants

Naturally occurring antioxidants are found in most plants and animal tissues. The majority of natural antioxidants are phenolic compounds and the most important groups are the tocopherols, flavonoids, and phenolic acids. Antioxidants are substances which significantly inhibit or delay oxidative processes such as lipid peroxidation even at low concentrations. Fermentation involves the transformation of organic substances into simpler compounds such as peptides, amino acids, and other nitrogenous compounds by bacterial or endogenous enzymes. While they are important contributors to the flavor and aroma of fermented products (Mackie et al. 1971, Raksakulthai and Haard 1992), some exhibit an antioxidant capacity (Kitts and Weiler 2003).

Amino acids such as tryptophan and histidine (Houlihan and Ho 1985), glycine and alanine (Hui-Chun et al. 2003) exhibit antioxidative properties. Tyrosine and lysine are generally accepted to be antioxidants (Wang and Gonzalez de Mejia 2005). Amino compounds such as amino acids and peptides can function as primary antioxidants and can also interact with other substances to form Maillard reaction products (MRPs) (Kitts and Weiler 2003). They are nonenzymatic browning reactions that occur in foods. Lysine, as one of the major amino acids in salt-fermented shrimp paste, could have reacted with another substance thus reflecting an increase in activity. Sugar–lysine (Wijewickreme et al. 1999, Jing and Kitts 2004), glucose-glycine (Yoshimura et al. 1997) and sugar-protein (Benjakul et al. 2005) model systems have been shown to exhibit antioxidant activity. In some cases, oxidation reactions show opposite effects on the antioxidant properties of foods. Partially oxidized polyphenols, for instance, exhibit higher antioxidant activity than that of nonoxidized phenols. Thermal processing at elevated temperature, for example, pasteurization, probably influence the transformation of antioxidants into a more active and resistant compound such as MRPs. Antioxidant efficiency of MRPs is influenced by factors such as ratio and type of amino acid compounds and sugar involved, temperature, pH, and water activity (Manzocco et al. 2001).

During the past few decades, significant attention has been paid to dairy and nondairy products containing probiotic bacteria. Today, probiotic microorganisms are available in the market in three different types for direct or indirect human consumption. They include

- Culture concentrate to be added to a food (dried or deep-frozen form) for industrial or home use
- Food products (fermented or nonfermented)
- Dietary supplements (drug products in powder, capsule, or tablet forms)

Consumption of probiotic cells *via* food products are the most popular and widespread way of their intake into the body. Functional foods, designer foods, or medicinal foods are defined as "foods that contain some health-promoting component(s) beyond traditional nutrients." Addition of probiotics is a way in which foods can be changed to become functional (FAO/WHO 2001). Different types of food matrices which have been used as probiotics include various types of cheese, ice cream, milk-based desserts, butter, mayonnaise, powder products or capsules, and fermented foods of vegetable origin (Tamime et al. 2005). In the production of probiotics, an important factor is the food substrate. Besides buffering the bacteria through the stomach, it may contain functional ingredients that interact with the probiotics, altering their activities. Fat content, type of protein, carbohydrates, and pH can affect probiotic growth and survival (Soccol et al. 2010).

Although cholesterol is an important component for body tissues, elevated blood cholesterol is a well-known major risk factor for coronary heart disease (CHD) (Aloglu and Oner 2006). It has been reported that hypercholesterolemia contributes to 45% of heart attacks in Western Europe and 35% of heart attacks in Central and Eastern Europe (Yusuf et al. 2004). CHD is the main cause of death in Canada, the United States, and many other countries around the world (Heart and Stroke Foundation of Canada 2000, American Heart Association 2002). WHO has predicted that by 2030, cardiovascular diseases will remain the leading causes of death, affecting approximately 23.6 million people around the world (WHO 2009). The risk of heart attack is three times higher in those with hypercholesterolemia compared with those who have normal blood lipid profiles (Homayouni et al. 2012). Also, each increase in the serum cholesterol concentration by 1% results in 2%–3% increase in the risk of CHD (Davis et al. 2005, Manson et al. 1992). In healthy adults, about 1 g of cholesterol is synthesized and 0.3 g is consumed per day. The body maintains a relatively constant amount of cholesterol (150–200 mg/dL). This is done mainly through controlling the level of *de novo* synthesis. Dietary intake of cholesterol in part regulates the level of cholesterol synthesis. These cholesterols are then used in the formation of membranes and in the synthesis of the steroid hormones and bile acids (Croft et al. 1988). Bile acid synthesis uses most of this cholesterol.

