Fermented Food: Should patients with cardiometabolic diseases go back to an Early Neolithic diet?

Mafra D[1,2,3], Borges NA[4], Alvarenga L[1], Ribeiro M[2,3], Fonseca L[1], Leal VO[5], Shiels PG[6], Stenvinkel P[7]

[1]Post Graduation Program in Medical Sciences - Federal Fluminense University, Niterói - Rio de Janeiro (RJ), Brazil
[2]Post Graduation Program in Nutrition Sciences - Federal Fluminense University, Niterói - Rio de Janeiro (RJ), Brazil
[3]Graduate Program in Biological Sciences – Physiology, Federal University of Rio de Janeiro (UFRJ), Rio de Janeiro (RJ), Brazil
[4]University of the State of Rio de Janeiro, Rio de Janeiro (RJ), Brazil
[5]Division of Nutrition, Pedro Ernesto University Hospital – University of the State of Rio de Janeiro, Rio de Janeiro (RJ), Brazil
[6]Wolfson Wohl Translational Research Centre, University of Glasgow, Garscube Estate, Switchback Road, Bearsden, Glasgow G61 1QH, UK
[7]Division of Renal Medicine, Department of Clinical Science, Technology and Intervention, Karolinska Instituted, Stockholm, Sweden

Corresponding author:
Denise Mafra
Rua Marquês de Paraná, 303 - Centro, Niterói - RJ, Brazil
Zip Code: 24070-035
Phone: +5521 985683003
E-mail: dmafra30@gmail.com

Word count: 10.000

Abstract

Fermentation has been used since the Early Neolithic period to preserve foods. It has inherent organoleptic and nutritive properties that bestow health benefits, including reducing inflammation and oxidative stress, supporting the growth of salutogenic microbiota, enhancing intestinal mucosal protection and promoting beneficial immunometabolic health effects. The fermentation of food with specific microbiota increases the production salutogenic bioactive compounds that can activate Nrf2 mediated cytoprotective responses and mitigate the effects of the 'diseasome of ageing' and its associated inflammageing, which presents as a prominent feature of obesity, type-2 diabetes, cardiovascular and chronic kidney disease. This review discusses the importance of fermented food in improving health span, with special reference to cardiometabolic diseases.

Keywords: fermented food, gut microbiota, inflammation, oxidative stress, cardiometabolic diseases.

Introduction

Natural fermentation of food has been in use since the Neolithic age and was popular among classical civilizations as a means of food preservation (HUANG, 2016). The degree and type of fermented food in the diet is contextualized by culture, lifestyle and geographical region. Fermentation is an anaerobic process whereby nutrients such as carbohydrates, are processed by microbial metabolism into end products comprising alcohols, gases, and acids. Besides preservation of the food, fermentation increases its range of available nutrients, changes its flavor and increase the digestibility of its constituents (Şanlier et al., 2019; Sibbesson, 2022). The most commonly used fermentation process incorporates lactic acid bacteria (LAB), however, alkaline, acetic acid, alcoholic fermentation has also been used. Typical examples of fermented foods include kefir, kimchi, cheese, pickles, chorizo, kombucha and beverages such as beer, whisky, and wine. All are highly valued due to their organoleptic properties (Şanlier et al., 2019; Sibbesson, 2022)

The fermentation process improves the nutritional value of foods, increasing the concentration of phenolic acids, flavonoids, short-chain fatty acids, vitamins and small peptides; all associated with health benefits (N. Kumar & Goel, 2019). For example, alkyl catechols such as 4-methyl catechol, 4-vinylcatechol, and 4-ethylcatechol, produced by the fermentation of phenolic acids (from fruits and vegetables) by Lactobacillus species are potent agonists of nuclear factor erythroid- 2 related factor (Nrf2), a master mediator of cellular stress defenses (Senger et al., 2016). These processes are not supported by a Western diet and modern food preservation methods, which has led to a reduction in dietary accquired alkyl catechols (Senger et al., 2016). Industrialization has also led to a diet based on processed, non-fermented foods. Consequently, with an industrialized Western diet, fewer fermented foods are being consumed; thus, new strategies are required to restore fermented food to the diet to enable support for a normative human microbiome. This is critical, as a normative microbiome established through natural selection over millennia in a non-industrialized world and now only found in a few traditional societies (Slattery et al., 2019), has evolved in concert with humans, while the modern industrialized microbiome has only evolved over several generations, hence our biology has had little time to adapt to its' associated health deficits. than a and that has not diet (Marco et al., 2020).

This is in keeping with the "*the old friend's hypothesis*" (Strachan, 1989), that postulates that a stimulated immune system is important for protection against 'burden of lifestyle diseases' that accumulate with age, such as cancer, dementia, cardiovascular disease (CVD), obesity, type-2 diabetes (T2D), and chronic kidney disease (CKD). Notably in traditional societies, such as Hadza hunter gatherers, there are higher levels of microbial richness and biodiversity than industrialised

societies (Schnorr et al., 2014). These include absence of *Bifidobacterium* and differences in microbial composition between the sexes. Additionally, their microbiota is configured to enhance the Hadza's ability to digest and extract nutrition from fibrous plant foods. Moreover, this alternate microbiome configuration helps maintain metabolic homeostasis through reduction of inflammatory factors, which are instead highly represented in the industralised metabolome (Turroni et al., 2016). Consequently, the Hadza are less prone to many features of the 'diseasome of ageing'.

Gut dysbiosis is a prominent feature of chronic burden of lifestyle diseases in industralised societies, where it has been shown that the risk of developing CVD and T2D may be reduced due to the actions of specific microbial metabolites from organisms supported by fermented food (Garcia-Gonzalez et al., 2021). For example, vitamin K derived from fermented food like natto (Japanese fermented soybeans) may have an important role in the reduction of osteoporotic fracture risk in women (Kojima et al., 2020). Furthermore, it has been suggested that fermented vegetables that support the growth of salutogenic Lactobacilli may be a potent source of Nrf2 activators and mitigate damage provoked by viruses, including COVID 19 (Bousquet et al., 2021, Mirashrafi et al. 2021). In this review we discuss the potential of fermented food in improving health span with focus on cardiometabolic diseases.

The food fermentation process

Based on the seminal observation in 1857 by Louis Pasteur that yeast is a living organism, studies on microbiology and pasteurization were initialized (Bach et al., 2020). As observed by Pasteur, microbes "capable of living without free oxygen" can use carbohydrates to produce energy in an anaerobic environment. In contrast to aerobic metabolism, in which oxygen is the receptor for the generated protons and electrons, the receptors for anaerobic derivatives are pyruvate and acetyl CoA (**Figure 1)**. Depending on the strain of organism, the fermentation process produces lactic, acetic, propionic, or butyric acids, ethanol even gamma-aminobutyric acid (GABA) from L-glutamate fermentation. During the fermentation process, hydrogen peroxide, carbon dioxide, antimicrobial peptides, and H_2S are also produced (The International Scientific Association for Probiotics and Prebiotics (ISAPP) Consensus Statement on Fermented Foods, 2021; Sun et al., 2017).

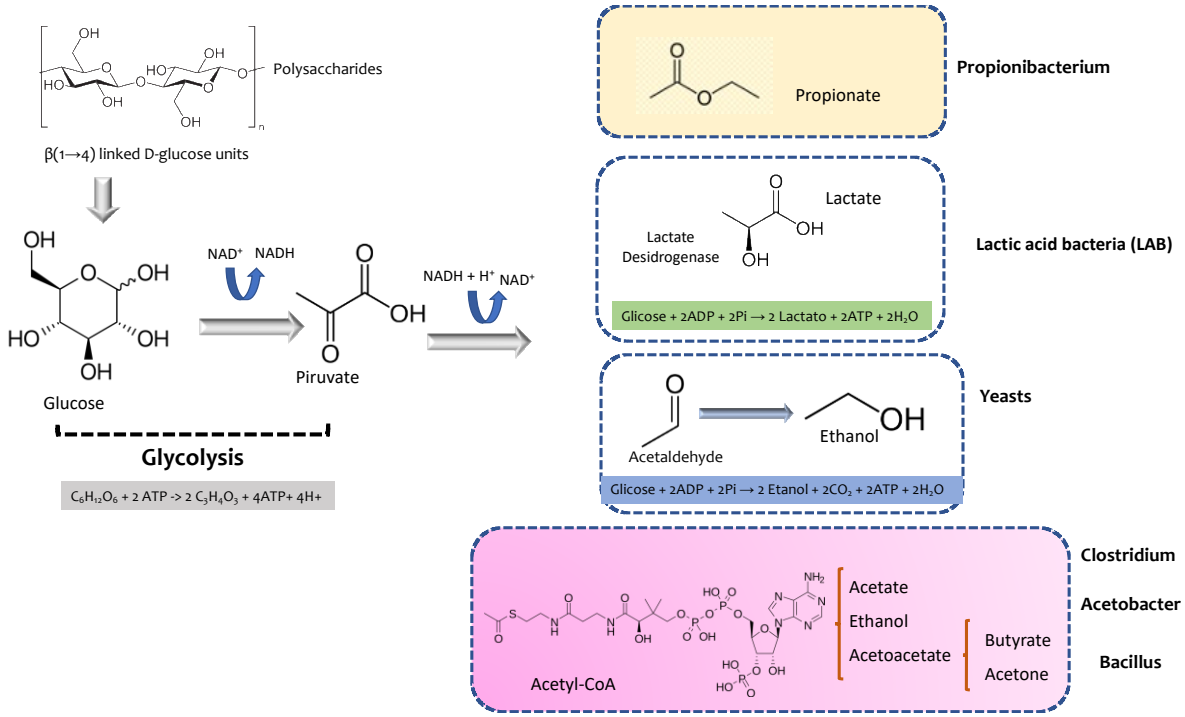

Figure 1. Carbohydrate fermentation and their end products.

Propionic acid bacteria (PAB), e.g., *P. freudenreichii*, are important for cheese production mainly Emmental and Swiss-type cheese, but also Feta and Raclette cheese. PAB use sugars (lactose and galactose) to produce acetate, CO_2 and propionate (Bücher et al., 2021). Gram-positive LAB from the Firmicutes group produce lactic acid during carbohydrate fermentation. Moreover, non-LAB bacteria are commonly used as aid in the fermentation process. Fermentation of fungi produces alcoholic beverages, such as sake and awamori, different kinds of cheese, such as Camembert and Roquefort and Asian fermented foods, such as miso and soy sauce.

Yeasts and fermentation

Yeasts are also important microorganisms in fermentation. These are members of the fungal kingdom, widely used in a range of common fermentation reactions, such as bread making (Voidarou et al., 2021). Saccharomyces is the most widely used yeast in the production of alcoholic beverages. Kluyveromyces is well-known to produce dairy products whereas Pichia and Yarrowia are used for vegetables, Candida, Wickerhamomyces, Metschnikowia, and Debaryomyces are used for fish and meat fermentation (Tamang & Lama, 2022). Additionally, Pseudomonas, has been shown to be critical for the fermentation of shark meat to produce hákarl (traditional dish from Iceland made with Greenland shark). Pseudomonas has also been reported to enable

detoxification of trimethylamine (TMA) or trimethylamine N-oxide (TMAO) present at high concentration in this fish, which is toxic before fermentation (N. Kumar & Goel, 2019).

Fermented food in the diet

The fermentation process can improve the organoleptic characteristics of food (i.e., taste, color, texture and odor) and increases its nutritional value, by lowering pH and enhancing synthesis of bacteriocins, acids and ethanol which contribute to the preservation of the food. Fermentation of food produces many important healthy substances including bioactive compounds, such as quercetin-3-glucoside, monacolin K, bacteriocin, amino acids and small peptides, exopolysaccharides, vitamin B complex, polyamines, conjugated linoleic acid (CLA), γ-aminobutyricacid (GABA), short-chain fatty acids (SCFA), phytoestrogen, indole alkaloid, genistein, daidzein, nitric oxide (**Figure 2**). In addition, the direct effect of consumption of specific bacteria promotes probiotic effects (Baruah et al., 2022a). Consequently, fermented food plays a crucial role in maintaining a normative balanced gut microbiota (Derrien & van Hylckama Vlieg, 2015; Kårlund et al., 2020).

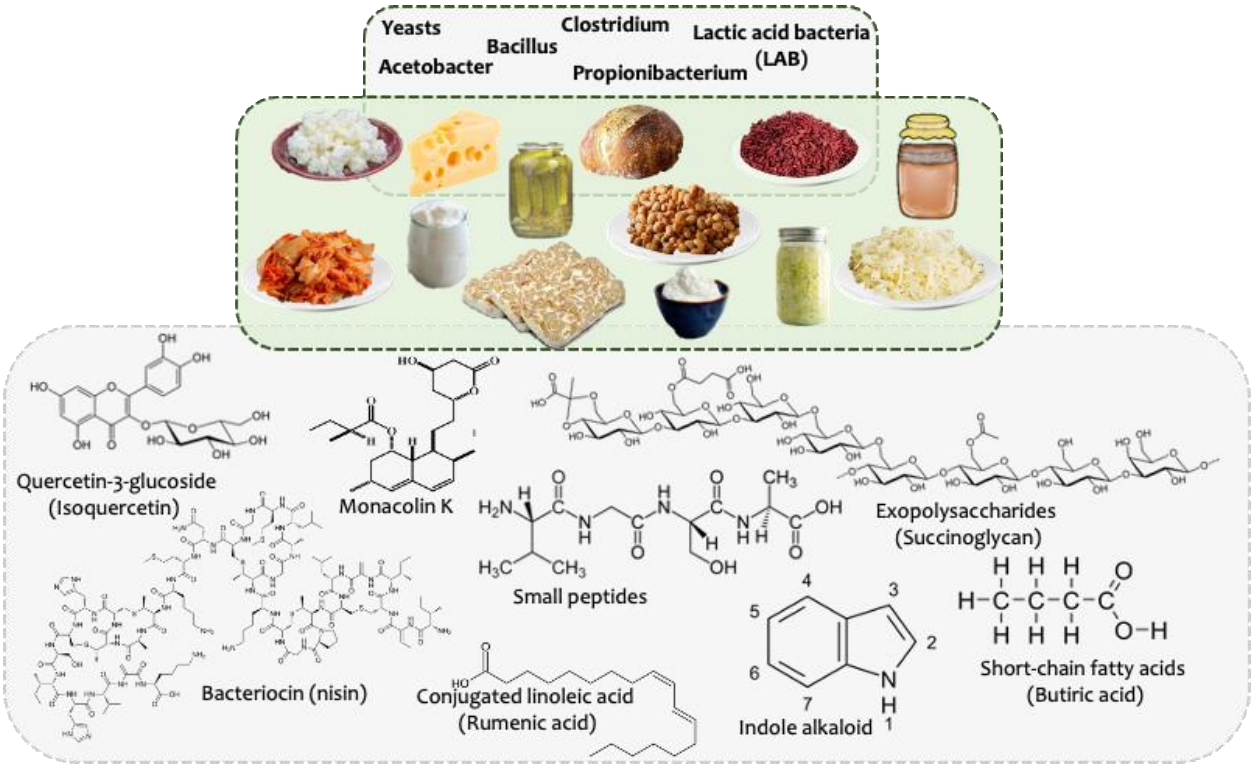

Figure 2. Examples of bioactive compounds produced by fermentation of foods.

Some examples of fermented foods with scientific evidence of health benefits (H. Chen et al., 2016; Devanthi & Gkatzionis, 2019; Dimidi et al., 2019; Pražnikar et al., 2020a; Rezac et al., 2018), such as dairy and fruits and vegetable-based fermented food, are listed in **Table 1.** Surprisingly, despite their known health benefits**,** with few exceptions, fermented foods are

generally absent as a recommended category in general dietary guidelines. As fermented food mitigates inflammation, control enteric diseases, and has anti-ageing, anti-hypertensive, anti-diabetic effects, the health benefits are potentially staggering (Baruah et al., 2022a; Marco et al., 2020), e.g., it has been suggested that fermented milk promotes longevity as LAB can modulate the gut microbiota, degrade carbohydrates (galactose and lactose) and branched-chain amino acids (including leucine), which are involved with activation of the target of rapamycin complex 1 (mTORC1), known as a key regulator of ageing (Melnik & Schmitz, 2021).

Fermented food may have a number of senotherapeutic properties(Das et al., 2020). A range of such food stuffs, such as genistein, spermidine and daidzein from fermented soybeans (Natto, Chungkookjang, Tempeh, Douchi), β-sitosterol and linoleic acid produced by Kimchi have also been described to have salutogenic properties including:

- Acting as an antioxidant and thus mitigate the effects of age-related oxidative damage.
- Extending health span (e.g., years of healthy living) via improving mitochondrial functions.
- Acting as anti-inflammatory that can combat inflammageing.

Table 1. Common fermented foods and dominant strains.