The cholesterol pool of the liver is used in two important ways. The liver utilizes part of it to produce bile salts, to be stored in the gall bladder as a part of bile, which ends up in the gut. There, the bile salts are involved in the emulsification of fats and in their ingestion and absorption. The rest of the cholesterol is used for other requirements of the body. To do this, the liver combines cholesterol from its pool with triglycerides and covers it with a particular protein so that it can be dissolved in the blood. These are somewhat large molecules, known as very low-density lipoproteins (VLDL). The liver then drains them into the blood. Lipoprotein lipase (LPL) exists in abundance all over the body, especially in the walls of the arteries. This enzyme is involved in removing triglycerides from VLDL cholesterol. In the process, the VLDL shrinks in size and a relatively larger portion of it is made up of what is called intermediate density lipoproteins, or IDL. As the process continues, and more triglycerides are taken away, what is left is a dense molecule referred to as low-density lipoprotein (LDL). This lipoprotein still maintains a large amount of cholesterol. The protein layer allows the tissues to use this cholesterol. It is the LDL receptors on these tissues that make this interaction possible. In tissues such as that of the liver, and the inner layer of the arterial wall, cholesterol is taken away from LDLs. Free radicals in the body are very reactive and oxidative compounds can oxidize LDL cholesterol and help the formation of atherosclerotic plaque in the arteries. Antioxidants in the body can inhibit this process (Jialal 1998). The liver also produces another type of lipoprotein, named high-density lipoprotein (HDL). This is different from VLDL, which is also produced in the liver. It has little triglyceride and cholesterol, and has a particular protein covering. HDL collects the surplus cholesterol that cholesterol metabolizing cells cannot utilize. Lecithin–cholesterol acyl transferase is an enzyme that is responsible for transporting surplus cholesterol back to HDL molecules. Unused cholesterol from arteries, liver, and other tissues are absorbed by HDL cholesterol. There is evidence that even some oxidized LDL can be removed by the LCAT and HDL cholesterol (Hockerstedt et al. 2004). As HDL circulates in the body and collects the cholesterol from tissues, it becomes mature and goes back to the liver. There, it is identified by its lipoprotein covering and is lodged in the liver's cholesterol pool.

Recent approaches and research work done for lowering blood cholesterol levels involve dietary management, behavior modification, regular exercise, and drug therapy (Dunn-Emke et al. 2001). Pharmacological agents available in the markets are used for the treatment of high cholesterol. Although they effectively reduce cholesterol levels, they are expensive and are known to have severe side effects (Bliznakov 2002). Lactic acid bacteria (LAB) with active bile salt hydrolase (BSH) or products containing them are suggested to lower cholesterol levels through interaction with host bile salt metabolism (De Smet et al. 1998). It has been reported by De Smet et al. (1995) that lactobacilli with active BSH have an advantage to survive and colonize the lower small intestine of the host where the enterohepatic cycle takes place and therefore BHS activity may be considered an important colonization factor. Sanders (2000) proposed a mechanism based on the ability of certain probiotic lactobacilli and bifidobacteria to deconjugate bile acids enzymatically, increasing their rates of excretion. Cholesterol being a precursor of bile acids, converts its molecules to bile acids replacing those lost during excretion and this leads to reduction in serum cholesterol. This mechanism could be operated in the control of serum cholesterol levels by conversion of deconjugated bile acids into secondary bile acids by colonic microbes.

Members of the gut microbiota in the large intestine of animals exhibit a variety of enzymatic activities with potential impact on animal health through biotransformation of secondary plant products and xenobiotic compounds (McBain and Macfarlane 1998, Heavey and Rowland 2004, Blaut and Clavel 2007). β-Glucuronidases liberate toxins and mutagens that glucuronate in the liver and excrete into the gut with the bile. This can lead to high local concentrations of carcinogenic compounds within the gut, thus increasing the risk of carcinogenesis (Gill and Rowland 2002). Furthermore, reuptake of the deconjugated compound from the gut and reglucuronidation in the liver leads to an enterohepatic circulation of xenobiotic compounds, which increases their retention time in the body. β-Glucosidases can exert either beneficial or harmful effects, as they form aglycones from a range of different plant glucosides, which might exhibit either toxic/mutagenic or health-promoting effects (Hill 1995, Manach et al. 2004). Some plant glucosides are also subject to deconjugation by host β-glucosidases in the upper gut and may subsequently be glucuronated by the host, making them a substrate for bacterial β-glucuronidases when they reach the colon with the bile (Manach et al. 2004). The resulting aglycones of plant polyphenols may be subjected to further degradation and biotransformation by the gut microbiota (Blaut et al. 2003, Atkinson et al. 2005). Morotomi (1996) reported that *Lactobacillus casei* Shirota strain, a lactic acid bacterium has potential for cancer chemoprevention.

Increased β-glucosidase activity upon soy consumption has been reported in human volunteers (Wiseman et al. 2004). Fecal β-glucuronidase activity increased in rodents after consumption of a high-protein high-fat diet (Eriyamremu et al. 1995) and decreased after consumption of diets high in carbohydrates (Shiau and Chang 1983, Gestel et al. 1994). It has also been reported that cancer patients exhibit higher β-glucuronidase activities than healthy controls (Kim and Jin 2001). Many *in vitro* tests need to be performed while screening for potential probiotic strains (Harzallah and Belhadj 2013). The first step in the selection of a probiotic LAB strain is the determination of its taxonomic classification, which may give an indication of the origin, habitat, and physiology of the strain. All these characteristics have important consequences on the selection of novel strains for probiotic use (Morelli 2007).

Intestinal microbiota is not homogeneous. The number of bacterial cells present in the mammalian gut shows a continuum that goes from 10^1 to 10^3 bacteria per gram of contents in the stomach and duodenum, progressing to 10^4–10^7 bacteria per gram in the jejunum and ileum and culminating in 10^{11}–10^{12} cells per gram in the colon (Sekirov et al. 2010). Additionally, the microbial composition varies between these sites. In addition to the longitudinal heterogeneity displayed by the intestinal microbiota, there is also a great deal of latitudinal variation in the microbiota composition. The microbiota present in the intestinal lumen differs significantly from the microbiota attached and embedded in this mucus layer as well as the microbiota present in the immediate proximity of the epithelium. For instance, *Bacteroides, Bifidobacterium, Streptococcus*, members of Enterobacteriaceae*, Enterococcus, Clostridium, Lactobacillus,* and *Ruminococcus* were all found in feces, whereas only *Clostridium, Lactobacillus,* and *Enterococcus* were detected in the mucus layer and epithelial crypts of the small intestine (Sekirov et al. 2010). β-Glucuronidase, β-glucosidase, and urease activity usually come from these colonic bacteria (Chadwick et al. 1992, Burne and Chen 2000). Urea, which is the end product of nitrogen metabolism, undergoes an enterohepatic circulation, being produced in the liver and then entering the intestinal tract by passive diffusion (Suzuki et al. 1979). Urease has been demonstrated to hydrolyze the substrate urea to form CO_2 and two molecules of NH_3 (Mobley et al. 1995). The NH_3 produced raises the pH of the cytoplasm, thereby buffering the bacteria under acidic environmental conditions. In addition, the NH_3 provides the bacterial cell with an easily assimilated source of nitrogen (Steyert and Kaper 2012).

Improving the viability of probiotic bacteria in different food products (especially fermented products) until the time of consumption has been the subject of hundreds of studies. Viability of probiotic microorganisms, namely, the number of viable and active cells per gram or milliliter of probiotic food products at the moment of consumption is the most critical value of these products which determines their medicinal efficacy (Tamime et al. 2005, Khorbekandi et al. 2011). The addition of L-cysteine, whey protein concentrate, and tryptone improved the viability of *Lactobacillus acidophilus* and bifidobacteria by providing growth factors as these probiotic bacteria lack proteolytic activity (Dave and Shah 1998). Protein derivatives promote probiotic survival due to several reasons namely, their nutritional value for the cells, reducing redox potential of the media as well as increasing buffering capacity of the media (which results in a smaller decrease in pH) (Dave and Shah 1998, Mortazavian et al. 2010). *Lactobacillus* species represent indigenous organisms of the mammalian gastrointestinal (GI) tract and have been used as probiotic agents for the treatment of GI infections and inflammatory bowel disease (IBD) (Madsen 2001, MacFarlane and Cummings 2002). *Lactobacillus* species have been isolated from the intestines of various mammals, including rodents (mice and rats), dogs, cats, ruminants, horses, nonhuman primates, and humans (Savage et al. 1968, Watanabe et al. 1977). These organisms are present in relatively high numbers in the GI tracts of mice and presumably play a beneficial role in healthy animals.

Saturated fatty acids undergo less peroxidation than their unsaturated counterparts. Indeed, supplementation with polyunsaturated as opposed to saturated fatty acids results in a statistically significant increase in lipid peroxidation in the plasma and liver (Song et al. 2000, Song and Miyazawa 2001, Shin 2003). Lactic acid bacteria are promising agents for protecting the liver (Segawa et al. 2008) and very useful as a functional food for maintaining human health (Velayudham et al. 2009). Inhibition of lipid peroxidation is commonly used for analysis of antioxidative activity (Ou et al. 2006). There are reports that have provided evidence of certain LAB possessing antioxidative activity (Kullisaar et al. 2002, Songisepp et al. 2005). Saide and Gilliland (2005) suggested that some lactobacilli strains are a source of dietary antioxidants. It was reported by a study providing new insights into the mechanisms by which LAB with antioxidative properties can help to protect the liver in mammals. Along with the change in dietary patterns to a "Western-style" diet, which contains very little fiber and is deficient in important nutrients, there has been a concurrent increase in the incidence of diseases such as obesity, cardiovascular disease, type 2 diabetes, colon cancer, and constipation (Reddy 1995, Lee and Lee 2000, Lim et al. 2006). Additionally, protective intestinal flora such as LAB are often damaged and reduced as a result of stress and consumption of a Western diet (Bengmark 2000). Intake of fermented foods which reports colonization of probiotic microflora not only can be a source of health-promoting ingredients but also a good source of antioxidants which can terminate or halt the vicious harmful cycle of ROS. There has been a dearth of information on the antioxidant potential of microbes prevalent in fermented foods or food ingredients, but with the benefits reported for fermented foods and associated microbes, there is an urgent need to bioprospect the antioxidant metabolites associated with fermented foods.