Food	Typical from	Made with	Strains
Cheese	USA, France	Milk	Mesophilic streptococci, lactococcus, and lactobacillus or thermophilic streptococci and lactobacillus.
Chongkukjang	Korea	Soybean	B. amyloliquefaciens, B. subtilis and B. licheniformis or by fungi such as R. oligosporus, Aspergillus oryzae and, Rhizopus oryzae
Dadih	Indonesia	Raw buffalo milk bamboo tubes and covered with banana leaves	Leuconostoc spp., Lactococcus spp., Klebsiella spp., Lactobacillus spp., Bifidobacterium spp., Streptococcus spp.
Douchi	China	Soybean	*Bacillus subtilis, Rhizopus oryzae, Aspergillus oryzae*
Kefir	North Caucasus	Goat, ewe, or cow milk	LAB, yeasts, fungi, Bacillus such as for e.g. Lactococcus lactis, Lactobacillus bulgaricus and Saccharomyces kefir
Kimchi	Korea	Cabbage or radish	Lactobacillus sakei, L. plantarum, L. brevis, Leuconostoc citreum, L. gasicomitatum, L. mesenteroides, Weissella cibaria, W. koreensis, W. confuse, L. carnosum, L. gelidum
Kombucha	China	Black and green tea	Komagataeibacter xylinus, Saccharomyces cerevisiae, Zygosaccharomyces bailii. Brettanomyces bruxellensis, Acetobacter pasteurianus, Acetobacter aceti, Acetobacter xylinum, Zygosaccharomyces spp., Gluconacetobacter

Miso	Japan	Soybean	Starter culture of Aspergillus oryzae plus Bacillus subtilis, Bacillus amyloliquefaciens, Staphylococcus gallinarum, Staphylococcus kloosii, Lactococcus sp.
Natto	Japan	Bean	*Bacillus subtilis, Bacillus natto.*
Pickles	China	Vegetables (mainly cucumber and mustard)	Lactobacillus paracasei
Red yeast rice	China	rice and red yeast	*Monascus purpureus*
Sauerkraut	Germany	Cabbage	L. plantarum, L. sakei, Candidatus accumulibacter phosphatis, Thermatoga spp., Pseudomonas rhizosphaerae, L. hokkaidonensis, L. rhamnosus, Leuconostoc carnosum, Clostridium saccharobutyrilicum, Rahnella aquatillis, Citrobacter freundii, Enterobacter cloacae, Bifidobacterium dentium, L. casei, L. delbrueckii, Staphylococcus epidermidis, L. curvatus, L. brevis, Weissella confusa, Lactococcus lactis, Enterobacteriaceae, Leuconostoc spp., Yarrowia brassicae
Sourdough	Middle East and Europe	Bread made with longer ferment	LAB and yeasts
Soy sauce	China	Soybean	Tetragenococcus halophilus and Zygosaccharomyces rouxii
Squid jeotgal	Korea	Fermented seafood	Bacillus velezensis Kh2-2
Tempeh	Indonesia	Soybean	Starter culture of Rhizopus oligoporus plus Enterococcus faecium, Rhizopus oryzae, Rhizopus oligoporus, Mucor indicus, Mucor circinelloides, Geotrichum candidum, Aureobasidium pullulans, Alternaria alternata, Cladosporium oxysporum, Trichosporon beigelii, Clavispora lusitaniae, Candida maltosa, Candida intermedia, Yarrowia lipolytica, Lodderomyces elongisporus, Rhodotorula mucilaginosa, Candida sake, Hansenula fabiani, Candida tropicalis, Candida parapsilosis, Pichia membranefaciens, Rhodotorula rubra, Candida rugosa, Candida curvata, Hansenula anomola
Vinegar	China	Grains (sorghum, rice or wheat) or fruit (apple or grapes)	Acetic acid bacteria
Yoghurt	Balkan regions and Asiatic Turkey	Milk	S. thermophiles, L. delbrueckii subsp. bulgaricus

Fermented food and inflammation: a role in regulating Nrf2 and NF-kB activity

An intermediate inflammatory phenotype, coincident with oxidative stress, mitochondrial dysfunction, tissue hypoxia, gut dysbiosis and depletion of Nrf2 are common features that drive the pathology of the ‘diseasome of ageing’, including cancer, T2D, dementia, hypertension, CVD, obesity and CKD (Shiels et al., 2021a). Chronic inflammation is characterized by a continuous inflammatory response, with consequent tissue dysfunction. The inflammatory process generates reactive oxygen species (ROS) and impairs maintenance of cellular antioxidant systems (Checa

& Aran, 2020) and the epigenetic landscape of ageing (Shiels et al., 2017). The impaired regulation of nuclear factor-kappa B (NF-κB) under such conditions is known to exacerbate such pathogenic processes in several inflammatory diseases (T. Liu et al., 2017). To activate NF-kB be, the IκB kinase (IKK) complex must phosphorylate and promote the degradation of the IκB that subsequently release NF-κB to the nucleus, inducing cytokine synthesis. These effects are mitigated or prevented by the action of the cytoprotective transcription factor Nrf2, which is responsible for activation of >300 antioxidant and cytoprotective genes (Abed et al., 2015; Checa & Aran, 2020; Stenvinkel et al., 2020).

As a range of bioactive compounds, such as sulforaphane, curcumin and alkyl catechols, stimulate Nrf2 they decrease chronic inflammation and improve the antioxidant responses (Alvarenga et al., 2020; Cardozo et al., 2021; De Almeida Alvarenga et al., 2019). Furthermore, the biotransformation of bioactive compounds such as oligopeptides, phenolic acids, and flavanols present in fermented food by LAB during the fermentation process potentiates antioxidant and anti-inflammatory action of such compounds by improving their bioavailability (Bautista-Expósito et al., 2019; Chiu et al., 2019; Khan et al., 2020; Senger et al., 2016; P. S. Wu et al., 2018).

Some types of fermented foods mitigate inflammatory processes by inhibiting Receptor Activator of NF-kB ligand (RANKL) (Ali et al., 2020; C. H. Jeong et al., 2018; J. W. Jeong et al., 2019) and Mitogen-Activated Protein Kinases (MAPK), such as ERK, p38, and JNK. Thus, the attenuation of the phosphorylation of these proteins, prevents the transcriptional activity of NF-κB (S. M. Kim et al., 2020; D. Y. Lee et al., 2016) resulting in reduced cytokines synthesis. Moreover, fermented foods can attenuate the inflammatory process through increase of IκB Kinase (IKK) expression/activity and inhibition of NF-kB Inhibitor alpha (IκBα) phosphorylation (Cheng & Pan, 2016; J. Y. Jung et al., 2015; S. M. Kim et al., 2020; Suo et al., 2015; Yoo et al., 2020) with a subsequent decrease of pro-inflammatory cytokines expression, such as tumor necrosis factor-alpha (TNF), and interleukin (IL) -1beta (β) (Ali et al., 2020; C. H. Jeong et al., 2018; J. W. Jeong et al., 2019).

In addition, fermented foods, especially kefir (fermented milk with LAB), prevent activation in the Nod-Like Receptor Pyrin domain containing (NLRP3) inflammasome and the maturation of cytokine IL-1 β and caspase 1 by blocking the NF-κB pathway (H. L. Chen et al., 2019). Fermented food products facilitate the dissociation of Keap1 from Nrf2 (Zhao & Shah, 2016) (increase the phosphorylation of extracellular signal-regulated kinase (ERK) (S. B. Ahn et al., 2018; Lin et al., 2018), and facilitate Nrf2 translocation to the nucleus (Ardiansyah et al., 2015; Bautista-Expósito et al., 2019; Khan et al., 2020). Consequently, there is an increase in the expressions of Nrf2-dependent phase II enzyme genes such as heme oxygenase-1 (HO-1) (S. Kim

et al., 2018; Park et al., 2020), catalase, glutathione peroxidase (GPx), superoxide dismutase (SOD), quinone oxidoreductase (NQO1) (Fuda et al., 2019). Indeed, a recent study showed that healthy individuals who consumed meals contained fermented food (cheese and sour cream) presented lower expression of genes related to inflammation, chemokine and cytokine signaling and lymphocyte activation (Rundblad et al., 2020). The action of several fermented foods on NF-κB and Nrf2 pathways *in vitro* and experimental studies are shown in **Table 2.**

Table 2. Summary of in vitro and in vivo studies involving fermented foods and their effects on inflammation and oxidative stress.

References	Sample	Intervention	Results
		In vitro	
La Marca et al. (2015) (La Marca et al., 2015)	Hepatocytes from Wistar male rats treated with 200 μM of H2O2	0.7 mg/ml of fermented powder of bean Lady Joy (*Phaseolus vulgaris L.*) for 24h	↑ Cytosol and mitochondrial GSH levels ↑ NQO1, CAT activity ↑ HO-1 and Nrf2 protein expression ↓ NF-κB protein expression and Endoplasmatic reticulum stress
Cheng & Pan (2016) (Cheng & Pan, 2016)	Hepatic stellate cells	30 μM of ankaflavin and monascin for 24h	↓ phospho-Akt/Akt ratio and NF-κB expression ↑ IκB expression ↔ MAPKs
Ahn et al. (2018) (S. B. Ahn et al., 2018)	Human hepatoma cell line HepG2	200 μM of palmitic acid and 0.04%-1.0% Fermented soymilk for 24h	↑ protein levels of Nrf2 ↓ phosphorylation of ERK ↓ ROS
Jeong et al. (2018) (C. H. Jeong et al., 2018)	Human colorectal cell line exposure to 1 μg/mL Escherichia coli LPS	Yogurt produced using 1, 2, or 3% Green tea powder for 15h	↓ ROS ↑ Nrf2 and HO-1 protein expression ↓ mRNA levels of IL-1β and TNF-□
Fuda et al. (2019) (Fuda et al., 2019)	Human hepatoma-derived cells	0−500 μM dose of Flazin (β-carboline-derived alkaloid) from Japanese fermented foods	↑ protein levels of Nrf2 in the nucleus fraction ↓ levels of Nrf2 in the cytoplasmic fraction ↑ Nrf2, NQO1, GCLC and GCL, HO-1, SOD, GR, GPx, CAT genes expression in the liver
Jeong et al. (2019) (J. W. Jeong et al., 2019)	RAW264.7 macrophage cells	100 ng/mL of Fermented Sea tangle extract for 72h	↓ RANKL and NF-κB expression ↓ ROS ↑ Nrf2 expression
Chiu et al. (2019) (Chiu et al., 2019)	RAW 264.7 macrophage cells	50–200 μg/ml ethyl acetate extract of fermented pine needle for 24h	↓ NO, PGE2, TNF-α, and IL-1β, IL-6 ↓ ROS ↓ iNOS, COX-2, and NF-KB p65 subunit protein expression
Kim et al. (2020) (S. M. Kim et al., 2020)	LPS-induced inflammation in RAW 264.7 murine macrophages	25, 50, 100, and 200 μg/mL fermented lotus root for 24h	↓ NF-κB and MAPKs activity ↓ NO production ↓ degradation of IκBα ↓ TNF-α, and IL-1β, IL-6 genes

Kim et al. (2020) (H. Y. Kim et al., 2020)	LPS-induced RAW264.7 macrophage cells	400 μg/mL fermented *Inula britannica*	↓ NO production ↓ TNF-α IL-1β, IL-6, iNOS, and COX-2 expression ↓ p-p65, ↓ IκBβ phosphorylation, and NF-κB activation ↓ MAPKs expression
Khan et al. (2020) (Khan et al., 2020)	RAW 264.7 macrophage cells treated with 1 μg/mL LPS	Antioxidant peptide MS15 from *Bacillus velezensis* obtained from Kimchi at dosages of 2.5, 5, 10, and 20 μM for 24h	↑ mRNA levels of CAT, GPx, SOD and Nrf2 ↓ ROS and NO ↑protein levels of HO-1
Tonolo et al. (2020) (Tonolo et al., 2020)	Caco-2 cells	0,05 mg/mL of bioactive peptides of fermented soybeans for 24h	↓ ROS, TBARS ↑ Nrf2 levels in the nucleus ↑ SOD, TrxR1, GR and NQO1
Park et al. (2020) (Park et al., 2020)	Hydrogen peroxide induced-MC3T3-E1 osteoblasts	Fermented Pacific oyster (*Crassostrea gigas*) extracts	↓ DNA damage and cytotoxicity ↑ mitochondrial membrane potential and cytosolic release of cytochrome C ↓ Bax/Bcl-2 expression and activity of caspase-9 and caspase-3 ↑ Nrf2 and HO-1 expression
Sha et al. (2021)(Sha et al., 2022)	Caco-2 cell	12 LAB strains isolated from Chinese fermented foods	↓ mRNA expression of DPP-4 ↓ TNF and MAPK signaling pathways
Kim et al. (2021)(S. Y. Kim et al., 2021)	Osteoblastic MC3T3-E1 cells	Fermented extract of sea tangle with Lactobacillus brevis (0 to 1000ug/mL)	↓ ROS ↑ Nrf2/HO-1 antioxidant pathway
Monmai et al. (2021)(Monmai et al., 2021)	RAW264.7 macrophage cells	fermented rice cake, + strawberry powder	↓ genes iNOS, IL-1β, IL-6, COX-2, and TNF-α ↓ NO
Paparo et al. (2021)(Paparo et al., 2021)	Caco-2 cells infected with SARS-CoV-2	milk fermented with L. Paracasei CBAL74 (48 h with 11.5 mg/mL)	In cells pretreated with L. Paracasei CBAL74: ↓ number of infected cells ↓ ACE2, IL-6, VEGFβ, IL-15, IL-1β ↔ TMPRSS2, MCP-1, TNF-α and CXCL1 expression
Sirilun et al. (2022)(Sirilun et al., 2022)	Colon adenocarcinoma (HT-29) cells	Thai purple rice (2.5 to 100ug/mL)	↓ IL-6, nitric oxide, iNOS, and COX-2 production ↑ IL-10

Wu et al. (2022)(H. Wu et al., 2022)	Hepatocarcinoma cells	Phenolic extracts from fermented barley (0 to 20 μg/mL)	↓ ROS ↑ viability and membrane integrity cell, ↑ SOD, GSH
Tobita et al. (2022)(Tobita & Meguro, 2022)	Macrophage cell line, J774.1	Bacillus subtilis BN strain - isolated from natto	↓ TLR-4, IL-12, NF-κB, and IκB kinase
Huang et al. (2021)(Huang et al., 2021)	HUVECs	Nattokinase (alkaline protease) from traditional food Natto (10 ng/mL)	↓ IL-17, IL-6, TNF-α, MCP-1 ↓ VEGF-induced cell migration ↑ Nrf2/HO-1 pathway
		In vivo	
Ardiansyah et al. (2015) (Ardiansyah et al., 2015)	Stroke-prone spontaneously hypertensive rats	4 and 20 g/kg of fermented barley extract for 3 weeks	↓ mRNA level of Nox1 ↑ mRNA expression of Nrf2, CAT, GPx, GR, and Prdx2 at 4g/kg dose
Zhao & Shah (2016) (Zhao & Shah, 2016)	Male Balb/c mice	8 ml/kg black tea yogurt for 8 weeks	↓MDA ↑Nrf2, GSH, γ-GCS, GR and GPx expression
Qian et al. (2016) (Qian et al., 2018)	Six-week-old SPF KM (Kunming) mice	1.0 x 10^9 CFU/kg of isolated lactic acid bacterium from Chinese pickled cabbage for 4 weeks	↑ SOD, GSH-Px, and GSH ↑ nNOS, eNOS, Cu/Zn-SOD, Mn-SOD, CAT, HO-1, Nrf2, and NQO1 genes ↓ NO and MDA
Xia et al.(2018) (Xia et al., 2018)	Mice model of alcoholic liver injury	0.625, 1.250 and 2.500 mL/kg of Shanxi aged vinegar for 2 weeks	↓ ROS, MDA, IL-1β ↓TLR4 expression, MyD88, p-IκB, p-NF-κB p65 ↑ IL-10, GSH-Px, SOD and CAT ↑ Nrf2, NQO1, HO-1 and GCLM protein expression ↓ iNOS and COX-2 activity and NO production
Moreno-Fernandez et al. (2019) (Moreno-Fernandez et al., 2019)	Male Wistar albino breed rats with anaemia	Fermented cow milk or fermented goat milk-based diet, with normal-Fe content for 4 weeks	↑TAS ↓8-OHdG, 15-F2t-isoprostanes and TBARS, AOPP ↓DNA oxidative damage in testis germ cells, IL-6 and TNF-α in fermented goat milk group ↑ NRF2 and PGC-1α protein expression in fermented goat milk group
Chen et al. (2019) (H. L. Chen et al., 2019)	Luciferase transgenic mice	150 mg/kg low-dose kefir peptide or 500 mg/kg high-dose kefir peptide for 4 weeks	↓ NF-κB, IL-lβ, IL-4 and TNF-α expression ↓ NLRP3, caspase-1 expression

Cui et al. (2020) (Cui et al., 2020)	Male C57BL/6J mice	Fermented soybean food (Low, 30 mg/kg; medium, 150 mg/kg; high, 750 mg/kg) for 3 weeks	↑LDH level ↑ expression levels of Nrf2, NQO1, GCLC and GCLM mRNA in the liver ↓ MDA in medium group
Ali et al. (2020) (Ali et al., 2020)	Adult male Sprague Dawley Strain rats with γ-irradiation inducing liver injury	5 ml/kg of kefir milk orally for 4 weeks	↓ NO and lipid peroxidation ↑ TAC, GSH level, and CAT activity ↓ MCP-1 and NF-κB gene expression
Zareian et al. (2020) (Zareian et al., 2020)	45 Spontaneously Hypertensive Rats	0.0065 g of fermented food (*idli*) with enhanced γ-aminobutyric acid for 10 weeks	↓ lipid peroxidation ↓ NF-κB and iNOS genes ↑ SOD, GR
Agista et al. (2021)(Agista et al., 2021)	Female mice in a post-colitis period	**Fermented rice bran** (diet supplemented with 10%) for 35 days	In intestine: ↓ IL-lβ, IL-6, TNF-α, CXd2 iNOS genes expression ↑ IκB□ mRNA level
Bae et al (2021) (Bae et al., 2021)	Mouse model of allergic rhinitis	**Fermented red ginseng** (6mg/day) for 2 weeks	↓IL-4 In lung: ↓IL-4, COX-2, iNOS expression
Garcia-Burgos (2021)(García-Burgos et al., 2022)	Anemic male rats	**Fermented goat´s or cow´s milk** with normal iron content or iron overload for 30 days	Fermented goat´s: ↑ INF-y, IL-4, IL-10 ↓TNF-α, MCP-1, IL-6, neutrophil/lymphocyte ratio
Cardoso et al. (2021)(Cardoso et al., 2021)	Rats fed a high-fat high-fructose diet	**Black and green tea kombuchas** (dilution equivalent to the 17mg total phenolics/kg/day) for 10 weeks	↓ neutrophil/lymphocyte ratio In liver: ↑ TAC, SOD and CAT activity ↓ NO ↔ MDA, TNF-α
Kaur et al. (2021) (Kaur et al., 2021)	Murine ulcerative colitis model	**Whey fermented** with *Lactobaccilus rhamnosus* (1.0 x 10^9CFU mL) for 4 weeks	In the intestinal fluid: ↓IL-4, TNF-α, CRP, MPO activity ↑TGF-β
Kumar et al. (2021) (M. R. Kumar et al., 2021)	BALB/c mice	Water kefir (10 or 2.5mL/kg) for 4 weeks	Both dosages: ↑ SOD activity in brain and spleen ↑ FRAP in brain and kidney In 2.5ml/kg dosage: ↓NO in kidney
Lee et al., 2021) (C. S. Lee et al., 2021)	Rat model of ovariectomy-induced post-menopausal primary osteoporosis.	**Milk products fermented** by *Lactobacillus plantarum* and *Lactobacillus fermentum* (1x 10^{10}CFU mL) for 8 weeks	↓ TNF-α, IL-1β In gut: ↓ TNF-α, IL-1β, IFN-y gene expression

Papai et al. (2021) (Pápai et al., 2021)	Murine colitis mouse model	**Yogurt** fermented by *Bifidobacterium animalis* and *Lactobacillus acidophilus* (200mcL/day) for 10 days	Yogurt fermented by Lactobacillus acidophilus: ↓MPO activity
Wang et al. (2021) (P. Wang et al., 2021)	LPS-induced sepsis in mouse model	**Kombucha** (free drinking or intragastric administration of 100mcl/100g) for 60 days	↓ IL-1β, IL-6, TNF-α In lung tissues: ↓ IL-1β, TNF-α, CCL-2, CXCL10 gene expression ↓NF-kB signaling
Zeng et al. (2021) (Zeng et al., 2021)	Colorectal cancer mice model	**Kefir** fermented for 24hour (200mcL) for 16 weeks	In colon tissue: ↓ TNF-α, IL-6, IL-17a protein levels and gene expression↓ NF-kB gene expression

Abbreviation: BUN: blood urea nitrogen; LA: lactic acid, LDH: lactate dehydrogenase, ALT: alanine aminotransferase; AST: aspartate aminotransferase, MDA: malondialdehyde, Nrf2: nuclear factor-erythroid 2-related factor 2, NQO1: NAD(P)H dehydrogenase [quinone] 1, GCLC: Glutamate-Cysteine Ligase Catalytic Subunit; GCLM: Glutamate-Cysteine Ligase Modifier Subunit, LPS: lipopolysaccharide, ROS: Reactive oxidative stress, HO-1: Heme Oxygenase 1, IL: Interleukin, TNF: tumor necrosis factor, AOPP: advanced oxidation protein products, TAS: total antioxidant status, TBARS: Thiobarbituric acid reactive substances, 8-OHdG: 8-hidroxy-2′-deoxyguanosine guanosine, PGC-1α: peroxisome-proliferator-activated receptor-γ coactivator-1α, CAT: catalase, GPx: glutathione peroxidase, SOD: superoxide dismutase, NO: Nitric oxide, TrxR1: thioredoxin reductase 1, GR: glutathione reductase, Prdx2: peroxiredoxin 2, Nox1: NADPH-oxidase 1, GSH: Glutathione, GSH-Px: glutathione peroxidase, nNOS: neuronal nitric oxide synthase, eNOS: endothelial nitric oxide synthase, Cu/Zn-SOD: cuprozinc-superoxide dismutase, Mn-SOD: manganese superoxide dismutase, *γ*-GCS*: γ*-glutamylcysteine synthetase, TAC: total anti-oxidant capacity, iNOS: NO synthase, cox-2: cyclooxygenase 2, NF-κB: nuclear factor Kappa B, MAPKs: mitogen-activated protein kinases; DPP-4: dipeptidyl peptidase-4; TLR-4: toll-like receptor 4; ACE2: receptor angiotensin-converting enzyme-2; IL: interleukin; VEGFβ, vascular endothelial growth factor-beta; MCP-1: Monocyte Chemoattractant Protein-1; CHCL1: C-X-C Motif Chemokine Ligand 1; TMPRSS2: transmembrane protease serine 2; HUVECs: Human umbilical vein endothelial cell

Fermented foods and gut microbiota

The gut microbiota exerts a marked influence on host metabolic homeostasis, and research demonstrate that good health and well-being require a healthy gut (Bell et al., 2018). Processed food – the hallmark of the Western diet – has recently been shown to drive microvascular disease via increased intestinal barrier permeability (Hall et al., 2020; Snelson et al., 2021). In keeping with this, it has recently been reported that differences in the microbiota are associated with ageing and health in the general population (Craven et al., 2021). It has been speculated that an industrialized microbiota due to many factors associated with the exposome of modern living, such as environmental cues, antibiotic exposure, processed food consumption, lack of plant-based diet, and mode of assisted birth, contribute to the burden of lifestyle diseases (Shiels et al., 2021b; Sonnenburg & Sonnenburg, 2019). Indeed, altered composition, diversity, and gut microbiota function have been described in several burden of lifestyle diseases including CKD (Mafra et al., 2019, 2020). In patients with CKD, gut dysbiosis leads to increased generation of toxic metabolites from microbial metabolism, resulting in increased circulating levels of gut-derived uremic toxins, which accumulate in the blood, promoting an intermediate inflammatory phenotype, metabolic disorders and progression and complications of CKD (Mafra et al., 2019, 2020). At the same time, it should be acknowledged that the uremic milieu enhances the fermentation process and both indoxyl sulphate and cresyl sulphate originate from dietary acid bacterial fermentation in the colon (Meijers & Evenepoel, 2011).

The expression of genes in the human intestinal tract, including genes involved in intestinal barrier function and immunity, can be modulated by the composition of the gut microbiota. As many immune cells reside in the gut an imbalanced gut microbiota affect the host's immune system function (Bell et al., 2018; Mohajeri et al., 2018). The gut microbiota is susceptible to environmental pressures, with the diet being crucial for gut microbiome variation (Mohajeri et al., 2018; Moschen et al., 2012). In this context, modern lifestyle and western diet lead to high exposure of harmful factors from foods such as xenobiotics, refined sugar, artificial sweeteners, processed meat and saturated fat, contributing to gut microbiota imbalance and disruption of the intestinal barrier, increases the host's susceptibility to immunological and metabolic disorders (Bell et al., 2018). On the other hand, probiotics, prebiotics, and bioactive compounds from vegetables have been pointed out as positive modulators of gut microbiota diversity and considered therapeutic agents for restoration of a normative gut microbiota (Mafra et al., 2019, 2020).

Fermented foods can contain up to 10^6 viable microbial cells/g (Dimidi et al., 2019; Marco et al., 2017) depending on the product type and processing. According to the hygiene hypothesis,

microbial exposures are essential for the normal development of the immune system. In this sense, the ingestion of "living fermented foods" can potentially introduce new transient bacteria into the host's gut microbiota, unlike the highly processed and sanitized foods typical of the western diet that limit microbial exposures (Marco et al., 2017). Thus, microorganisms present in fermented products could exert immunomodulatory effects that benefit health in burden of lifestyle diseases.

Fermented foods also provide polysaccharides and polyphenols with prebiotic action. Prebiotic oligosaccharides are formed as products from food fermentation (Aslam et al., 2020; Cho et al., 2015; Poutanen et al., 2009). These compounds act as substrates for fermentation by colonic bacteria, promoting health benefits to the gastrointestinal tract (Aslam et al., 2020; Poutanen et al., 2009). Moreover, particular LAB found more frequently in dairy fermented foods and present in other non-dairy foods such as fermented vegetables, meat, and cereals, produce bioactive molecules named exopolysaccharides (EPSs) during fermentation (Mathur et al., 2020). EPSs are long-chain bacterial glycan polymers secreted to the environment during growth, attributed to the gut microbiota (Mathur et al., 2020; Welman & Maddox, 2003) and considered effector molecules involved in the interaction among probiotics, the intestinal barrier and gut microbiota of the host (Castro-Bravo et al., 2018). It has been hypothesized that EPSs form a biofilm layer in the gut that helps probiotic bacteria to colonize and remain established for prolonged periods. Moreover, EPS has been postulated to have an antagonist role against bacterial pathogens (Castro-Bravo et al., 2018; Welman & Maddox, 2003). Another effect attributed to EPSs short-chain fatty acids (SCFAs) production, which contributes to the maintenance of the intestinal barrier (Oerlemans et al., 2021; Salazar et al., 2016). EPSs also interact with the gastrointestinal tract's mucosal immune system through different receptors present on the immune cells. Recently, C-type lectin receptors (CLRs), expressed on cells like monocytes, macrophages, and dendritic cells, have gained attention due to their ability to recognize bacterial EPS and trigger signaling pathways resulting in immunomodulatory effects (Castro-Bravo et al., 2018; Oerlemans et al., 2021).

Table 3 lists clinical trials involving fermented foods and their effects on gut microbiota in conditions such as metabolic syndrome, inflammatory bowel disease, irritable bowel syndrome and healthy individuals. No clinical trials involving CKD patients have yet been conducted. Commonly, the authors have attributed the observed results to specific components of the studied foods/ beverages, such as polyphenols in wine and or Lactobacillus in Kefir (Moreno-Indias et al., 2016; Yılmaz et al., 2019). However, it can be hypothesized that, together, the components present in fermented foods could act synergistically, potentiating each other's actions, conferring benefits to the gut microbiota and, consequently, to the host’s health.

Table 3. Summary of randomized clinical trials involving fermented foods and their effects on gut microbiota.

References	Sample	Intervention	Results
Nielsen et al. (2018)(Nielsen et al., 2018)	34 IBS patients	75 g of **unpasteurized sauerkraut** (contained viable LAB) or pasteurized sauerkraut for 6 weeks	In both groups: Gastrointestinal symptoms improved and changed gut microbiota composition unpasteurized sauerkraut group: ↑ *Lactobacillus plantarum* and *Lactobacillus brevis*
Nagino et al. (2017)(Nagino et al., 2018)	60 healthy premenopausal women	200mL/d of **fermented soymilk** (*Lactobacillus casei* Shirota YIT 9029) or unfermented soymilk for 8 weeks	fermented soymilk: *Lactobacillaceae* ↑, *Bifidobacteriaceae* tended to ↑, *Enterobacteriaceae*, *Porphyromonadaceae*, and *Ruminococcaceae* ↓
Bellikci-Koyu et al. (2019)(Bellikci-Koyu et al., 2019b)	22 patients with MetS	180 mL/d of **kefir or** unfermented milk for 12 weeks	↑ in the relative abundance of Actinobacteria compared to the baseline. ↔ relative abundance of Bacteroidetes, Proteobacteria or Verrucomicrobia.
Yılmaz et al. (2018)(Yılmaz et al., 2019)	45 patients with IBD	400 mL/d of **kefir** or no kefir intake for 4 weeks	↑ *Lactobacillus* in feces in the kefir group
Alvarez et al. (2020)(Alvarez et al., 2020)	96 healthy adults	1 or 3 bottles/day of **fermented milk** (*Lactobacillus paracase*i subsp. paracasei CNCM I-1518 and CNCM I-3689 and *Lactobacillus rhamnosus* CNCM I-3690) or control (non-fermented dairy drink) for 2 weeks	↔ alpha or beta-diversity between groups or doses; Few bacterial genera were dose- and consumption period-responsive. Functional contribution to the gut microbiome
Burton et al. (2020)(KJ et al., 2020)	Study 1: 14 healthy young men Study 2: 11 healthy adults	**Study 1:** 400 g /day of **fermented yogurt** (*Lactobacillus delbrueckii* spp. bulgaricus, *Streptococcus thermophilus*, *Lactobacillus rhamnosus* GG ATCC 53103). Control: acidified milk for 2 weeks **Study 2:** 100 g of **Gruyère cheese** (fermented dairy)	Fermented Food: ↓ circulating and urinary TMAO ↔ association with gut microbiota taxa.

		Control: 600 mL of milk or 600 mL of soya drink, performed 6 h and 24 h after consumption	
Ba et al. (2021)(Ba et al., 2021)	36 healthy adults	4 treatments: control yogurt smoothie (YS), yogurt smoothie with BB-12 added prefermentation (PRE), yogurt smoothie with BB-12 added postfermentation (POST), and capsule containing BB-12 (CAP) for 4 weeks	YS versus CAP: ↑ percentage of Streptococcus PRE and POST: ↑ percentage of *Bifidobacterium animalis* BB-12 consumption: ↔ fecal SCFA
Beghin et al. (2021)(Béghin et al., 2021)	70 infants breastfed	3 infant formulas: bioactive compounds (short-chain alactooligosaccharides (scGOS)/long-chain fructo-oligosaccharides (lcFOS) 9:1) and prebiotics (FERM/scGOS/lcFOS); prebiotics (scGOS/lcFOS); or bioactive compounds (FERM); compared to a standard cow's milk-based control formula (Control) for 6 months.	At four months of age: ↑ the median SIgA concentration in the FERM/ scGOS/ lcFOS group compared to the Control group. ↑ Bifidobacterium over time in all groups. FERM/scGOS/lcFOS combination = microbiota composition and metabolic activity closer to the breastfed infants' microbiome
Guillemard et al. (2021)(Guillemard et al., 2021)	136 adults under 14-day Hp treatment	*Test product:* fermented milk containing Lp CNCM I-1518, Lp CNCM I-3689, and Lr CNCM I-3690 strains and four yogurt strains. *Control product:* acidified milk, depleted in lactose, containing phosphoric acid, and Carboxy Methyl Cellulose. Two bottles (100 g/bottle) of Test or Control; for 28 days.	In test product group: - Intra-subject beta-diversity distance from baseline was lower ↓ abundant of Enterobacteriaceae, including Escherichia-Shigella and Klebsiella ↑ concentrations of SCFA and valerate
Hric et al. (2021)(Hric et al., 2021)	22 healthy females	**WLP group**: weight loss program (WLP) + exercise training sessions (3 times a week – 30 minutes) or **WLPB group**: 30-day WLP + Bryndza cheese + exercise for 4 weeks	Between the groups: ↔ relative abundance of bacteria at the phylum level, alpha diversity within the groups: ↑ abundance of order *Erysipelotrichales* WLPB group: ↑ abundance of the genera *Lactococcus* and *Streptococcus* ↑ genus level of *Phascolarctobacterium* and *Butyricimonas* (SCFA producing bacteria) ↓ family *Lachnospiraceae*

Kageyama et al. (2021) (Kageyama et al., 2021)	10 patients with SMID	Malted rice amazake (35g/d) or control group for 6 weeks. All patients were divided into 3 groups according their fecal bacteria compositions: Group 1 (n=5): higher abundance of Firmicutes. Group 2 (n=4): higher abundance of Actinobacteria. Group 3 (n=1): higher abundance of Proteobacteria.	Overall: ↔ alpha diversity ↑ Lactobacillales order ↓ Constipation Assessment Scale (CAS) and constipation symptoms. ↓ Enterobacteriaceae and *Escherichia-Shigella*, Proteobacteria ↔ *Blautia* genus, Clostridiales Group 1: ↓ Proteobacteria ↑ changes in the higher abundance *Bifidobacterium* genus Group 2: ↔ abundance of *Bifidobacterium*, Enterobacteriaceae and *Escherichia-Shigella*
Liu et al. (2021)(Y. Liu et al., 2021)	182 Chinese participants with *H. pylori* (HP) infection	**FRB group**: high-fibre whole grain rye + fermented rye bran (with *Lactiplantibacillus plantarum* (DSMZ13890) 10^9UFC mL-1) or **RW group**: high-fibre whole grain rye + refined wheat for 12 weeks	FRB group: ↑ abundance of *Romboutsia* (genus *Clostridium*) and *Faecalibacterium* ↓ abundance of *Bilophila* ↑ fecal acetic acid concentration ↓ isobutyric acid and 2-methylbutyric acid Both groups: ↔ butyric acid concentrations
Merensteins et al. (2021)(Merenstein et al., 2021)	62 healthy individuals	**BB-12 group:** antibiotic (amoxicillin/clavulanate for 7 days + strawberry-flavored yogurt beverage (100mL daily) + *Streptococcus thermophilus* and *Lactobacillus bulgaricus or* **Control group:** antibiotics + strawberry-flavored yogurt beverage (100mL daily) for 14 days	↓ fecal acetate levels in both groups following antibiotic administration. Control group: ↓ relative abundance of 48 taxa (several members of Firmicutes phylum and enrichment in *Bacteroides* and *Enterobacter* ↓community diversity greater deviation in the AUC analysis BB-12 group: ↑ *Bifidobacterium animalis*

			stable taxonomic attenuated antibiotic-induced decreases and more rapid return to the baseline of butyrate, acetate and propionate levels
Morales et al. (2021)(Márquez-Morales et al., 2021)	45 medical students from the SISCO Inventory of Academic Stress	100 mL of a beverage fermented with lactic acid bacteria (3 × 108 cfu/mL) or Control group (100 mL of coconut water) for 8 weeks	Intervention group: ↓ perception of academic stress ↑phyla Firmicutes and Bacteroidetes ↔ Gammaproteobacteria Control group: ↑ phylum Firmicutes
Wang et al. (2021)(R. Wang et al., 2021)	BALB/c mice constipation-induced 50 adults with functional constipation	BALB/c mice: Bifidobacterium animalis subsp. lactis MN-Gup by gavage for 14 days. Humans: 100 ml of yogurt containing 10^{10} cfu B. animalis subsp. lactis MN-Gup) or Placebo group: 100 ml of yogurt containing Streptococcus thermophilus + Lactobacillus bulgaricus for 4 weeks	Animal study: ↓ first black stool defecation time ↑increased black faecal wet weight, black faecal number and the gastric intestinal transit rate Human study: ↑ Defecation frequency, stool consistency, straining and incomplete feeling during defecation ↑ acetate-producing Bifidobacterium, Ruminoccaceae_UCG-002 and Ruminoccaceae_UCG-005
Wastyk et al. (2021)(Wastyk et al., 2021)	36 healthy adults	High-fibre diet or high-fermented-foods diet for 10 weeks	Fermented diet ↑ microbiome diversity ↓ inflammatory signals and activity Fibre diet: ↑ microbiome function (CAZymes, SCFAs)
Zhang et al. (2021)(Zhang et al., 2021)	82 patients with constipation	100 mL of Fermented yogurt (*Lacticaseibacillus paracasei* strain Shirota) for 9 weeks	↔ constipation-symptom (PAC-SYM) scores ↓ rectal tearing or bleeding after a bowel movement and stool symptom subscale ↑ Adlercreutzia, Megasphaera and Veillonella levels ↓ Rikenellaceae, Sutterella and Oscillibacter ↓ IL-6 levels

Abbreviations: SMID: severe motor and intellectual disabilities; TMAO: trimethylamine N-oxide; MetS: Metabolic syndrome; RCT: Randomized Clinical Trial; IBD: inflammatory bowel disease; IBS: irritable bowel syndrome; LAB: lactic acid bacteria; LPS: lipopolysaccharides.