19.5 Conclusion

Fermented foods and beverages have occupied an important place in dietary habits and have been a part of the food culture of many communities across the world. The traditional technology behind the development and processing of fermented foods was basically meant for preserving and improving their nutritional value. Fermented foods enhance the flavor and aroma and improve the digestibility of the fermented materials. Texturing and/or biologically active agents' production could be envisaged directly *in situ* of food. Traditionally fermented products have attracted the attention of the food industry because of the involvement of GRAS organisms along with the rheological properties of the products. The health benefits of fermented foods have been an attention gatherer and the beneficial effects of fermented products have been widely reported. The probiotic aspects of fermented foods have focused largely on specific health promoting activities. Among important health protectors and promoters, antioxidant compounds have largely been envisaged as artificial supplements which invariably carry certain risks. Therefore, it is felt that antioxidants from fermented foods can be a potential source for replacing synthetic antioxidants that are available for human use, and thus larger attention is needed to explore and bioprospect antioxidants from fermented foods.

References

Aloglu, H. and Z. Oner. 2006. Assimilation of cholesterol in broth, cream and butter by probiotic bacteria. *European Journal of Lipid Science and Technology* 108(9): 709–713.

Atkinson, C., C.L. Frankenfeld, and J.W. Lampe. 2005. Gut bacterial metabolism of the soy isoflavone daidzein: Exploring the relevance to human health. *Experimental Biology and Medicine* 230: 155–170.

Aungulu, G. 2007. Activity of gaseous phase steam distilled propolis extracts on peroxidation and hydrolysis of rice lipids. *Journal of Food Engineering* 80: 850–858.

Bengmark, S. 2000. Colonic food: Pre- and probiotics. *American Journal of Gastroenterology* 95(Suppl. 1): 5–7.

Benjakul, S., W. Lertittikul, and F. Bauer. 2005. Antioxidant activity of Maillard reaction products from a porcine plasma protein-sugar model system. *Food Chemistry* 93: 189–196.

Bennett J.W. and M.A. Klich. 1992. *Aspergillus: Biology and Industrial Applications*, in J. W. Bennett and M. A. Klich, Eds. 21: 134–137.

Bennett, J.W. 1985. Taxonomy of fungi and biology of the Aspergillus, *Biology of Industrial Microorganisms*, in A. L. Demain and N. A. Solomon, Eds. London: The Benjamin Cummings Publishing Company, Inc., 29: 359–406.

Berghofer, E., B. Grzeskowiad, N. Mundigler, W. B. Sentall, and J. Walcak. 1998. Antioxidant properties of faba bean, soybean and oat tempeh. *International Journal of Food Science and Nutrition* 49: 45–54.

Blaut, M. and T. Clavel. 2007. Metabolic diversity of the intestinal microbiota: Implications for health and disease. *The Journal of Nutrition* 137: 751S–755S.

Blaut, M., L. Schoefer, and A. Braune. 2003. Transformation of flavonoids by intestinal microorganisms. *International Journal for Vitamin and Nutrition Research* 73: 79–87.

Bliznakov, B.G. 2002. Lipid-lowering drugs (statins), cholesterol, coenzyme Q10. The baycol case—A modern Pandoras box. *Biomedice and Pharmacotherapy* 56(1): 56–59.

Burne, R.A. and Y.Y.M. Chen. 2000. Bacterial ureases in infectious diseases. *Microbes and Infection* 2: 533–542.

Chadwick, R.W., S.E. George, and L.D. Claxton. 1992. Role of the gastrointestinal mucosa and microflora in the bioactivation of dietary and environmental mutagens or carcinogens. *Drug Metabolism Reviews* 24: 425–492.

Croft, J.B., J.L. Cresnta, L.S. Webber, S.R. Srinivasan, D.S. Freedman, G.L. Burke, and G.S. Berenson. 1988. Cardiovascular risk in parents of children with extreme lipoprotein cholesterol levels. *Southern Medical Journal* 81(3): 341–353.

Dave, R.I. and N.P. Shah. 1998. Ingredient supplementation effects on viability of probiotic bacteria in yogurt. *Journal of Dairy Science* 81: 2804–2816.

Davis, J., M.J. Iqbal, J. Steinle, J. Oitker, D.A. Higginbotham, R.G. Peterson, and W.J. Banz. 2005. Soy protein influences the development of the metabolic syndrome in male obese ZDFxSHHF rats. *Hormonal Metabolism Research* 37: 316–25.

De Smet. I., L. Van Hoorde, M.V. Woestyne, H. Christiaens, and W. Verstraete. 1995. Significance of bile salt hydrolase activity of lactobacilli. *Journal of Applied Bacteriology* 79: 292–301.

De Smet. I., P. De Boever, and W. Verstraete. 1998. Cholesterol lowering in pigs through enhanced bacterial bile salt hydrolase activity. *British Journal of Nutrition* 79: 185–194.

Diaz-Batalla. L., J.M. Widholm, G.C. Fahey, E. Castano-Tostado, and O. Paredes-Lopez. 2006. Chemical components with health implications in wild and cultivated Mexican common bean seeds (*Phaseolus vulgaris* L.). *Journal of Agricultural and Food Chemistry* 54(6): 2045–2052.

Dunn-Emke, S., G. Weider, and D. Ornish. 2001. Benefits of a low-fat-based diet. *Obesity Research* 9(11): 731.

Eriyamremu, G.E., V.E. Osagie, O.I. Alufa, M.O. Osaghae, and F.A. Oyibu. 1995. Early biochemical events in mice exposed to cycas and fed a Nigerian-like diet. *Annals of Nutrition and Metabolism* 39: 42–51.

FAO. 1998. Fermented fruits and vegetables—A global perspective, FAO Agricultural Services Bulletin No. 134, Rome.

Gestel, G, P. Besancon, and J.M. Rouanet. 1994. Comparative evaluation of the effects of two different forms of dietary fibre (rice bran vs. wheat bran) on rat colonic mucosa and faecal microflora. *Annals of Nutrition and Metabolism* 38: 249–256.

Gibbs, B.F., A. Zougman, R. Masse, and C. Mulligan. 2004. Production and characterization of bioactive peptides from soy hydrolysate and soy-fermented food. *Food Research International* 37: 123–131.

Gill, C.I.R. and I.R. Rowland. 2002. Diet and cancer: Assessing the risk. *British Journal of Nutrition* 88: S73–S87.

GokturkBaydar, N., G. Ozkan, and S. Yasar. 2007. Evaluation of the antiradical and antioxidant potential of grape extracts. *Food Control* 18: 1131–1136.

Hammes, W.P. 1990. Bacterial starter cultures in food production. *Food Biotechnology* 12: 383–397.

Harzallah, D. and H. Belhadj. 2013. Lactic acid bacteria as probiotics: Characteristics, selection criteria and role in immunomodulation of human GI mucosal barrier. *Lactic Acid Bacteria—R & D for Food, Health and Livestock Purposes*, in Dr. J. Marcelino Kongo Ed., ISBN: 978-953-51-0955-6. InTech, DOI: 10.5772/50732.

Heavey, P.M. and I.R. Rowland. 2004. Gastrointestinal cancer. *Best Practice and Research Clinical Gastroenterology* 18: 323–336.

Hesseltine, C.W. 1981. Future of fermented foods. *Process Biochemistry* 16: 2–16.

Hill, M.J. 1995. Carbohydrate metabolism: Role of gut bacteria in human toxicology and pharmacology, in M J Hill Ed. London, UK: Taylor & Francis, 95–104.

Hockerstedt, A., M. Jauhiainen, and M.J. Tikkanen. 2004. Lecithin/cholesterol acyltransferase induces estradiol esterification in high-density lipoprotein, increasing its antioxidant potential. *The Journal of Clinical Endocrinology and Metabolism* 89(10): 5088–5093.

Holzapfel, W.H. and U. Schillinger. 2002. Introduction to pre- and probiotics. *Food Research International* 35: 109–116.

Homayouni, A., L. Payahoo, and A. Azizi. 2012. Effects of probiotics on lipid profile: A review. *American Journal of Food Technology* 7: 251–265.

Horii, M., T. Ide, K. Kawashima, and T. Yamamoto. 1990. Hypo cholesterolemic activity of desalted miso in rats fed an atherogenic diet. *Nippon Shokuhin Kogaku Kaishi* 37:148–153.

Houlihan, C.M. and C. Ho. 1985. Natural antioxidants in flavor chemistry of fats and oils. *American Oil Chemists' Society*, in D. Min, T. H. Smouse Eds., 117–142. American Oil Chemists' Society.

Hui-Chun W., Shiau C., Chen H., and Chiou T. 2003. Antioxidant activities of carnosine, anserine, some free amino acids and their combination. *Journal of Food and Drug Analysis* 11: 48–153.

Ikeda, Y. and D. M. Long. 1990. The molecular basis of brain injury and brain edema the role of oxygen free radicals. *Neurosurgery* 27: 1–11.

Iqbal, S., M.I. Bhanger, and F. Anwar. 2005. Antioxidant properties and components of some commercially available varieties of rice bran in Pakistan. *Food Chemistry* 2: 265–272.

Ishida-Fujii, K., R. Sato, S. Goto, X.P. Yang, S. Hirano, and M. Sato. 2007. Prevention of pathogenic *Escherichia coli* infection in mice and stimulation of macrophage activation in rats by oral administration of probiotic *Lactobacillus casei* 1–5. *Bioscience, Biotechnology and Biochemistry* 71*:* 866–873.

Jialal, I. 1998. Evolving lipoprotein risk factors: Lipo-protein (a) and oxidized low-density lipoprotein. *Clinical Chemistry* 44: 1827–1832.

Jing, H. and D. Kitts. 2004. Antioxidant activity of sugar-lysine Maillard reaction products in cell free and cell culture systems. *Archives of Biochemistry and Biophysics* 429: 154–163.

Kampa, M., V.I. Alexaki, G. Notas, A.P. Nifli, A. Nistikaki, A. Hatzoglou, E. Bakogeorgou, E. Kouimtzoglou, G. Blekas, and D. Boskou. 2003. Anti proliferative and apoptotic effects of selective phenolic acids on T47D human breast cancer cells: Potential mechanisms of action. *Breast Cancer Research* 6: R63–R74.

Kanazawa, T., T. Osanai, X.S. Zhang, T. Uemura, X.Z. Yin, K. Onoder, Y. Oike, and K. Ohkubo. 1995. Protective effects of soy protein on the peroxidizability of lipoproteins in cerebrovascular disease. *Journal of Nutrition* 125: 639S–646S.