Fermented foods and diabetes mellitus

It has reported that fermented foods could effectively protect against T2D. A meta-analysis carried out with seven cohort studies has reported that the consumption of 200g of yoghurt per day, the standard commercialized portion, is sufficient to reduce the risk of developing T2D by up to 14% (Aune et al., 2013). This effect has been confirmed by others (M. Chen et al., 2014; Gijsbers et al., 2016), the most significant benefits were observed using low-fat yoghurts. A recent meta-analysis investigated the beneficial effect of kefir on diabetes complications, and the results pointed out a significant reduction in fasting blood sugar and insulin without a significant effect on glycated hemoglobin (Salari et al., 2021). During the fermentation process, several metabolites with anti-diabetic potential are produced, such as phytoestrogen, bioactive peptides, quercetin-3-glucoside and monacolin K (Baruah et al., 2022b). LABs play an essential role in preventing the colonization of exogenous bacteria and reducing the toxigenic and mutagenic effects of endogenous bacteria (Torres et al., 2019; Yao et al., 2017). In T2D, probiotics such as fermented milk fortified with *Lactobacillus acidophilus La-5, Bifidobacterium animalis subsp lactis BB-12 or Lactobacillus Plantarum OLL2712*, improve glycemic control and reduced inflammatory profile (Tonucci et al., 2017; Toshimitsu et al., 2020). Although scientific evidence indicates that yoghurt has the best positive impact on the risk of T2D (Gille et al., 2018), other dairy products, such as cheese (Aune et al., 2013; Gao et al., 2013), fermented milk (Aune et al., 2013; Drouin-Chartier et al., 2016) and milk (Jakubowicz & Froy, 2013; Rice et al., 2011) may have similar benefits (Mohamed & Schaalan, 2018; Takahashi et al., 2021).

The mechanisms that explain the association of dairy consumption with a reduction in the risk of T2D have not been fully elucidated (Aune et al., 2013). However, it has been suggested that whey protein exert insulinotropic activities and decreasing glucose levels through its bioactive peptides and amino acids (Jakubowicz & Froy, 2013). Recently, L6 myotubes cells treated with 3 Douchi-derived peptides (soybean fermented) activated glucose pathways such as AMPK, p38 MAPK, and p44/42 MAPK, promoting the GLUT4 translocation, leading to glucose uptake (Yu et al., 2022).

Moreover, the beneficial anti-diabetic effects of fermentation are not limited to dairy products alone. A positive association has also been ascribed to the consumption of Kimchi, which has been reported to result in better endurance and insulin sensitivity in experimental studies (An et al., 2013; Islam & Choi, 2009). Additionally, fermentable drinks rich in polyphenols, such as red wine, has been reported to have health beneficial effects in the context of T2D (Chiva-Blanch et al., 2013; Szkudelski & Szkudelska, 2011). Other randomized controlled trials and results regarding the effects of fermentable foods on T2D are described in **Table 4**.

Table 4. Summary of randomized clinical trials involving fermented foods and their effects on patients with Diabetes Mellitus.

References	Sample	Intervention	Results
Ejtahed et al. (2011)(H. S. Ejtahed et al., 2011)	60 patients with T2D and LDL-C > 2.6 mmol/L	300g/d of probiotic yogurt containing Lactobacillus acidophilus La5 and Bifidobacterium lactis Bb12 or 300g/d of conventional yogurt for 6 weeks	In probiotic group: ↓ TC and LDL-c
Ejtahed et al. (2012)(Hanie S. Ejtahed et al., 2012)	64 patients with T2D	300g/d of probiotic yogurt containing Lactobacillus acidophilus La5 and Bifidobacterium lactis Bb12 or 300g/d of conventional yogurt for 6 weeks	In probiotic group: ↓ FPG, HB A1c. ↑ erythrocyte SOD, GPX activities and total antioxidant status. Both groups: ↓ MDA
An et al. (2013)(An et al., 2013)	21 individuals with pre-diabetes	100g of fresh kimchi/meal or 100g of fermented kimchi/meal for 8 weeks (4 weeks of washout)	Both types of Kimchi: ↓ BW, BMI, and WC. Fermented kimchi: ↓ insulin resistance, systolic and diastolic BP; ↑ insulin sensitivity, QUICKI and disposition index values
Oh et al. (2014)(Oh et al., 2014)	42 subjects with impaired fasting glucose or TD2	2.7g/d (3 capsules) of fermented red ginseng or 2.7 g/d of dry yeast for 4 weeks	Group 1: ↓ postprandial glucose levels ↑ postprandial insulin levels compared to the placebo group. AUC improvement. ↔ fasting glucose, insulin and lipid profiles
Hove et al. (2015)(Hove et al., 2015)	41 patients with T2D	300mL/d of milk fermented with L. helveticus or 300mL/d artificially acidified milk for 12 weeks	Fermented milk: ↓ daytime and 24-h HR but did not ↓ 24-h systolic or diastolic BP, day or night, compared to placebo. ↔HbA1c, plasma lipids, CRP, plasminogen activator inhibitor 1 and TNFα between groups. ↑ Serum glucose in the placebo group
Golan et al. (2017)(Golan et al., 2017)	48 patients with T2D	150mL/d of dry red wine (16,9g of ethanol + 270,1mg of gallic acid equivalent of total phenols), 150mL/d of dry white wine (15,8g of ethanol + 38,5mg of gallic acid equivalent of total phenols) or 150mL/d of mineral water for 2 years	Wine consumption did not promote weight gain or abdominal adiposity.
Ahn et al. (2018)(H. Y. Ahn et al., 2018)	60 individuals with pre-diabetes or newly diagnosed T2D	40g of a mixture of Jerusalem artichoke and fermented soy powder or powdered rice flour for 12 weeks	Fermented soy: ↓ fasting glucose, glucose within 60 min, AUC, HOMA-IR, urinary level 8-epi-PGF2α and FFAs.

Golan et al. (2018)(Golan et al., 2018)	174 patients with T2D	150mL/d of dry red wine (16,9g of ethanol), 150mL/d of dry white wine (15,8g of ethanol) or 150mL/d of mineral water for 2 years	Carotid TPV progression was not observed. But, in subgroup analyses, those with the highest detected carotid plaque burden who were assigned to wine may have had a regression of plaque burden after two years
Yanni et al. (2021)(Yanni et al., 2019)	33 overweight/obese T2D patients	200g/d of non-fat yogurt enriched with vitamins B1, B5 and B6 or conventional yogurt for 12 weeks	yogurt enriched: ↓ body weight and BMI ↓ energy intake when compared to group 2 Conventional: ↓ IL-6
Toshimitsu et al. (2020)(T. T et al., 2020)	130 Prediabetic adults	112 g yogurt containing heat-treated Lactobacillus *plantarum* OLL2712 (> 5 × 109 cells/112 g of yogurt) or placebo yogurt for 12 weeks	Yogurt with OLL2712: ↓ HbA1c placebo: ↑ inflammation marker levels and HOMA-IR ↔FPG
Schmidt et al. (2021) (Schmidt et al., 2021)	67 participants with metabolic syndrome	Limited dairy diet: 3 servings/week of nonfat milk Low-fat dairy diet: 3.3 servings/d of low-fat dairy Full-fat dairy diet: 3.3 servings/d of full fat dairy	↔ Insulinogenic index and glucose sensitivity in all groups ↓ Insulin sensitivity and ↑ HOMA-IR in both dairy groups ↑ Fasting insulin in low-fat dairy group ↓ Oral disposition index in the full-fat group
Nikooyeh et al. (2021) (Nikooyeh et al., 2021)	75 T2D patients	D-fortified -yogurt drink (DY): 500mL/d of DY - 1000IU vitamin D and 300mg of calcium Ca+D-fortified-yogurt drink (CDY): 500mL/d of CDY - 1000IU vitamin D and 500mg of calcium Plain yogurt drink (PY): 500mL PY - no detectable vitamin D and 300mg of calcium	↑ Serum adiponectin, ↓ BMI, FM and HbA1c in DY and CDY groups ↑SIRT1 and SIRT6 in CDY group compared to baseline ↑SIRT1 in DY and CDY groups compared with PY group Changes of serum 25(OH)D concentrations were a significant predictor of changes of serum adiponectin, Hb1Ac and FM.

Abbreviations: T2D: Diabetes Mellitus type2; LDL-C: Low-density lipoprotein cholesterol; TC: Total Cholesterol; SOD: superoxide dismutase; GPX: glutathione peroxidase; MDA: malondialdehyde; Vit D: Vitamin D; PTH: parathormone; HbA1c: Hemoglobin glycated; FPG: fasting plasma glucose; TAG: triacylglycerol; HOMA-IR: homeostasis model assessment of insulin resistance; BW: body weight; BMI: body mass index; WC: waist circumference; FM: total body fat mass; Quicki: Quantitative Insulin Check Index; hs-CRP: High-Sensitivity C-Reactive Protein; AUC: glucose areas under the response curve; FFAs: Free fatty acids; TPV: total plaque volume; TNFα: tumor necrosis factor alpha; CRP: C-reactive protein; HR: heart rate; BP: Blood pressure; FRG: Fermented red ginseng; SIRT: sirtuin; interleukin-6:IL-6.

Fermented food in obesity

As reported above, fermented food has beneficial effects on insulin resistance, inflammation, high body index mass or abdominal adiposity. Thus, fermented food may be a nutritional strategy to reduce body weight and complications caused by obesity. Indeed, recent analysis with 4,886 males and 7,431 females from Korea National Health and Nutrition Examination Survey VI, to evaluate the abdominal obesity risk with Korean health eating index (MKHEI), which is rich in fermented food as kimchi and pickled vegetables and fermented beans, showed that in women, the MKHEI scores were negatively related with abdominal obesity (Yang et al., 2022). Clinical trials (**Table 5**) have shown that interventions with fermented food (most with yoghurt) can reduce body mass index (BMI), visceral adiposity also, reduce LDL cholesterol (Madjd et al., 2016; Manzanarez-Quín et al., 2021), including alteration in the genes involved with lipid metabolism (Seo et al., 2017).

Some mechanisms are proposed to activation of PPARα by metabolites formed from fermented food such as conjugated linoleic acid (CLA) or octadecenoic acid and even by components from the bacterial, leading to β-oxidation of fatty acids (D. H. Kim et al., 2017). Intestinal hormones involved with satiety (cholecystokinin, glucagon-like peptide 1, gastric inhibitory peptide) may be stimulated by protein hydrolysates from fermented milk (Chaudhari et al., 2017). Bioactive compounds formed by fermentation process as surface layer proteins, exopolysaccharide, lipoteichoic found in kefir, may regulate the inflammation, attenuating inflammatory pathways (NF-κB and NLRP3 inflammasome), commonly seen in obesity (E. Kim et al., 2021). Moreover, probiotic, polyphenols and bacteriocins produced by fermented food can modulate the gut microbiota composition, mitigating dysbiosis (Ağagündüz et al., 2021; Zhou et al., 2021). Finally, probiotics from fermented food can activate mRNA expression of thermogenic proteins, reducing adiposity and also inflammatory cytokines (Pothuraju et al., 2016). Isoflavone and isoflavonoid aglycone produced by Cheonggukjang (fermented soybean paste) induce insulin secretion in pancreas and in preadipocytes, which inhibit lipid accumulation, (I. S. Kim et al., 2021).

Table 5. Randomized clinical trials involving fermented foods and obesity.

References	Sample	Intervention	Results
Cha et al. (2014)(Cha et al., 2014)	51 overweight subjects	9.8 g/day of doenjang (fermented soybean paste) or placebo for 12 weeks	In doenjang group ↓ visceral fat area and ↑ CAT in subjects with a mutant T allele of PPAR-γ2
Han et al. (2015) (Han et al., 2015)	24 obese women	180 g of fresh or fermented kimchi per day for 8 weeks	In fermented kimchi ↑*Bacteroides* and *Prevotella* ↓*Blautia*
Madjd et al. (2016) (Madjd et al., 2016)	89 overweight and obese women	400g/day of probiotic yoghurt or low-fat yoghurt during a hypoenergetic program for 12 weeks	↔ weight loss, FPG, HDL, TG in both groups In probiotic yoghurt ↓ TC, LDL ↓ HOMA-IR, 2-h postprandial glucose ↓ fasting insulin levels
Byun et al. (2016)(Byun et al., 2016)	120 overweight/obese adults	35 g/day of freeze-dried Chungkookjang (Korean fermented soybean) or placebo for 12 weeks	Chungkookjang group In women - ↓ fat %, WC, lean body mass, waist-to-hip ratio ↓CRP ↑ApoA1
Fathi et al. (2017)(Fathi et al., 2017)	75 overweight or obese premenopausal women	2 servings/d of low-fat dairy products, milk or kefir for 8 weeks	Kefir ↓ TC, LDLC, ↓ non-HDLC, TC/HDLC ↓ LDLC/HDLC
Lee et al. (2017) (Y. Lee et al., 2017)	60 Sixty overweight/obese adults	32 g/day Kochujang (a Korean fermented soybean-based red pepper paste) or placebo for 12 weeks	↔body composition, insulin resistance, or antioxidant biomarkers In Kochujang group ↓ TG, TG/HDL except on individuals with mutant PPARγ2 T allele
Mohammadi-Sartang et al. (2018)(Mohammadi-Sartang et al., 2018)	87 adults with MetS	500mg/day of fortified yoghurt (whey protein, calcium, vitamin D, prebiotic fibre and probiotic cultures) or a low-fat plain yoghurt for 10 weeks	Fortified Yoghurt ↓ HOMA-IR ↓BMI, WC, fat% ↓TG, QUICKI

			↑ total 25-hydroxyvitamin D (25(OH)D) levels, HDL
Zarrati et al. (2019) (Zarrati et al., 2019)	60 obese or overweight adults	200 g/day of probiotic yoghurt (Lactobacillus acidophilus La5, Bifidobacterium BB12 and Lactobacillus casei DN001) or regular yoghurt for 8 weeks	Yoghurt ↔BMI, WC, adropin, nesfatin-1
Rezazadeh et al. (2019) (Rezazadeh et al., 2019)	44 adults with MetS	300g/d of probiotic yoghurt (Lactobacillus acidophilus La5 and Bifidobacterium lactis Bb12) or a regular yoghurt for 8 weeks	Yoghurt ↓FPG, insulin, HOMA-IR, Quicki ↓VCAM-1, PAI-1
Asgharian et al. (2020) (Asgharian et al., 2020)	130 overweight and obese pregnant women	100 g/day of probiotic or conventional yoghurt group for 14 weeks (from 24 weeks until delivery)	Yoghurt ↓FPG ↓2-h OGTT
Chen et al. (2019)(Y. Chen et al., 2019)	100 obese women (with NAFLD and MetS)	220 g/d of yoghurt or milk for 24 weeks	Yoghurt: ↓ insulin resistance, fasting insulin, ALT, intrahepatic lipid, TC, fat mass, WC ↓ LPS, FGF-21, TNF-α ↓ relative abundance of the Firmicutes phylum, Clostridia and Erysipelotrichia classes, Clostridiales and Erysipelotrichales orders ↑ relative abundance of the Negativicutes class, Selenomonadales order, Acidaminococcaceae family, and Phascolarctobacterium genus,
Razmpoosh et al. (2020)(Razmpoosh et al., 2020)	70 women with overweight/obesity	Low energy diet contained 50 g of condensed processed yoghurt or a low energy diet without yoghurt for 8 weeks	Yoghurt: ↓ LDL, TG, ↓ BMI, fat%, WC ↓ SBP
Pražnikar et al. (2020) (Pražnikar et al., 2020b)	28 overweight adults	300 mL kefir or 300mL milk supplementation for 3 weeks	↑ serum zonulin levels (intestinal barrier marker) + mood

Santurino et al. (2020)(Santurino et al., 2020)	68 overweight and obese subjects (BMI 27 – 40)	60g/d of goat cheese with PUFA + CLA or 60g/d goat cheese (control) for 12 weeks	Enriched goat cheese ↑ HDL, Apo B ↓ CRP
Pan et al. (2020)(Pan et al., 2020)	30 patients with MetS	fermented barley - wheat flour compound noodle or whole wheat noodles group for 8 weeks	Fermented food group: ↓ glucose level, HbA1c, and TG ↓ fat mass, fat rate, and visceral fat ↑ muscle mass and basal metabolic rate
Noer et al. (2021)(Noer et al., 2021)	13 young females (BMI 25-30)	Breakfast with fermented soybean or control after an overnight fast	Breakfast with fermented food: ↓ plasma acyl-ghrelin ↑ plasma insulin 30% greater than control ↑ plasma arginine levels ↔ appetite questionnaire

Abbreviations: FPG: fasting plasma glucose; CAT: catalase; OGTT: oral glucose tolerance test; MetS: metabolic syndrome; LPS: lipopolysaccharides; PUFA: polyunsaturated fatty acids; NAFLD: nonalcoholic fatty liver disease; ALT: alanine aminotransferase; FGF-21: fibroblast growth factor 21; CLA: conjugated linolenic acid; SBP: systolic blood pressure; WC: waist circumference; BMI: body mass index; TC: total cholesterol; TG: triglycerides; LDL: low density lipoprotein cholesterol; HDL: high-density lipoprotein cholesterol; ApoB: apolipoprotein B; CRP: C-reactive protein; HOMA-IR: homeostasis model assessment of insulin resistance; Quicki: quantitative insulin sensitivity check index; VCAM-1: vascular cell adhesion molecule cell; PAI-1: plasminogen activator inhibitor.