Kanda, A., Y. Hoshiyama, and T. Kawaguchi. 1999. Association of lifestyle parameters with the prevention of hypertension in elderly Japanese men and women: A four-year follow-ip of normotensive subjects. *Asia Pacific Journal of Public Health* 11: 77–81.

Kapila. S., P.R. Vibha, and P.R. Sinha. 2006. Antioxidative and hypocholesterolemic effect of *Lactobacillus casei* ssp. *casei* (biodefensive properties of lactobacilli). *Indian Journal of Medical Science* 60*:* 361–370.

Khorbekandi, H., A.M. Mortazavian, and S. Iravani. 2011. Technology and stability of probiotic in fermented milks. *Probiotic and Prebiotic Foods: Technology, Stability and Benefits to the Human Health*, in N. Shah, A. G. Cruz, and J. A. F. Faria Eds. New York: Nova Science Publishers, 131–169.

Kim, D.H. and Y.H. Jin. 2001. Intestinal bacterial β-glucuronidase activity of patients with colon cancer. *Archives of Pharmacal Research* 24: 564–567.

Kim, H.G., H.G. Cho, E.Y. Jeong, J.H. Lim, S.H. Lee, and H.S. Lee. 2006. Growth inhibiting activity of active component isolated from *Terminalia chebula* fruits against intestinal bacteria. *Journal of Food Protection* 69(9): 2205–2209.

Kitts D. and K. Weiler. 2003. Bioactive proteins and peptides from food sources: Applications of bioprocesses used in isolation and recovery. *Current Pharmaceutical Design* 9(16): 1309–1323.

Kovacic, P. and J.D. Jacintho. 2001. Mechanisms of carcinogenesis: Focus on oxidative stress and electron transfer. *Current Medicinal Chemistry* 8: 396–773.

Kozakiewicz, Z. 1989. Aspergillus species on stored products. *Mycol. Pap*. 161: 1–187.

Kristinova, V., M. Revilija, S. Ivar, and R. Turid. 2009. Antioxidant activity of phenolic acids in lipid oxidation catalyzed by different prooxidants. *Journal of Agricultural and Food Chemistry* 57: 10377–10385, PMid: 19817371.

Kullisaar, T., M. Zilmer, M. Mikelsaar, T. Vihalemm, H. Annuk, C. Kairane, and A. Kilk. 2002. Two antioxidative lactobacilli strains as promising probiotics. *International Journal of Food Microbiology* 72: 215–224.

Kumar. V., A. Rani, A. Dixit, D. Bhatnagar, and G.S. Chauhan. 2009. Relative changes in tocopherols, isoflavones and antioxidative properties of soybean during different reproductive stages. *Journal of Agricultural and Food Chemistry* 57: 2705–2710.

Kumar, V., A. Rani, A.K. Dixit, D. Pratap, and D. Bhatnagar. 2010. A comparative assessment of total phenolic content, ferric reducing-anti-oxidative power, free radical-scavenging activity, vitamin C and isoflavones content in soybean with varying seed coat colour. *Food Research International* 43: 323–328.

Lee, N.K., C.W. Yun, S.W. Kim, H.I. Chang, C.W. Kang, and H.D. Paik. 2005. Screening of lactobacilli derived from chicken feces and partial characterization of *Lactobacillus acidophilus* A12 as an animal probiotics. *Journal of Microbiology and Biotechnology* 18*:* 338–342.

Lee, S.M. and W.K. Lee. 2000. Inhibition effects of lactic acid bacteria (LAB) on the azoxymethane-induced colonic preneoplastic lesions. *The Journal of Microbiology* 38: 169–175.

Lesca, P. 1983. Protective effects of ellagic acid and other plant phenols on benzo[a]pyrene-induced neoplasia in mice. *Carcinogenesis* 4: 1651–1653.

Lim, K.S., S.J. You, B.K. An, and C.W. Kang. 2006. Effects of dietary garlic powder and copper cholesterol content characteristics of chicken eggs. *Asian-Australasian Journal of Animal Science* 19: 582–586.

Lin, J-Y. and C-Y. Tang. 2007. Determination of total phenolic and flavonoid contents in selected fruits and vegetables, as well as their stimulatory effects on mouse splenocyte proliferation. *Food Chemistry* 101(1): 140–7.

MacFarlane, G.T. and J.H. Cummings. 2002. Probiotics, infection and immunity. *Current Opinion in Infectious Disease* 15: 501–506.

Mackie, I.M., R. Hardy, and G. Hobbs. 1971. Fermented fish products, FAO, Rome.

Madamanchi, N.R., A. Vendrov, and M.S. Runge. 2005. Oxidative stress and vascular disease, *Arteriosclerosis. Thrombosis and Vascular Biology*. 25*:* 29–38.

Madsen, K. 2001. The use of probiotics in gastrointestinal disease. *Canadian Journal of Gastroenterology* 15: 817–822.

Manach, C., A. Scalbert, C. Morand, C. Remesy, and L. Jiménez. 2004. Polyphenols: Food sources and bioavailability. *American Journal of Clinical Nutrition* 79: 727–747.

Manson, J.E., H. Tosteson, P.M. Ridker, S. Satterfield, P. Hebert, and G.T. Oconnor. 1992. The primary prevention of myocardial infarction. *The New England Journal of Medicine* 326: 1406–1416.

Manzocco, L., S. Calliaris, D. Mastrocola, M.C. Nicoli, and C. Lerici. 2001. Review of nonenzymatic browning and antioxidant capacity of processed food. *Trends in Food Science Technology* 11: 340–346.

McBain, A.J. and G.T. Macfarlane. 1998. Ecological and physiological studies on large intestinal bacteria in relation to production of hydrolytic and reductive enzymes involved in formation of genotoxic metabolites. *Journal of Medical Microbiology* 47: 407–416.

McCord, J.M. 2000. The evolution of free radicals and oxidative stress. *American Journal of Medicine* 108: 652–659.

Melo, E.A. and N.B. Guerra. 2002. Ação antioxidante de compostos fenólicos atualmente presentes em alimentos. Boletim Sociedade Brasileira de Ciência e Tecnologia-SBCTA 36: 1–11.

Mendiola, J. et al. 2010. Design of natural food antioxidant ingredients through a chemometric approach. *Journal of Agricultural and Food Chemistry* 58: 787–792.

Mobley, H.L., M.D. Island, and R.P. Hausinger. 1995. Molecular biology of microbial ureases. *Microbiological Reviews* 59: 451–480.

Moon, J.K. and T. Shibamoto. 2009. Antioxidant assays for plant and food components. *Journal of Agricultural and Food Chemistry* 57: 1655–1666.

Morelli, L. 2007 *in vitro* assessment of probiotic bacteria: From survival to functionality. *International Dairy Journal* 17: 1278–1283.

Morotomi, M. 1996. Properties of *Lactobacillus casei* shirota strain as probiotics. *Asia Pacific Journal of Clinical Nutrition* 5: 29–30.

Mortazavian, A.M., R. Khosrokhvar, H. Rastegar, and G.R. Mortazaei. 2010. Effects of dry matter standardization order on biochemical and microbiological characteristics of freshly made probiotic Doogh (Iranian fermented milk drink). *Italian Journal of Food Science* 22: 98–102.

Ohara, M., H. Lu, K. Shiraki, Y. Ishimura, T. Uesaka, O. Katoh, and H. Watanabe. 2002. Prevention by long-term fermented miso of induction of colonic aberrant crypt foci by azoxymethane in F344 rats, *Oncology Reports* 9: 69–73.

Ou, C.C., J.L. Ko, and M.Y. Lin. 2006. Antioxidative effects of intracellular extracts of yogurt bacteria on lipid peroxidation and intestine 407 cells. *Journal of Food and Drug Analysis* 14(3): 304–310.

Parola, M., and G. Robino. 2001. Oxidative stress-related molecules and liver fibrosis. *Journal of Hepatology* 35: 297–306.

Rajapakse, N., E. Mendis, W.K. Jung, J.Y. Je, and S.K. Kim. 2005. Purification of a radical scavenging peptide from fermented mussel sauce and its antioxidant properties. *Food Research International* 38: 175–182.

Raksakulthai N. and N. Haard. 1992. Correlation between the concentration of peptides and amino acids and the flavor of fish sauce. *International Food Research Journal* 7: 286–290.

Raper, K.B. and D.I. Fennell. 1965. *The Genus Aspergillus*, Baltimore: Williams and Wilkins, 686.

Reddy, B.S. 1995. Nutritional factors and colon cancer. *Critical Reviews in Food Science and Nutrition* 35: 175–190.

Rege, N.N., U.N. Thatte and S.A. Dahanuka. 1999. Adaptogenic properties of six rasayana herbs used in Ayurvedic medicine. *Phytotherapy Research* 13(4): 275–291.

Saide, J.A. and S.E. Gilliland. 2005. Antioxidative activity of lactobacilli measured by oxygen radical absorbance capacity. *Journal of Dairy Science* 88: 1352–1357.

Saleem, A., M. Husheem, P. Harkonen, and K. Pihlaja. 2002. Inhibition of cancer cell growth by crude extract and the phenolics of *Terminalia chebula* retz fruit. *Journal of Ethnopharmacology* 81(3): 327–336.

Sanders, M.E. 2000. Considerations for use of probiotic bacteria to modulate human health. *The Journal of Nutrition* 130: 384S–390S.

Santiago, L.A., M. Hiramatsu, and A. Mori. 1992. Japanese soybean paste miso scavenges free radicals and inhibits lipid peroxidation. *Journal of Nutritional Science and Vitaminology* 38: 297–304.

Sastraatmadja, D.D., F. Tomita, and T. Kasai. 2002. Production of high-quality oncom, a traditional Indonesian fermented food, by the inoculation with selected mold strains in the form of pure culture and solid inoculum. *J. Graduate School of Agriculture*, Hokkaido University 70: 111–127.

Savage, D.C., R. Dubos, and R. Schaedler. 1968. The gastrointestinal epithelium and its autochthonous bacterial flora. *The Journal of Experimental Medicine* 127: 67–76.

Segawa, S., Y. Wakita, H. Hirata, and J. Watari. 2008. Oral administration of heat-killed *Lactobacillus brevis* SBC8803 ameliorates alcoholic liver disease in ethanol containing diet-fed C57BL/6N mice. *International Journal Food Microbiology* 128: 371–377.