Fermented Food and cardiovascular diseases

Hypertension is a major cardiovascular risk factors that could be targeted nutritionally. One nutritional strategy is the consumption of fermented foods, such as milk, cheese, and yoghurt, as milk fermentation produces many peptides (called antihypertensive peptides) such as Val-Pro-Pro (VPP) and Ile-Pro-Pro (IPP) that are involved in the inhibition of the angiotensin-converting enzyme (L. M. Beltrán-Barrientos et al., 2016; Lilia M. Beltrán-Barrientos et al., 2018a; Mamo, 2016; Nestel & Mori, 2022; Rai et al., 2017; Udenigwe & Mohan, 2014). A direct relationship between intake of fermented dairy products and blood pressure regulation has been documented (Lilia M. Beltrán-Barrientos et al., 2018b). Usinger *et al*. (2010) observed that individuals with borderline hypertension had lower systolic blood pressure after intervention with fermented milk inoculated with *Lactococcus lactis* and *Lactobacillus helveticus* (Usinger et al., 2010). Moreover, a study of patients with metabolic syndrome reported a significant reduction in both systolic and diastolic blood pressure after ingestion of 180mL of Kefir per day for 12 weeks (Bellikci-Koyu et al., 2019a).

Other cardiometabolic risk factors include the lipid profile. As fermented food reduces total cholesterol, LDL cholesterol, and triglycerides, it exerts additional cardioprotective effects (Lilia M. Beltrán-Barrientos et al., 2018a; Nestel & Mori, 2022). Correspondingly, supplementation with kefir, milk, kimchi, cheonggukjang and red ginseng cheonggukjang, reduced total cholesterol and LDL-c levels (Choi et al., 2013; Pražnikar et al., 2020b). Moreover, a drink prepared with skimmed milk and *Streptococcus thermophilus* reduced MDA-LDL/LDL cholesterol ratio and blood pressure (Ito et al., 2017). Similar beneficial effects have been observed in a clinical trial involving healthy individuals who received different fermented foods derived from milk, where levels of trimethylamine-N-oxide TMAO, a derivative of the proinflammatory microbial metabolite trimetylamine (TMA), were lower than in controls (Burton et al., 2020). Furthermore, recent evidence supports that consumption of dairy foods is inversely associated with cardiovascular outcomes and that patients with CVD may enjoy the salutogenic effects of these foods (Nestel & Mori, 2022; Silva et al., 2022). Several studies describing the consumption of dairy products and other fermented foods and their relationship with cardiovascular health are shown in **Table 6**.

Table 6. Summary of randomized clinical trials involving fermented foods and their effects on patients with cardiovascular disease.

References	Sample	Intervention	Results
Kim et al. (2011)(E. K. Kim et al., 2011)	22 overweight and obese subjects	300g/d of fresh Kimchi or 300g/d of fermented Kimchi for 4 weeks (2 weeks of washout)	Both groups: ↓ weight, BMI, body fat. Fermented: ↓waist-hip ratio, BP, fasting glucose and insulin, TC, MCP-1 and leptin. Fresh: ↓TAG, E-selectin and adiponectin.
Nestel et al. (2013) (Nestel et al., 2013)	12 overweight/obese subjects	Full-fat fermented dairy or Full-fat non-fermented dairy diet for 3 weeks, and Low-fat dairy diet (for 2 weeks) consumed between and at the end of the full-fat dairy dietary periods	Low-fat dairy diet: ↓MCP-1, macrophage inflammatory protein-1α, hs-CRP, LDL-c and HDL-c Full-fat non-fermented dairy: ↑IL-6 and sphingomyelin Full-fat fermented dairy: ↓ IL-6
Thorning et al. (2015) (Thorning et al., 2015)	14 overweight postmenopausal women	**Cheese diet**: high cheese intervention (96-120g/d).; **Meat diet**: nondairy, high content of high-fat processed and unprocessed meat; **Carb diet**: nondairy, low-fat, high-carbohydrate for 2 weeks each	Cheese diet: 5% higher HDL-c, 8% higher ApoA-I and 5% lower ApoB: ApoA-I ratio than Carb diet; Meat diet: 8% higher HDL-c and 4% higher ApoA-I than Carb diet. Fecal fat, energy, and bile acid excretion Cheese diet: 40% higher fecal fat excretion than Carb diet and 16% higher than Meat diet; 28% higher fecal bile acid excretion than Carb diet; higher taurine-conjugated bile acids excretion than other diets; lower deconjugated bile acids excretion than Meat diet.
Hütt et al. (2015) (Hütt et al., 2015)	Study 1: 82 healthy adults. Study 2: 43 healthy adults	**Probiotic cheese** (cheese containing L. plantarum) and control cheese (50g/d). **Probiotic yogurt** (yogurt containing L. plantarum TENSIA®) and control yogurt (150g/d) for 3 weeks (2 weeks of washout)	Both probiotic groups (cheese and yogurt): ↓diastolic BP and LDL-c Probiotic cheese: ↓systolic BP
Fathi et al. (2017) (Fathi et al., 2017)	75 Iranian women	4 servings/d of kefir drink or 4 servings/d of dairy products or 2 servings/d of low-fat dairy products for 8 weeks	Kefir and milk group: ↓TC, LDL-c, non-HDL-c, TC/HDL-c ratio and LDL-c/HDL-c ratio.

Escudero-López et al. (2017) (Escudero-López et al., 2018)	30 healthy subjects	500mL/d of fermented and pasteurized orange beverage or no fermented food for 2 weeks (3 weeks of washout)	Experimental group: ↑ORAC, ↓uric acid, CAT activity, TBARS and oxLDL
Tenore et al. (2019) (Carlo Tenore et al., 2019)	90 individuals with CVD risk factors	125g/d of Annurca apple puree group or 125g/d of Lactofermented Annurca apple puree or 125 g of lactofermented Annurca apple puree + LAB for 16 weeks	All groups: ↑HDL-c levels and ↓TMAO levels, but fermented puree exerted the highest influence on these parameters. All groups: strong ↑Bifidobacterium and Lactobacillus population and ↓Bacteroides and Enterococcus genera, but non fermented puree exerted the highest influence on these parameters.
Jung et al. (2021) (S. M. Jung et al., 2021)	27 men and women (aged 29–75 y) with CVD risk factors	Two packets (12.5g each) daily of a fermented powdered soy product, or an isoenergic control powder made from germinated brown rice, for 12 weeks	Fermented soy powder product: ↓ Reduces Total and LDL Cholesterol

Abbreviations: BMI: body mass index; BP: blood pressure; CVD: cardiovascular disease; TC: total cholesterol; LDL-c: low-density lipoprotein cholesterol; HDL-c: high-density lipoprotein cholesterol; ApoA: apolipoprotein A; ApoB: apolipoprotein B; TAG: triacylglycerol; MCP-1: monocyte chemoattractant protein-1; hs-CRP: high-sensitivity c-reactive protein; IL-6: interleukin 6; ORAC: oxygen radical absorbance capacity; CAT: catalase; TBARS: thiobarbituric acid reactive substance; oxLDL: oxidized LDL; NO: nitric oxide; TMAO: trimethylamine-N-oxide.

Could fermented food benefit patients with chronic kidney disease?

As fermented foods have beneficial effects on both diabetes and hypertension, the two most common causes of CKD, it could also be a nutritional strategy to prevent CKD. Indeed, fermented food may mitigate many complications associated with CKD progression and its accompanying inflammation, reduced Nrf2, expression, increased oxidative stress levels and gut dysbiosis (Mafra et al., 2020). Studies in pre-clinical experimental models (**Table 7**) report amelioration of blood, morphological and histological parameters associated with kidney damage following consumption of a range of fermented foods.

Few studies have evaluated the effects of fermented foods in clinical outcomes in CKD or in patients at risk of CKD. In T2D nephropathy patients Nakamura et al. (2009)(Nakamura et al., 2009) evaluated the effects of ingestion of 118mL (4oz) of red or white wine on proteinuria and markers of oxidative stress over a six-months period. In response to red wine, urinary 8-hydroxydeoxyguanosine (a marker of DNA damage) and liver-type fatty acid-binding protein (an indicator of clinical progression of CKD) were reduced. However, only patients with a S-creatinine level <1.5mg/dL or 24-h creatinine clearance >80mL/min, were included. It remains to be determined if the reno-protective effects of red wine are linked to a reduction in oxidative stress by polyphenolic content. As no beneficial effects were observed after white wine it is not likely that they were attributed to fermented compounds and red wine having a high content of the senotherapeutic compound resveratrol, can act as a modulator of cellular ageing processes. In a prospective, randomized crossover study, Migliori *et al*. (2015)(M et al., 2015) studied the effects of white wine (4mL/kg body weight ≈ 2-3 glasses/daily) plus olive oil versus olive oil alone in healthy subjects and CKD stages 3-4. They observed that CRP and IL-6 decreased after white wine + olive oil intake; however, there was no significant variation with olive oil only intake. As white wine contains simple phenols, such as tyrosol and hydroxytyrosol, also characteristic of extra-virgin olive oil, this may explain the results. As the anti-inflammatory effects presented were attributed to white wine only, other bioactive compounds from the wine fermentation process may be involved in these beneficial findings. An analysis of the National Health and Nutrition Examination Survey (NHANES) has shown that wine consumption < 1 glass per day, compared to abstinence, was related to lower prevalence of urinary albumin/creatinine ratio (UACR) ≥30mg/g but not low eGFR) (J. T et al., 2018).

A secondary analysis of NHANES conducted by Yacoub *et al.* (2016), showed promising findings related to yoghurt consumption. Frequent yoghurt use (≥3 weekly) was associated with decreased risk for proteinuria (UACR ≥ 30mg/g). The amelioration of

dysbiosis induced by yoghurt use could positively impact systemic inflammation and, thus, renal dysfunction (Yacoub et al., 2016). Accordingly, in a study with 9,229 subjects with normal kidney function, daily intake of fermented vegetables was not associated with the incidence of CKD (GFR <60mL/min) after eight years of follow-up. However, the two highest tertiles of fermentable vegetable intake were associated with a 14% lower risk of incident proteinuria compared to the lowest tertile (Jhee et al., 2019). Taken together, although studies with fermented foods in humans are still scarce and focused on few foods, such as yoghurt, wine, and vegetables, the results seem encouraging regarding the prevention/deceleration of CKD and the modulation of the inflammatory status.

Table 7. Experimental studies involving effects of food fermented on chronic kidney disease models.

References	Sample	Intervention	Results
Minamiyama et al. (2002) (Minamiyama et al., 2002)	Male rats (cisplatin-induced CKD)	Control; Control + AOB 6.5% (AOB: antioxidant Biofactor from **fermentation of grains** (wheat germ, soybeans, rice bran, tear grass, sesame, wheat, citron, green tea, green leaf extract and malted rice) or Cisplatin-induced CKD+ AOB 6.5%	AOB: ↓ renal dysfunction and intestinal damage, DNA oxidation and lipid peroxidation induced by cisplatin.
Du et al. (2019)(Du et al., 2019)	Male CKD induced by HFD	Control, HFD, Control + FTE (**Fu brick tea aqueous extract - fermentation**); HFD + FTE (400 mg/kg) *400mg/kg = ~62 g dry tea/day for a person (70kg)*	***HFD + FTE:*** ↓ body, kidney and epididymis fat weight (so, prevent hypertrophy of kidney), ↓ TG, LDL-C, ↑ glucose tolerance and insulin sensitivity. Renoprotection and mitigate insulin resistance (↓ SIRP-α expression, ↑ p-IRS1/IRS1, p-PI3K/PI3K, and p-Akt/Akt ratio and ↓ Skeletal muscle FoxO1)
Prasetyo (2019)(Prasetyo et al., 2020)	Pyelonephritic rats (by LPS)	Control, LPS, LPS + **lactobacillus plantarum IS-10506** isolated from fermented buffalo milk *dadih*	*Lactobacillus* -↑ *IL-10,* ↑ *activation and proliferation of renal tubular steam cell*
He et al. (2020)(He et al., 2020)	Female mice (adenine-induced CKD)	Control; CKD model control; CKD with IMB (**fermented soy extract with koji fermentation** (Aspergillu soryzae) and LAB (Pediococcus parvulus and Enterococcus faecium) or LAP (oligo-lactic acid product from fermentation of sugar beet and corn with Lactobacillus): *IMB at 250 mg/kg BW (IMB-L) *IMB at 1000 mg/kg BW (IMB-H) *LAP at 1000 mg/kg BW (LAP-L) *LAP at 2000 mg/kg BW (LAP-H) *IMB-L/LAP-L combination *IMB-H/LAP-H combination	**IMB and LAP:** ↓ MCP-1, IL-1, TLR-4, F4/80, TGF-β1, and IL-1β genes in the kidneys LAP-L: ↓ inflammation; ↓ tubular dilation, ↓ IL-6 and ↓ TIMP-1 plasma levels. LAP-H: ↓ IL-12p70; IMB-H ↓ tubulointerstitial atrophy, ↓ TIMP-1; IMB-L/LAP-L combination: ↓ tubular dilation and interstitial inflammation, ↓ IL-12p70 and ↓ TIMP-1 plasma levels. IMB-H/LAP-H: ↓ IL-6 and IFN-γ and ↓ TIMP-1 plasma levels. **Gut Microbiota:** All groups (except IMB-L/LAP-L): ↑ *Clostridium leptum* *LAP-H:* ↑ *Clostridium coccoides*

			IMB-L: ↑ *Clostridium coccoides, Bifidobacterium* genus, *Bacteroides fragilis* group, and *Clostridium leptum*
Xiao et al. (2020)(Xiao et al., 2020)	Male rats (model of hyperuricemia)	Control, Hyperuricemia model + **LAB strain** (isolated from pickles)	*LAB:* ↓ kidney damage. ↑ *Cr and BUN in all groups (compared to control group)*
Chan et al. (2020)(Chan et al., 2020)	Male rat with nephropathy in streptozotocin-induced diabetes	Control, Diabetic control (DC); Diabetics with different doses of ***Bacillus subtilis*-fermented red bean** (natto-red bean) extract: Low dose (100mg/kg) (DC-L) Medium dose (200mg/kg) (DC-M) High (500mg/kg) (DC-H)	*Prevent diabetic nephropathy by improving antioxidant status and inhibiting inflammation in renal tissue* ***All natto groups compared to DC:*** ↑ *adiponectin*, ↓ urinary albumin excretion, ↓ ROS and AG*E*, ↑ *GSH* *DC-M:* ↑ CrCl, ↑ *renal SOD activity,* ↓ CRP, ↓ renal TNF-α and MCP-1
Xi e al. (2020)(Xi et al., 2020)	Male SanHua geese (*Anser domestica*)	**Experiment 1:** 160, 180, 200, and 220g of protein/kg **Experiment 2:** effect on **fermented food** on gout gosling caused by HPD control diet: control diet + fermented feed (seed sourdough prepared with multiple-strain culture (Lactobacillus plantarum, Bacillus subtilis, Saccharomyces, and so on); HPD; HPD + fermented food	***Experiment 1****:* ↑UA, Cr, BUN, XO activity according to the level of protein intake; ***Experiment 2:*** *fermented food* ↓ *gout incidence;* ↓ XO activity*;* ↓*UA and Cr levels;* ↑*Lactobacillus* ↓ *enterococcus.*

Abbreviations: AOB: antioxidant biofact, AGEs: advanced glycation end-product, AFRW: alcohol free-red wine, BUN: blood urea nitrogen, Cr: creatinine, CKD: chronic kidney disease, CRP: C-reactive protein, DC: diabetic control E: ethanol, FOXO1: forkhead box protein O1, FTE: Fu brick tea aqueous extract, HFD: high fat diet, HPD: high protein diet, GSH: glutathione, IL-1: interleukin-1, IL-6: interleukin-6, IFN-y: interferon-y, IL12p70: interleukin-12p70, IL-1b: interleukin-1B, IMB: fermented soy extract, IRS-1: insulin receptor substrate-1, LPS: lipopolysaccharide, LAP: oligo-lactic acid product, LAB: lactobacillus, LDL-C: low-density lipoprotein cholesterol, MCP-1: monocyte chemoattractant protein–1, ROS: reactive oxygen species, RW: red wine, SOD: superoxide dismutase, SIRP-α: signal regulatory protein-α; STZ: streptozotocin, TGFb: transforming growth factor, TG: triglycerides, TIMP-1: inhibitor of metalloproteinases 1, TLR4: toll-like receptor 4, TNF-α: tumor necrosis factor, CrCl: *creatinine clearance*; UAE: urinary albumin excretion, UA: uric acid, XO: xanthine oxidase.

Final considerations and conclusions

Fermented foods are promising nutritional agents with the potential for adjunctive treatment for cardiometabolic diseases, including CKD. Fermented foods have the potential to control inflammation and oxidative stress by decreasing NF-kB activation and activate Nrf2 expression, which decrease proinflammatory cytokines and an increase antioxidant protective system. Furthermore, fermented foods modulate the intestinal microbiota preventing intestinal dysbiosis. Due to these salutogenic properties the consumption of fermented foods may benefit patients with both T2D and CVD. Fermented food may also be effective in reducing insulin resistance, serum glucose levels and enhancing health beneficial lipid profiles, with a consequent decrease in the risk of clinical complications due to the disease (**Figure 3**). Regular intake of fermented foods should be taken into consideration for nutritional treatment in CKD. Studies also need to show if consumption of fermented foods can prevent kidney damage and decrease proteinuria. As sufficiently powered studies in CKD are scarce, this literature review should motivate the renal research community to conduct clinical studies with fermented foods.

Another critical issue is ensuring patients include more fermented food in their diet, ideally supported by nutritional education initiatives.

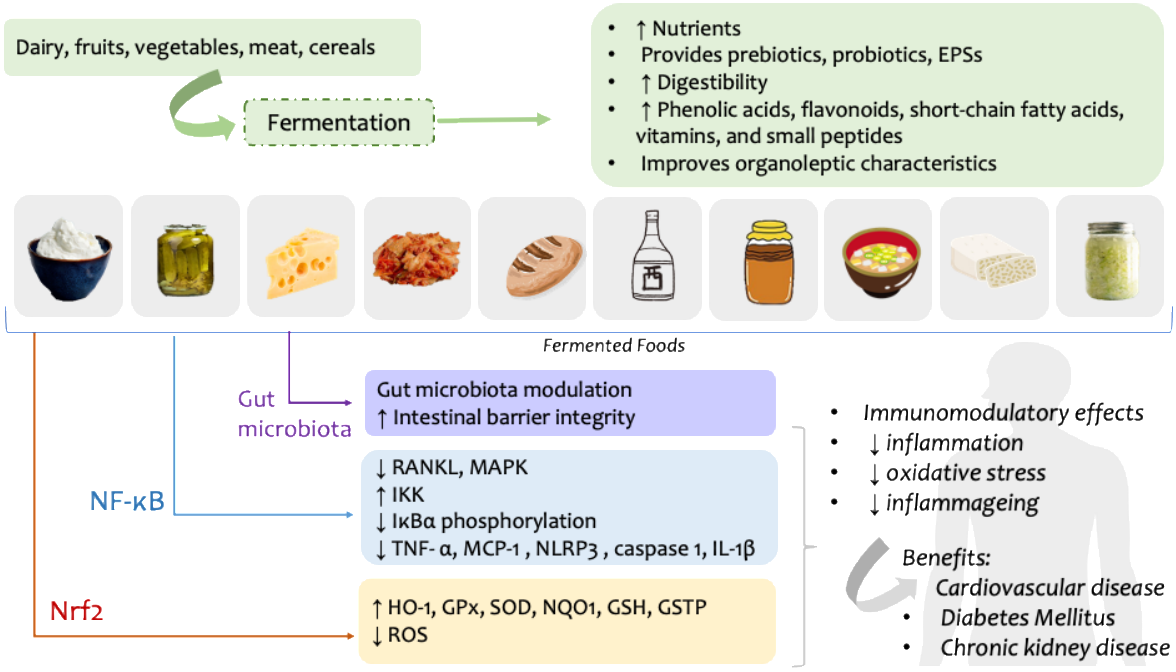

Figure 3. Summary of the Fermented Food characteristics and possible effects on human health. Compounds present in fermented food (such as sourdough bread, kefir, Kimchi, cheeses, pickles, chorizo, natto, tempeh, kombucha, beer, whisky, wine, among others) may promote beneficial effects in patients with cardiometabolic diseases through their actions in

modulating gut microbiota and nuclear transcription factors expression, such as NF-κB and Nrf2. EPSs: exopolysaccharides; GPx: Glutathione Peroxidase; GSH: Glutathione; GSTP: Glutathione S-transferase pi; HO-1: Heme Oxygenase-1; IKK: IκB Kinase; IL-1β: Interleukin-1beta β; IκBα: NF-kappa-B Inhibitor alpha; MAPK: Mitogen-Activated Protein Kinases; MCP-1: Monocyte; Chemoattractant Protein-1; NF-κB: nuclear factor-kappa B; NLRP3: Nod-Like Receptor Pyrin domain containing; NQO1: Quinone Oxidoreductase; Nrf2: nuclear erythroid factor 2; RANKL: Receptor Activator of NF-kappaB Ligand; SOD: Superoxide Dismutase; TNF- α: Tumor Necrosis Factor-alpha.

Acknowledgments

This study was supported by Conselho Nacional de Pesquisa (CNPq) number 200162/2020-9, and Fundação de Amparo à Pesquisa do Estado do Rio de Janeiro (FAPERJ) number E-26/202.524/2019.

Declaration of interest statement

There are no conflicts of interest to declare.

References

Abed, D. A., Goldstein, M., Albanyan, H., Jin, H., & Hu, L. (2015). Discovery of direct inhibitors of Keap1-Nrf2 protein-protein interaction as potential therapeutic and preventive agents. *Acta Pharmaceutica Sinica B*, *5*(4), 285–299. https://doi.org/10.1016/j.apsb.2015.05.008

Ağagündüz, D., Yılmaz, B., Şahin, T. Ö., Güneşliol, B. E., Ayten, Ş., Russo, P., Spano, G., Rocha, J. M., Bartkiene, E., & Özogul, F. (2021). Dairy Lactic Acid Bacteria and Their Potential Function in Dietetics: The Food-Gut-Health Axis. *Foods (Basel, Switzerland)*, *10*(12). https://doi.org/10.3390/FOODS10123099

Agista, A. Z., Rusbana, T. B., Islam, J., Ohsaki, Y., Sultana, H., Hirakawa, R., Watanabe, K., Nochi, T., Ardiansyah, Budijanto, S., Yang, S. C., Koseki, T., Aso, H., Komai, M., & Shirakawa, H. (2021). Fermented rice bran supplementation prevents the development of intestinal fibrosis due to dss-induced inflammation in mice. *Nutrients*, *13*(6). https://doi.org/10.3390/nu13061869

Ahn, H. Y., Kim, M., Seo, C. R., Yoo, H. J., Lee, S. H., & Lee, J. H. (2018). The effects of Jerusalem artichoke and fermented soybean powder mixture supplementation on blood glucose and oxidative stress in subjects with prediabetes or newly diagnosed type 2 diabetes. *Nutrition & Diabetes*, *8*(1). https://doi.org/10.1038/S41387-018-0052-Y

Ahn, S. B., Wu, W. H., Lee, J. H., Jun, D. W., Kim, J., Kim, R., Lee, T. B., & Jun, J. H. (2018). Fermented soymilk alleviates lipid accumulation by inhibition of SREBP-1 and activation of NRF-2 in the hepatocellular steatosis model. *Journal of Microbiology and Biotechnology*, *28*(2), 236–245. https://doi.org/10.4014/jmb.1707.07061

Ali, O. S. M., Amin, N. E. D., Abdel Fattah, S. M., & Abd El-Rahman, O. (2020). Ameliorative effect of kefir against γ-irradiation induced liver injury in male rats: impact on oxidative stress and inflammation. *Environmental Science and Pollution Research*, *27*(28), 35161–35173. https://doi.org/10.1007/s11356-020-09833-7

Alvarenga, L., Salarolli, R., Cardozo, L. F. M. F., Santos, R. S., de Brito, J. S., Kemp, J. A., Reis, D., de Paiva, B. R., Stenvinkel, P., Lindholm, B., Fouque, D., & Mafra, D. (2020). Impact of curcumin supplementation on expression of inflammatory

transcription factors in hemodialysis patients: A pilot randomized, double-blind, controlled study. *Clinical Nutrition*, *39*(12), 3594–3600. https://doi.org/10.1016/j.clnu.2020.03.007

Alvarez, A. S., Tap, J., Chambaud, I., Cools-Portier, S., Quinquis, L., Bourlioux, P., Marteau, P., Guillemard, E., Schrezenmeir, J., & Derrien, M. (2020). Safety and functional enrichment of gut microbiome in healthy subjects consuming a multi-strain fermented milk product: a randomised controlled trial. *Scientific Reports*, *10*(1). https://doi.org/10.1038/S41598-020-72161-W

An, S. Y., Lee, M. S., Jeon, J. Y., Ha, E. S., Kim, T. H., Yoon, J. Y., Ok, C. O., Lee, H. K., Hwang, W. S., Choe, S. J., Han, S. J., Kim, H. J., Kim, D. J., & Lee, K. W. (2013). Beneficial effects of fresh and fermented kimchi in prediabetic individuals. *Annals of Nutrition and Metabolism*, *63*(1–2), 111–119. https://doi.org/10.1159/000353583

Ardiansyah, Shirakawa, H., Giriwono, P. E., Oguchi, K., Ueda, K., Hokazono, H., Hiwatashi, K., Takahashi, S., Sato, S., & Komai, M. (2015). Fermented barley extract supplementation ameliorates metabolic state in stroke-prone spontaneously hypertensive rats. *Bioscience, Biotechnology and Biochemistry*, *79*(11), 1876–1883. https://doi.org/10.1080/09168451.2015.1052772

Asgharian, H., Homayouni-Rad, A., Mirghafourvand, M., & Mohammad-Alizadeh-Charandabi, S. (2020). Effect of probiotic yoghurt on plasma glucose in overweight and obese pregnant women: a randomized controlled clinical trial. *European Journal of Nutrition*, *59*(1), 205–215. https://doi.org/10.1007/S00394-019-01900-1

Aslam, H., Green, J., Jacka, F. N., Collier, F., Berk, M., Pasco, J., & Dawson, S. L. (2020). Fermented foods, the gut and mental health: a mechanistic overview with implications for depression and anxiety. In *Nutritional Neuroscience* (Vol. 23, Issue 9, pp. 659–671). Taylor and Francis Ltd. https://doi.org/10.1080/1028415X.2018.1544332

Aune, D., Norat, T., Romundstad, P., & Vatten, L. J. (2013). Dairy products and the risk of type 2 diabetes: A systematic review and dose-response meta-analysis of cohort studies. *American Journal of Clinical Nutrition*, *98*(4), 1066–1083. https://doi.org/10.3945/ajcn.113.059030

Ba, Z., Lee, Y., Meng, H., Kris-Etherton, P. M., Rogers, C. J., Lewis, Z. T., Mills, D. A., Furumoto, E. J., Rolon, M. L., Fleming, J. A., & Roberts, R. F. (2021). Matrix Effects on the Delivery Efficacy of Bifidobacterium animalis subsp. lactis BB-12 on Fecal Microbiota, Gut Transit Time, and Short-Chain Fatty Acids in Healthy Young Adults. *MSphere*, *6*(4). https://doi.org/10.1128/MSPHERE.00084-21

Bach, S., Colas, P., & Blondel, M. (2020). Budding yeast, a model and a tool⋯ also for biomedical research. In *Medecine/Sciences* (Vol. 36, Issue 5, pp. 504–513). Editions EDK. https://doi.org/10.1051/medsci/2020077

Bae, C. H., Kim, J., Nam, W., Kim, H., Kim, J., Nam, B., Park, S., Lee, J., & Sim, J. (2021). Fermented Red Ginseng Alleviates Ovalbumin-Induced Inflammation in Mice by Suppressing Interleukin-4 and Immunoglobulin e Expression. *Journal of Medicinal Food*, *24*(6), 569–576. https://doi.org/10.1089/jmf.2020.4854

Baruah, R., Ray, M., & Halami, P. M. (2022a). Preventive and therapeutic aspects of fermented foods. *Journal of Applied Microbiology*. https://doi.org/10.1111/jam.15444

Baruah, R., Ray, M., & Halami, P. M. (2022b). Preventive and Therapeutic aspects of Fermented Foods. *Journal of Applied Microbiology*. https://doi.org/10.1111/JAM.15444

Bautista-Expósito, S., Peñas, E., Frias, J., & Martínez-Villaluenga, C. (2019). Pilot-scale produced fermented lentil protects against t-BHP-triggered oxidative stress by activation of Nrf2 dependent on SAPK/JNK phosphorylation. *Food Chemistry*, *274*, 750–759. https://doi.org/10.1016/j.foodchem.2018.09.012

Béghin, L., Tims, S., Roelofs, M., Rougé, C., Oozeer, R., Rakza, T., Chirico, G., Roeselers, G., Knol, J., Rozé, J. C., & Turck, D. (2021). Fermented infant formula (with Bifidobacterium breve C50 and Streptococcus thermophilus O65) with prebiotic oligosaccharides is safe and modulates the gut microbiota towards a microbiota closer to that of breastfed infants. *Clinical Nutrition (Edinburgh, Scotland)*, *40*(3), 778–787. https://doi.org/10.1016/J.CLNU.2020.07.024

Bell, V., Ferrão, J., Pimentel, L., Pintado, M., & Fernandes, T. (2018). One health, fermented foods, and gut microbiota. In *Foods* (Vol. 7, Issue 12). MDPI Multidisciplinary Digital Publishing Institute. https://doi.org/10.3390/foods7120195

Bellikci-Koyu, E., Sarer-Yurekli, B. P., Akyon, Y., Aydin-Kose, F., Karagozlu, C., Ozgen, A. G., Brinkmann, A., Nitsche, A., Ergunay, K., Yilmaz, E., & Buyuktuncer, Z. (2019a). Effects of regular kefir consumption on gut microbiota in patients with metabolic syndrome: A parallel-group, randomized, controlled study. *Nutrients*, *11*(9), 2089. https://doi.org/10.3390/nu11092089

Bellikci-Koyu, E., Sarer-Yurekli, B. P., Akyon, Y., Aydin-Kose, F., Karagozlu, C., Ozgen, A. G., Brinkmann, A., Nitsche, A., Ergunay, K., Yilmaz, E., & Buyuktuncer, Z. (2019b). Effects of Regular Kefir Consumption on Gut Microbiota in Patients with Metabolic Syndrome: A Parallel-Group, Randomized, Controlled Study. *Nutrients*, *11*(9), 2089. https://doi.org/10.3390/NU11092089

Beltrán-Barrientos, L. M., Hernández-Mendoza, A., Torres-Llanez, M. J., González-Córdova, A. F., & Vallejo-Córdoba, B. (2016). Invited review: Fermented milk as antihypertensive functional food. *Journal of Dairy Science*, *99*(6), 4099–4110. https://doi.org/10.3168/jds.2015-10054

Beltrán-Barrientos, Lilia M., González-Córdova, A. F., Hernández-Mendoza, A., Torres-Inguanzo, E. H., Astiazarán-García, H., Esparza-Romero, J., & Vallejo-Cordoba, B. (2018a). Randomized double-blind controlled clinical trial of the blood pressure–lowering effect of fermented milk with Lactococcus lactis: A pilot study2. *Journal of Dairy Science*, *101*(4), 2819–2825. https://doi.org/10.3168/jds.2017-13189

Beltrán-Barrientos, Lilia M., González-Córdova, A. F., Hernández-Mendoza, A., Torres-Inguanzo, E. H., Astiazarán-García, H., Esparza-Romero, J., & Vallejo-Cordoba, B. (2018b). Randomized double-blind controlled clinical trial of the blood pressure–lowering effect of fermented milk with Lactococcus lactis: A pilot study2. *Journal of Dairy Science*, *101*(4), 2819–2825. https://doi.org/10.3168/jds.2017-13189

Bousquet, J., Anto, J. M., Czarlewski, W., Haahtela, T., Fonseca, S. C., Iaccarino, G., Blain, H., Vidal, A., Sheikh, A., Akdis, C. A., Zuberbier, T., Hamzah Abdul Latiff, A., Abdullah, B., Aberer, W., Abusada, N., Adcock, I., Afani, A., Agache, I., Aggelidis, X., … Zubrinich, C. (2021). Cabbage and fermented vegetables: From death rate heterogeneity in countries to candidates for mitigation strategies of severe COVID-19. *Allergy: European Journal of Allergy and Clinical Immunology*, *76*(3), 735–750. https://doi.org/10.1111/all.14549

Bücher, C., Burtscher, J., & Domig, K. J. (2021). Propionic acid bacteria in the food industry: An update on essential traits and detection methods. *Comprehensive Reviews in Food Science and Food Safety*, *20*(5), 4299–4323. https://doi.org/10.1111/1541-4337.12804

Burton, K. J., Krüger, R., Scherz, V., Münger, L. H., Picone, G., Vionnet, N., Bertelli, C., Greub, G., Capozzi, F., & Vergères, G. (2020). Trimethylamine-N-oxide postprandial response in plasma and urine is lower after fermented compared to non-fermented dairy consumption in healthy adults. *Nutrients*, *12*(1), 1–16. https://doi.org/10.3390/nu12010234

Byun, M. S., Yu, O. K., Cha, Y. S., & Park, T. S. (2016). Korean traditional Chungkookjang

improves body composition, lipid profiles and atherogenic indices in overweight/obese subjects: a double-blind, randomized, crossover, placebo-controlled clinical trial. *European Journal of Clinical Nutrition*, *70*(10), 1116–1122. https://doi.org/10.1038/EJCN.2016.77

Cardoso, R. R., Moreira, L. D. P. D., De Campos Costa, M. A., Toledo, R. C. L., Grancieri, M., Nascimento, T. P. Do, Ferreira, M. S. L., Da Matta, S. L. P., Eller, M. R., Duarte Martino, H. S., & De Barros, F. A. R. (2021). Kombuchas from green and black teas reduce oxidative stress, liver steatosis and inflammation, and improve glucose metabolism in Wistar rats fed a high-fat high-fructose diet. *Food and Function*, *12*(21), 10813–10827. https://doi.org/10.1039/d1fo02106k

Cardozo, L. F. M. F., Alvarenga, L. A., Ribeiro, M., Dai, L., Shiels, P. G., Stenvinkel, P., Lindholm, B., & Mafra, D. (2021). Cruciferous vegetables: Rationale for exploring potential salutary effects of sulforaphane-rich foods in patients with chronic kidney disease. *Nutrition Reviews*, *79*(11), 1204–1224. https://doi.org/10.1093/nutrit/nuaa129

Carlo Tenore, G., Caruso, D., Buonomo, G., D'avino, M., Ciampaglia, R., Maisto, M., Schisano, C., Bocchino, B., & Novellino, E. (2019). Lactofermented Annurca Apple Puree as a Functional Food Indicated for the Control of Plasma Lipid and Oxidative Amine Levels: Results from a Randomised Clinical Trial. *Nutrients*, *11*(1). https://doi.org/10.3390/NU11010122

Castro-Bravo, N., Wells, J. M., Margolles, A., & Ruas-Madiedo, P. (2018). Interactions of surface exopolysaccharides from bifidobacteriumand lactobacilluswithin the intestinal environment. In *Frontiers in Microbiology* (Vol. 9, Issue OCT). Frontiers Media S.A. https://doi.org/10.3389/fmicb.2018.02426

Cha, Y. S., Park, Y., Lee, M., Chae, S. W., Park, K., Kim, Y., & Lee, H. S. (2014). Doenjang, a Korean fermented soy food, exerts antiobesity and antioxidative activities in overweight subjects with the PPAR-γ2 C1431T polymorphism: 12-week, double-blind randomized clinical trial. *Journal of Medicinal Food*, *17*(1), 119–127. https://doi.org/10.1089/JMF.2013.2877

Chan, K.-C., Kok, K.-E., Huang, K.-F., Weng, Y.-L., & Chung, Y.-C. (2020). Effects of fermented red bean extract on nephropathy in streptozocin-induced diabetic rats. *Food & Nutrition Research*, *64*. https://doi.org/10.29219/fnr.v64.4272