Sekirov, I., S.L. Russell, L.C.M. Antunes, and B.B. Finlay. 2010. Gut microbiota in health and disease. *Physiological Reviews* 90: 859–904.

Shiau, S.Y. and G.W. Chang. 1983. Effects of dietary fiber on fecal mucinase and β-glucuronidase activity in rats. *The Journal of Nutrition* 113: 138–144.

Shin, S.J. 2003. Vitamin E modulates radiation-induced oxidative damage in mice fed a high-lipid diet. *Journal of Biochemistry and Molecular Biology* 36: 190–195.

Soccol, C.R., L.P. de Souza Vandenberghe, M.R. Spier, A.B.P. Medeiros, and C.T. Yamaguishi. 2010. The potential of probiotics: A review. *Food Technology and Biotechnology* 48: 413–434.

Song, J.H. and T. Miyazawa. 2001. Enhanced level of n-3 fatty acid in membrane phospholipids induces lipid peroxidation in rats fed dietary docosahexaenoic acid oil. *Atherosclerosis* 155: 9–18.

Song, J.H., K. Fujimoto, and T. Miyazawa. 2000. Polyunsaturated (n-3) fatty acids susceptible to peroxidation are increased in plasma and tissue lipids of rats fed docosahexaenoic acid-containing oils. *The Journal of Nutrition* 130: 3028–3033.

Songisepp, E., J. Kals, Kullisaar, R. Mandar, P. Hutt, M. Zilmer, and M. Mikelsaar. 2005. Evaluation of the functional efficacy of an antioxidative probiotic in healthy volunteers. *Nutrition Journal* 4: 22.

Steyert, S.R. and J.B. Kaper. 2012. Contribution of urease to colonization by shiga toxin-producing *Escherichia coli*. *Infection and Immunity* 80: 2589–2600.

Suzuki, K., Y. Benno, T. Mitsuoka, S. Takebe, K. Kobashi, and J. Hase. 1979. Urease-producing species of intestinal anaerobes and their activities. *Applied and Environmental Microbiology* 37(3): 379–382.

Tamime, A.Y., M. Saarela, A.K. Sondergaard, V.V. Mistry, and N.P. Shah. 2005. Production and maintenance of viability of probiotic micr-organisms in dairy products. *Probiotic Dairy Products*, in A.Y. Tamime, Ed. Oxford, UK: Blackwell Publishing, 44–51.

Tanaka, T., T. Kojima, T. Kawamori, A. Wang, M. Suzui, K. Okamoto, and H. Mori. 1993. Inhibition of 4-nitroquinoline-1-oxide-induced rat tongue carcinogenesis by the naturally occurring plant phenolics caffeic, ellagic, chlorogenic and ferulic acids. *Carcinogenesis* 14: 1321–1325.

Velayudham, A., A. Dolganiuc, M. Ellis, J. Petrasek, K. Kodys, P. Mandrekar, and G. Szabo. 2009. VSL3 probiotic treatment attenuates fibrosis without changes in steatohepatitis in a diet-induced nonalcoholic steatohepatitis model in mice. *Hepatology* 49: 989–997.

WHO. 2009. Global prevalence of vitamin A deficiency in populations at risk 1995–2005: WHO global database on vitamin A deficiency. Geneva, World Health Organization.

Wang, W. and E. Gonzalez de Mejia. 2005. A new frontier in soy bioactive peptides that may prevent age-related chronic diseases. *Comprehensive Reviews in Food Science and Food Safety* 4: 63–78.

Watanabe, T., M. Morotomi, N. Suegara, Y. Kawai, and M. Mutai. 1977. Distribution of indigenous lactobacilli in the digestive tract of conventional and gnotobiotic rats. *Microbiology and Immunology* 2: 183–191.

Wijewickreme, A.N., Z. Krejpcio, and D. Kitts. 1999. Hydroxyl scavenging activity of glucose, fructose and ribose-lysine model Maillard products. *Journal of Food Science* 64: 457–461.

Wiseman, H., K. Casey, E.A. Bowey, R. Duffy, M. Davies, I.R. Rowland, A.S. Lloyd, A. Murray, R. Thompson, and D.B. Clarke. 2004. Influence of 10 wk of soy consumption on plasma concentrations and excretion of isoflavonoids and on gut microflora metabolism in healthy adults. *American Journal of Clinical Nutrition* 80: 692–699.

Xie, P., S. Chen, Y. Liang, X. Wang, R. Tian, and R. Upton. 2006. Chromatographic fingerprinting analysis—A rational approach for quality assessment of traditional Chinese herbal medicine. *Journal of Chromatography A* 1112(1–2): 171–180.

Yoshimura Y., T. Ijima, T. Watanabe, and H. Nakazawa. 1997. Antioxidative effect of Maillard reaction products using glucose-glycine model system. *Journal of Agriculture Food Chemistry* 45: 4106–4109.

Yusuf S., S. Hawken, S. Ounpuu, T. Dans, A. Avezum, F. Lanas, M. McQueen et al. 2004. INTERHEART study investigators effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): Case–control study. *The Lancet* 364: 937–952.