Chaudhari, D. D., Singh, R., Mallappa, R. H., Rokana, N., Kaushik, J. K., Bajaj, R., Batish, V. K., & Grover, S. (2017). Evaluation of casein & whey protein hydrolysates as well as milk fermentates from lactobacillus helveticus for expression of gut hormones. *Indian Journal of Medical Research*, *146*(September), 409–419. https://doi.org/10.4103/ijmr.IJMR_802_15

Checa, J., & Aran, J. M. (2020). Reactive oxygen species: Drivers of physiological and pathological processes. *Journal of Inflammation Research*, *13*, 1057–1073. https://doi.org/10.2147/JIR.S275595

Chen, H., Chen, T., Giudici, P., & Chen, F. (2016). Vinegar Functions on Health: Constituents, Sources, and Formation Mechanisms. *Comprehensive Reviews in Food Science and Food Safety*, *15*(6), 1124–1138. https://doi.org/10.1111/1541-4337.12228

Chen, H. L., Hung, K. F., Yen, C. C., Laio, C. H., Wang, J. L., Lan, Y. W., Chong, K. Y., Fan, H. C., & Chen, C. M. (2019). Kefir peptides alleviate particulate matter <4 μm (PM4.0)-induced pulmonary inflammation by inhibiting the NF-κB pathway using luciferase transgenic mice. *Scientific Reports*, *9*(1), 1–13. https://doi.org/10.1038/s41598-019-47872-4

Chen, M., Sun, Q., Giovannucci, E., Mozaffarian, D., Manson, J. A. E., Willett, W. C., & Hu, F. B. (2014). Dairy consumption and risk of type 2 diabetes: 3 cohorts of US adults and an updated meta-analysis. *BMC Medicine*, *12*(1). https://doi.org/10.1186/s12916-

014-0215-1
Chen, Y., Feng, R., Yang, X., Dai, J., Huang, M., Ji, X., Li, Y., Okekunle, A. P., Gao, G., Onwuka, J. U., Pang, X., Wang, C., Li, C., Li, Y., & Sun, C. (2019). Yogurt improves insulin resistance and liver fat in obese women with nonalcoholic fatty liver disease and metabolic syndrome: a randomized controlled trial. *The American Journal of Clinical Nutrition*, *109*(6), 1611–1619. https://doi.org/10.1093/AJCN/NQY358
Cheng, C. F., & Pan, T. M. (2016). Ankaflavin and Monascin Induce Apoptosis in Activated Hepatic Stellate Cells through Suppression of the Akt/NF-κB/p38 Signaling Pathway. *Journal of Agricultural and Food Chemistry*, *64*(49), 9326–9334. https://doi.org/10.1021/acs.jafc.6b03700
Chiu, H. F., Wang, H. M., Shen, Y. C., Venkatakrishnan, K., & Wang, C. K. (2019). Anti-inflammatory properties of fermented pine (Pinus morrisonicola Hay.) needle on lipopolysaccharide-induced inflammation in RAW 264.7 macrophage cells. *Journal of Food Biochemistry*, *43*(11), e12994. https://doi.org/10.1111/jfbc.12994
Chiva-Blanch, G., Urpi-Sarda, M., Ros, E., Valderas-Martinez, P., Casas, R., Arranz, S., Guillén, M., Lamuela-Raventós, R. M., Llorach, R., Andres-Lacueva, C., & Estruch, R. (2013). Effects of red wine polyphenols and alcohol on glucose metabolism and the lipid profile: A randomized clinical trial. *Clinical Nutrition*, *32*(2), 200–206. https://doi.org/10.1016/j.clnu.2012.08.022
Cho, S. K., Shin, S. Y., Lee, S. J., Li, L., Moon, J. S., Kim, D. J., Im, W. T., & Han, N. S. (2015). Simple synthesis of isomaltooligosaccharides during Sauerkraut fermentation by addition of Leuconostoc starter and sugars. *Food Science and Biotechnology*, *24*(4), 1443–1446. https://doi.org/10.1007/s10068-015-0185-x
Choi, I. H., Noh, J. S., Han, J. S., Kim, H. J., Han, E. S., & Song, Y. O. (2013). Kimchi, a Fermented Vegetable, improves serum lipid profiles in healthy young adults: Randomized clinical trial. *Journal of Medicinal Food*, *16*(3), 223–229. https://doi.org/10.1089/jmf.2012.2563
Craven, H., McGuinness, D., Buchanan, S., Galbraith, N., McGuinness, D. H., Jones, B., Combet, E., Mafra, D., Bergman, P., Ellaway, A., Stenvinkel, P., Ijaz, U. Z., & Shiels, P. G. (2021). Socioeconomic position links circulatory microbiota differences with biological age. *Scientific Reports*, *11*(1). https://doi.org/10.1038/s41598-021-92042-0
Cui, J., Xia, P., Zhang, L., Hu, Y., Xie, Q., & Xiang, H. (2020). A novel fermented soybean, inoculated with selected Bacillus, Lactobacillus and Hansenula strains, showed strong antioxidant and anti-fatigue potential activity. *Food Chemistry*, *333*, 127527. https://doi.org/10.1016/j.foodchem.2020.127527
Das, G., Paramithiotis, S., Sundaram Sivamaruthi, B., Wijaya, C. H., Suharta, S., Sanlier, N., Shin, H. S., & Patra, J. K. (2020). Traditional fermented foods with anti-aging effect: A concentric review. *Food Research International (Ottawa, Ont.)*, *134*. https://doi.org/10.1016/J.FOODRES.2020.109269
De Almeida Alvarenga, L., Borges, N. A., Moreira, L. D. S. G., Resende Teixeira, K. T., Carraro-Eduardo, J. C., Dai, L., Stenvinkel, P., Lindholm, B., & Mafra, D. (2019). Cranberries-potential benefits in patients with chronic kidney disease. *Food and Function*, *10*(6), 3103–3112. https://doi.org/10.1039/c9fo00375d
Derrien, M., & van Hylckama Vlieg, J. E. T. (2015). Fate, activity, and impact of ingested bacteria within the human gut microbiota. In *Trends in Microbiology* (Vol. 23, Issue 6, pp. 354–366). Elsevier Ltd. https://doi.org/10.1016/j.tim.2015.03.002
Devanthi, P. V. P., & Gkatzionis, K. (2019). Soy sauce fermentation: Microorganisms, aroma formation, and process modification. *Food Research International (Ottawa, Ont.)*, *120*, 364–374. https://doi.org/10.1016/J.FOODRES.2019.03.010
Dimidi, E., Cox, S. R., Rossi, M., & Whelan, K. (2019). Fermented foods: Definitions and

characteristics, impact on the gut microbiota and effects on gastrointestinal health and disease. In *Nutrients* (Vol. 11, Issue 8). MDPI AG. https://doi.org/10.3390/nu11081806

Drouin-Chartier, J. P., Brassard, D., Tessier-Grenier, M., Côté, J. A., Labonté, M. É., Desroches, S., Couture, P., & Lamarche, B. (2016). Systematic review of the association between dairy product consumption and risk of cardiovascular-related clinical outcomes. *Advances in Nutrition*, *7*(6), 1026–1040. https://doi.org/10.3945/an.115.011403

Du, H., Wang, Q., & Yang, X. (2019). Fu Brick Tea Alleviates Chronic Kidney Disease of Rats with High Fat Diet Consumption through Attenuating Insulin Resistance in Skeletal Muscle. *Journal of Agricultural and Food Chemistry*, *67*(10), 2839–2847. https://doi.org/10.1021/acs.jafc.8b06927

Ejtahed, H. S., Mohtadi-Nia, J., Homayouni-Rad, A., Niafar, M., Asghari-Jafarabadi, M., Mofid, V., & Akbarian-Moghari, A. (2011). Effect of probiotic yogurt containing Lactobacillus acidophilus and Bifidobacterium lactis on lipid profile in individuals with type 2 diabetes mellitus. *Journal of Dairy Science*, *94*(7), 3288–3294. https://doi.org/10.3168/JDS.2010-4128

Ejtahed, Hanie S., Mohtadi-Nia, J., Homayouni-Rad, A., Niafar, M., Asghari-Jafarabadi, M., & Mofid, V. (2012). Probiotic yogurt improves antioxidant status in type 2 diabetic patients. *Nutrition (Burbank, Los Angeles County, Calif.)*, *28*(5), 539–543. https://doi.org/10.1016/J.NUT.2011.08.013

Escudero-López, B., Ortega, Á., Cerrillo, I., Rodríguez-Griñolo, M. R., Muñoz-Hernández, R., Macher, H. C., Martín, F., Hornero-Méndez, D., Mena, P., Del Rio, D., & Fernández-Pachón, M. S. (2018). Consumption of orange fermented beverage improves antioxidant status and reduces peroxidation lipid and inflammatory markers in healthy humans. *Journal of the Science of Food and Agriculture*, *98*(7), 2777–2786. https://doi.org/10.1002/JSFA.8774

Fathi, Y., Ghodrati, N., Zibaeenezhad, M. J., & Faghih, S. (2017). Kefir drink causes a significant yet similar improvement in serum lipid profile, compared with low-fat milk, in a dairy-rich diet in overweight or obese premenopausal women: A randomized controlled trial. *Journal of Clinical Lipidology*, *11*(1), 136–146. https://doi.org/10.1016/J.JACL.2016.10.016

Fuda, H., Miyanaga, S., Furukawa, T., Umetsu, S., Joko, S., Roan, Y., Suzuki, H., Hui, S. P., Watanabe, M., & Chiba, H. (2019). Flazin as a Promising Nrf2 Pathway Activator. *Journal of Agricultural and Food Chemistry*, *67*(46), 12844–12853. https://doi.org/10.1021/acs.jafc.9b04600

Gao, D., Ning, N., Wang, C., Wang, Y., Li, Q., Meng, Z., Liu, Y., & Li, Q. (2013). Dairy Products Consumption and Risk of Type 2 Diabetes: Systematic Review and Dose-Response Meta-Analysis. In *PLoS ONE* (Vol. 8, Issue 9). Public Library of Science. https://doi.org/10.1371/journal.pone.0073965

García-Burgos, M., Moreno-Fernandez, J., Díaz-Castro, J., M Alférez, M. J., & López-Aliaga, I. (2022). Fermented goat's milk modulates immune response during iron deficiency anemia recovery. *Journal of the Science of Food and Agriculture*, *102*(3), 1114–1123. https://doi.org/10.1002/jsfa.11448

Garcia-Gonzalez, N., Battista, N., Prete, R., & Corsetti, A. (2021). Health-promoting role of lactiplantibacillus plantarum isolated from fermented foods. *Microorganisms*, *9*(2), 1–30. https://doi.org/10.3390/microorganisms9020349

Gijsbers, L., Ding, E. L., Malik, V. S., De Goede, J., Geleijnse, J. M., & Soedamah-Muthu, S. S. (2016). Consumption of dairy foods and diabetes incidence: A dose-response meta-analysis of observational studies. *American Journal of Clinical Nutrition*, *103*(4), 1111–1124. https://doi.org/10.3945/ajcn.115.123216

Gille, D., Schmid, A., Walther, B., & Vergères, G. (2018). Fermented food and non-communicable chronic diseases: A review. In *Nutrients* (Vol. 10, Issue 4, p. 448). MDPI AG. https://doi.org/10.3390/nu10040448

Golan, R., Shai, I., Gepner, Y., Harman-Boehm, I., Schwarzfuchs, D., Spence, J. D., Parraga, G., Buchanan, D., Witkow, S., Friger, M., Liberty, I. F., Sarusi, B., Ben-Avraham, S., Sefarty, D., Bril, N., Rein, M., Cohen, N., Ceglarek, U., Thiery, J., … Henkin, Y. (2018). Effect of wine on carotid atherosclerosis in type 2 diabetes: a 2-year randomized controlled trial. *European Journal of Clinical Nutrition*, *72*(6), 871–878. https://doi.org/10.1038/S41430-018-0091-4

Golan, R., Shelef, I., Shemesh, E., Henkin, Y., Schwarzfuchs, D., Gepner, Y., Harman-Boehm, I., Witkow, S., Friger, M., Chassidim, Y., Liberty, I. F., Sarusi, B., Serfaty, D., Bril, N., Rein, M., Cohen, N., Ben-Avraham, S., Ceglarek, U., Stumvoll, M., … Shai, I. (2017). Effects of initiating moderate wine intake on abdominal adipose tissue in adults with type 2 diabetes: a 2-year randomized controlled trial. *Public Health Nutrition*, *20*(3), 549–555. https://doi.org/10.1017/S1368980016002597

Guillemard, E., Poirel, M., Schäfer, F., Quinquis, L., Rossoni, C., Keicher, C., Wagner, F., Szajewska, H., Barbut, F., Derrien, M., & Malfertheiner, P. (2021). A Randomised, Controlled Trial: Effect of a Multi-Strain Fermented Milk on the Gut Microbiota Recovery after Helicobacter pylori Therapy. *Nutrients*, *13*(9). https://doi.org/10.3390/NU13093171

Hall, K. D., Ayuketah, A., Brychta, R., Cai, H., Cassimatis, T., Chen, K. Y., Chung, S. T., Costa, E., Courville, A., Darcey, V., Fletcher, L. A., Forde, C. G., Gharib, A. M., Guo, J., Howard, R., Joseph, P. V., McGehee, S., Ouwerkerk, R., Raisinger, K., … Zhou, M. (2020). Erratum: Ultra-Processed Diets Cause Excess Calorie Intake and Weight Gain: An Inpatient Randomized Controlled Trial of Ad Libitum Food Intake (Cell Metabolism (2019) 30(1) (67–77.e3), (S1550413119302487), (10.1016/j.cmet.2019.05.008)). *Cell Metabolism*, *32*(4), 690. https://doi.org/10.1016/j.cmet.2020.08.014

Han, K., Bose, S., Wang, J. H., Kim, B. S., Kim, M. J., Kim, E. J., & Kim, H. (2015). Contrasting effects of fresh and fermented kimchi consumption on gut microbiota composition and gene expression related to metabolic syndrome in obese Korean women. *Molecular Nutrition & Food Research*, *59*(5), 1004–1008. https://doi.org/10.1002/MNFR.201400780

He, L. X., Abdolmaleky, H. M., Yin, S., Wang, Y., & Zhou, J. R. (2020). Dietary fermented soy extract and oligo-lactic acid alleviate chronic kidney disease in mice via inhibition of inflammation and modulation of gut microbiota. *Nutrients*, *12*(8), 1–15. https://doi.org/10.3390/nu12082376

Hove, K. D., Brøns, C., Færch, K., Lund, S. S., Rossing, P., & Vaag, A. (2015). Effects of 12 weeks of treatment with fermented milk on blood pressure, glucose metabolism and markers of cardiovascular risk in patients with type 2 diabetes: a randomised double-blind placebo-controlled study. *European Journal of Endocrinology*, *172*(1), 11–20. https://doi.org/10.1530/EJE-14-0554

Hric, I., Ugrayová, S., Penesová, A., Rádiková, Ž., Kubáňová, L., Šardzíková, S., Baranovičová, E., Klučár, Ľ., Beke, G., Grendar, M., Kolisek, M., Šoltys, K., & Bielik, V. (2021). The Efficacy of Short-Term Weight Loss Programs and Consumption of Natural Probiotic Bryndza Cheese on Gut Microbiota Composition in Women. *Nutrients*, *13*(6). https://doi.org/10.3390/NU13061753

HUANG, Y. (2016). Fermented Food and Ancient Civilization. *DEStech Transactions on Social Science, Education and Human Science, 3rd International Conference on Social Science (ICSS*, 1307–1309. https://doi.org/10.12783/dtssehs/icss2016/9181

Huang, Z., Kin Ng, T., Chen, W., Sun, X., Huang, D., Zheng, D., Yi, J., Xu, Y., Zhuang, X., & Chen, S. (2021). Nattokinase attenuates retinal neovascularization via modulation of nrf2/ho-1 and glial activation. *Investigative Ophthalmology and Visual Science*, *62*(6). https://doi.org/10.1167/IOVS.62.6.25

Hütt, P., Songisepp, E., Rätsep, M., Mahlapuu, R., Kilk, K., & Mikelsaar, M. (2015). Impact of probiotic Lactobacillus plantarum TENSIA in different dairy products on anthropometric and blood biochemical indices of healthy adults. *Beneficial Microbes*, *6*(3), 233–243. https://doi.org/10.3920/BM2014.0035

Islam, M. S., & Choi, H. (2009). Antidiabetic effect of Korean traditional Baechu (Chinese Cabbage) kimchi in a type 2 diabetes model of rats. *Journal of Medicinal Food*, *12*(2), 292–297. https://doi.org/10.1089/jmf.2008.0181

Ito, M., Kusuhara, S., Yokoi, W., Sato, T., Ishiki, H., Miida, S., Matsui, A., Nakamori, K., Nonaka, C., & Miyazaki, K. (2017). Streptococcus thermophilus fermented milk reduces serum MDA-LDL and blood pressure in healthy and mildly hypercholesterolaemic adults. *Beneficial Microbes*, *8*(2), 171–178. https://doi.org/10.3920/BM2016.0102

Jakubowicz, D., & Froy, O. (2013). Biochemical and metabolic mechanisms by which dietary whey protein may combat obesity and Type 2 diabetes. *Journal of Nutritional Biochemistry*, *24*(1), 1–5. https://doi.org/10.1016/j.jnutbio.2012.07.008

Jeong, C. H., Ryu, H., Zhang, T., Lee, C. H., Seo, H. G., & Han, S. G. (2018). Green tea powder supplementation enhances fermentation and antioxidant activity of set-type yogurt. *Food Science and Biotechnology*, *27*(5), 1419–1427. https://doi.org/10.1007/s10068-018-0370-9

Jeong, J. W., Ji, S. Y., Lee, H., Hong, S. H., Kim, G. Y., Park, C., Lee, B. J., Park, E. K., Hyun, J. W., Jeon, Y. J., & Choi, Y. H. (2019). Fermented sea tangle (Laminaria japonica Aresch) Suppresses RANKL-induced osteoclastogenesis by scavenging ROS in RAW 264.7 Cells. *Foods*, *8*(8), 290. https://doi.org/10.3390/foods8080290

Jhee, J. H., Kee, Y. K., Park, J. T., Chang, T. I., Kang, E. W., Yoo, T. H., Kang, S. W., & Han, S. H. (2019). A Diet Rich in Vegetables and Fruit and Incident CKD: A Community-Based Prospective Cohort Study. *American Journal of Kidney Diseases*, *74*(4), 491–500. https://doi.org/10.1053/j.ajkd.2019.02.023

Jung, J. Y., Shin, J. S., Lee, S. G., Rhee, Y. K., Cho, C. W., Hong, H. Do, & Lee, K. T. (2015). Lactobacillus sakei K040706 evokes immunostimulatory effects on macrophages through TLR 2-mediated activation. *International Immunopharmacology*, *28*(1), 88–96. https://doi.org/10.1016/j.intimp.2015.05.037

Jung, S. M., Haddad, E. H., Kaur, A., Sirirat, R., Kim, A. Y., Oda, K., Rajaram, S., & Sabaté, J. (2021). A Non-Probiotic Fermented Soy Product Reduces Total and LDL Cholesterol: A Randomized Controlled Crossover Trial. *Nutrients*, *13*(2), 1–16. https://doi.org/10.3390/NU13020535

Kageyama, S., Inoue, R., Hosomi, K., Park, J., Yumioka, H., Suka, T., Kurohashi, Y., Teramoto, K., Yasmin Syauki, A., Doi, M., Sakaue, H., Mizuguchi, K., Kunisawa, J., & Irie, Y. (2021). Effects of Malted Rice Amazake on Constipation Symptoms and Gut Microbiota in Children and Adults with Severe Motor and Intellectual Disabilities: A Pilot Study. *Nutrients*, *13*(12). https://doi.org/10.3390/NU13124466

Kårlund, A., Gómez-Gallego, C., Korhonen, J., Palo-Oja, O. M., El-Nezami, H., & Kolehmainen, M. (2020). Harnessing microbes for sustainable development: Food fermentation as a tool for improving the nutritional quality of alternative protein sources. *Nutrients*, *12*(4). https://doi.org/10.3390/nu12041020

Kaur, H., Gupta, T., Kapila, S., & Kapila, R. (2021). Protective effects of potential probiotic: Lactobacillus rhamnosus (MTCC-5897) fermented whey on reinforcement of

intestinal epithelial barrier function in a colitis-induced murine model. *Food and Function*, *12*(13), 6102–6116. https://doi.org/10.1039/d0fo02641g

Khan, M. M., Kim, Y. K., Bilkis, T., Suh, J. W., Lee, D. Y., & Yoo, J. C. (2020). Reduction of oxidative stress through activating the nrf2 mediated ho-1 antioxidant efficacy signaling pathway by ms15, an antimicrobial peptide from bacillus velezensis. *Antioxidants*, *9*(10), 1–21. https://doi.org/10.3390/antiox9100934

Kim, D. H., Jeong, D., Kang, I. B., Kim, H., Song, K. Y., & Seo, K. H. (2017). Dual function of Lactobacillus kefiri DH5 in preventing high-fat-diet-induced obesity: direct reduction of cholesterol and upregulation of PPAR-α in adipose tissue. *Molecular Nutrition & Food Research*, *61*(11). https://doi.org/10.1002/MNFR.201700252

Kim, E. K., An, S. Y., Lee, M. S., Kim, T. H., Lee, H. K., Hwang, W. S., Choe, S. J., Kim, T. Y., Han, S. J., Kim, H. J., Kim, D. J., & Lee, K. W. (2011). Fermented kimchi reduces body weight and improves metabolic parameters in overweight and obese patients. *Nutrition Research (New York, N.Y.)*, *31*(6), 436–443. https://doi.org/10.1016/J.NUTRES.2011.05.011

Kim, E., Lee, H. G., Han, S., Seo, K. H., & Kim, H. (2021). Effect of Surface Layer Proteins Derived from Paraprobiotic Kefir Lactic Acid Bacteria on Inflammation and High-Fat Diet-Induced Obesity. *Journal of Agricultural and Food Chemistry*, *69*(50), 15157–15164. https://doi.org/10.1021/ACS.JAFC.1C05037

Kim, H. Y., Bae, W. Y., Yu, H. S., Chang, K. H., Hong, Y. H., Lee, N. K., & Paik, H. D. (2020). Inula britannica fermented with probiotic Weissella cibaria D30 exhibited anti-inflammatory effect and increased viability in RAW 264.7 cells. *Food Science and Biotechnology*, *29*(4), 569–578. https://doi.org/10.1007/s10068-019-00690-w

Kim, I. S., Hwang, C. W., Yang, W. S., & Kim, C. H. (2021). Current Perspectives on the Physiological Activities of Fermented Soybean-Derived Cheonggukjang. *International Journal of Molecular Sciences*, *22*(11). https://doi.org/10.3390/IJMS22115746

Kim, S. M., Park, E. J., Kim, J. Y., Choi, J., & Lee, H. J. (2020). Anti-inflammatory effects of fermented lotus root and linoleic acid in lipopolysaccharide-induced raw 264.7 cells. *Life*, *10*(11), 1–15. https://doi.org/10.3390/life10110293

Kim, S., Woo, M., Kim, M., Noh, J. S., & Song, Y. O. (2018). Neuroprotective Effects of the Methanol Extract of Kimchi, a Korean Fermented Vegetable Food, Mediated Via Suppression of Endoplasmic Reticulum Stress and Caspase Cascade Pathways in High-Cholesterol Diet-Fed Mice. *Journal of Medicinal Food*, *21*(5), 489–495. https://doi.org/10.1089/jmf.2017.4103

Kim, S. Y., Cha, H. J., Hwangbo, H., Park, C., Lee, H., Song, K. S., Shim, J. H., Noh, J. S., Kim, H. S., Lee, B. J., Kim, S., Kim, G. Y., Jeon, Y. J., & Choi, Y. H. (2021). Protection against oxidative stress-induced apoptosis by fermented sea tangle (Laminaria japonica aresch) in osteoblastic MC3T3-E1 cells through activation of Nrf2 signaling pathway. *Foods*, *10*(11). https://doi.org/10.3390/foods10112807

KJ, B., R, K., V, S., LH, M., G, P., N, V., C, B., G, G., F, C., & G, V. (2020). Trimethylamine- N-Oxide Postprandial Response in Plasma and Urine Is Lower After Fermented Compared to Non-Fermented Dairy Consumption in Healthy Adults. *Nutrients*, *12*(1). https://doi.org/10.3390/NU12010234

Kojima, A., Ikehara, S., Kamiya, K., Kajita, E., Sato, Y., Kouda, K., Tamaki, J., Kagamimori, S., & Iki, M. (2020). Natto Intake is Inversely Associated with Osteoporotic Fracture Risk in Postmenopausal Japanese Women. *Journal of Nutrition*, *150*(3), 599–605. https://doi.org/10.1093/jn/nxz292

Kumar, M. R., Yeap, S. K., Mohamad, N. E., Abdullah, J. O., Masarudin, M. J., Khalid, M., Leow, A. T. C., & Alitheen, N. B. (2021). Metagenomic and phytochemical analyses of kefir water and its subchronic toxicity study in BALB/c mice. *BMC Complementary*

Medicine and Therapies, *21*(1). https://doi.org/10.1186/s12906-021-03358-3
Kumar, N., & Goel, N. (2019). Phenolic acids: Natural versatile molecules with promising therapeutic applications. *Biotechnology Reports*, *24*. https://doi.org/10.1016/j.btre.2019.e00370
La Marca, M., Pucci, L., Bollini, R., Russo, R., Sparvoli, F., Gabriele, M., & Longo, V. (2015). Antioxidant effect of a fermented powder of Lady Joy bean in primary rat hepatocytes. *Cellular and Molecular Biology Letters*, *20*(1), 102–116. https://doi.org/10.1515/cmble-2015-0007
Lee, C. S., Kim, J. Y., Kim, B. K., Lee, I. O., Park, N. H., & Kim, S. H. (2021). Lactobacillus-fermented milk products attenuate bone loss in an experimental rat model of ovariectomy-induced post-menopausal primary osteoporosis. *Journal of Applied Microbiology*, *130*(6), 2041–2062. https://doi.org/10.1111/jam.14852
Lee, D. Y., Shin, M. S., & Shin, K. S. (2016). Characterization of Macrophage-Activating Polysaccharide Isolated from Fermented Brown Rice. *Journal of Medicinal Food*, *19*(12), 1147–1154. https://doi.org/10.1089/jmf.2016.3742
Lee, Y., Cha, Y. S., Park, Y., & Lee, M. (2017). PPARγ2 C1431T Polymorphism Interacts with the Antiobesogenic Effects of Kochujang, a Korean Fermented, Soybean-Based Red Pepper Paste, in Overweight/Obese Subjects: A 12-Week, Double-Blind Randomized Clinical Trial. *Journal of Medicinal Food*, *20*(6), 610–617. https://doi.org/10.1089/JMF.2016.3911
Lin, X., Xia, Y., Wang, G., Xiong, Z., Zhang, H., Lai, F., & Ai, L. (2018). Lactobacillus plantarum AR501 Alleviates the Oxidative Stress of D-Galactose-Induced Aging Mice Liver by Upregulation of Nrf2-Mediated Antioxidant Enzyme Expression. *Journal of Food Science*, *83*(7), 1990–1998. https://doi.org/10.1111/1750-3841.14200
Liu, T., Zhang, L., Joo, D., & Sun, S. C. (2017). NF-κB signaling in inflammation. *Signal Transduction and Targeted Therapy*, *2*(March), 1–9. https://doi.org/10.1038/sigtrans.2017.23
Liu, Y., Xue, K., Iversen, K. N., Qu, Z., Dong, C., Jin, T., Hallmans, G., Åman, P., Johansson, A., He, G., & Landberg, R. (2021). The effects of fermented rye products on gut microbiota and their association with metabolic factors in Chinese adults - an explorative study. *Food & Function*, *12*(19), 9141–9150. https://doi.org/10.1039/D1FO01423D
M, M., V, P., R, de la T., M, F., M, C., A, B., D, M.-A., A, S., S, P., & C, R. (2015). Anti-inflammatory effect of white wine in CKD patients and healthy volunteers. *Blood Purification*, *39*(1–3), 218–223. https://doi.org/10.1159/000371570
Madjd, A., Taylor, M. A., Mousavi, N., Delavari, A., Malekzadeh, R., Macdonald, I. A., & Farshchi, H. R. (2016). Comparison of the effect of daily consumption of probiotic compared with low-fat conventional yogurt on weight loss in healthy obese women following an energy-restricted diet: a randomized controlled trial. *The American Journal of Clinical Nutrition*, *103*(2), 323–329. https://doi.org/10.3945/AJCN.115.120170
Mafra, D., Borges, N. A., Lindholm, B., Shiels, P. G., Evenepoel, P., & Stenvinkel, P. (2020). Food as medicine: targeting the uraemic phenotype in chronic kidney disease. In *Nature Reviews Nephrology* (Vol. 17, Issue 3, pp. 153–171). Nature Research. https://doi.org/10.1038/s41581-020-00345-8
Mafra, D., Borges, N., Alvarenga, L., Esgalhado, M., Cardozo, L., Lindholm, B., & Stenvinkel, P. (2019). Dietary components that may influence the disturbed gut microbiota in chronic kidney disease. In *Nutrients* (Vol. 11, Issue 3). MDPI AG. https://doi.org/10.3390/nu11030496
Mamo, G. (2016). Anaerobes as sources of bioactive compounds and health promoting

tools. *Advances in Biochemical Engineering/Biotechnology*, *156*, 433–464. https://doi.org/10.1007/10_2016_6

Manzanarez-Quín, C. G., Beltrán-Barrientos, L. M., Hernández-Mendoza, A., González-Córdova, A. F., & Vallejo-Cordoba, B. (2021). Invited review: Potential antiobesity effect of fermented dairy products. *Journal of Dairy Science*, *104*(4), 3766–3778. https://doi.org/10.3168/JDS.2020-19256

Marco, M. L., Heeney, D., Binda, S., Cifelli, C. J., Cotter, P. D., Foligné, B., Gänzle, M., Kort, R., Pasin, G., Pihlanto, A., Smid, E. J., & Hutkins, R. (2017). Health benefits of fermented foods: microbiota and beyond. In *Current Opinion in Biotechnology* (Vol. 44, pp. 94–102). Elsevier Ltd. https://doi.org/10.1016/j.copbio.2016.11.010

Marco, M. L., Hill, C., Hutkins, R., Slavin, J., Tancredi, D. J., Merenstein, D., & Sanders, M. E. (2020). Should There Be a Recommended Daily Intake of Microbes? *Journal of Nutrition*, *150*(12), 3061–3067. https://doi.org/10.1093/jn/nxaa323

The International Scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement on fermented foods, 18 Nature Reviews Gastroenterology and Hepatology 196 (2021). https://doi.org/10.1038/s41575-020-00390-5

Márquez-Morales, L., El-Kassis, E. G., Cavazos-Arroyo, J., Rocha-Rocha, V., Martínez-Gutiérrez, F., & Pérez-Armendáriz, B. (2021). Effect of the intake of a traditional mexican beverage fermented with lactic acid bacteria on academic stress in medical students. *Nutrients*, *13*(5). https://doi.org/10.3390/nu13051551

Mathur, H., Beresford, T. P., & Cotter, P. D. (2020). Health benefits of lactic acid bacteria (Lab) fermentates. In *Nutrients* (Vol. 12, Issue 6, pp. 1–16). MDPI AG. https://doi.org/10.3390/nu12061679

Meijers, B. K. I., & Evenepoel, P. (2011). The gut-kidney axis: Indoxyl sulfate, p-cresyl sulfate and CKD progression. *Nephrology Dialysis Transplantation*, *26*(3), 759–761. https://doi.org/10.1093/ndt/gfq818

Melnik, B. C., & Schmitz, G. (2021). Pasteurized non-fermented cow's milk but not fermented milk is a promoter of mTORC1-driven aging and increased mortality. *Ageing Research Reviews*, *67*. https://doi.org/10.1016/J.ARR.2021.101270

Merenstein, D., Fraser, C. M., Roberts, R. F., Liu, T., Grant-Beurmann, S., Tan, T. P., Smith, K. H., Cronin, T., Martin, O. A., Sanders, M. E., Lucan, S. C., & Kane, M. A. (2021). Bifidobacterium animalis subsp. lactis BB-12 Protects against Antibiotic-Induced Functional and Compositional Changes in Human Fecal Microbiome. *Nutrients*, *13*(8). https://doi.org/10.3390/NU13082814

Minamiyama, Y., Takemura, S., Toyokuni, S., Nishino, Y., Yamasaki, K., Hai, S., Yamamoto, S., & Okada, S. (2002). Amelioration of cisplatin toxicity by a fermented grain food product. *BioFactors (Oxford, England)*, *16*(3–4), 105–115. https://doi.org/10.1002/BIOF.5520160306

Mohajeri, M. H., Brummer, R. J. M., Rastall, R. A., Weersma, R. K., Harmsen, H. J. M., Faas, M., & Eggersdorfer, M. (2018). The role of the microbiome for human health: from basic science to clinical applications. *European Journal of Nutrition*, *57*, 1–14. https://doi.org/10.1007/s00394-018-1703-4

Mohamed, W. A., & Schaalan, M. F. (2018). Antidiabetic efficacy of lactoferrin in type 2 diabetic pediatrics; Controlling impact on PPAR-γ, SIRT-1, and TLR4 downstream signaling pathway. *Diabetology and Metabolic Syndrome*, *10*(1), 1–12. https://doi.org/10.1186/s13098-018-0390-x

Mohammadi-Sartang, M., Bellissimo, N., Totosy de Zepetnek, J. O., Brett, N. R., Mazloomi, S. M., Fararouie, M., Bedeltavana, A., Famouri, M., & Mazloom, Z. (2018). The effect of daily fortified yogurt consumption on weight loss in adults with metabolic syndrome: A 10-week randomized controlled trial. *Nutrition, Metabolism, and*

Cardiovascular Diseases : NMCD, *28*(6), 565–574. https://doi.org/10.1016/J.NUMECD.2018.03.001

Monmai, C., Nam, J. H., Lim, J. H., Rod-in, W., Lee, T. H., & Park, W. J. (2021). Anti-inflammatory activities of the mixture of strawberry and rice powder as materials of fermented rice cake on RAW264.7 macrophage cells and mouse models. *Food Science and Biotechnology*, *30*(11), 1409–1416. https://doi.org/10.1007/s10068-021-00929-5

Moreno-Fernandez, J., Alférez, M. J. M., López-Aliaga, I., & Diaz-Castro, J. (2019). Protective effects of fermented goat milk on genomic stability, oxidative stress and inflammatory signalling in testis during anaemia recovery. *Scientific Reports*, *9*(1), 2232. https://doi.org/10.1038/s41598-018-37649-6

Moreno-Indias, I., Sánchez-Alcoholado, L., Pérez-Martínez, P., Andrés-Lacueva, C., Cardona, F., Tinahones, F., & Queipo-Ortuño, M. I. (2016). Red wine polyphenols modulate fecal microbiota and reduce markers of the metabolic syndrome in obese patients. *Food and Function*, *7*(4), 1775–1787. https://doi.org/10.1039/c5fo00886g

Moschen, A. R., Wieser, V., & Tilg, H. (2012). Dietary factors: Major regulators of the Gut's microbiota. In *Gut and Liver* (Vol. 6, Issue 4, pp. 411–416). https://doi.org/10.5009/gnl.2012.6.4.411

Nagino, T., Kaga, C., Kano, M., Masuoka, N., Anbe, M., Moriyama, K., Maruyama, K., Nakamura, S., Shida, K., & Miyazaki, K. (2018). Effects of fermented soymilk with Lactobacillus casei Shirota on skin condition and the gut microbiota: a randomised clinical pilot trial. *Beneficial Microbes*, *9*(2), 209–218. https://doi.org/10.3920/BM2017.0091

Nakamura, T., Fujiwara, N., Sugaya, T., Ueda, Y., & Koide, H. (2009). Effect of red wine on urinary protein, 8-hydroxydeoxyguanosine, and liver-type fatty acid-binding protein excretion in patients with diabetic nephropathy. *Metabolism: Clinical and Experimental*, *58*(8), 1185–1190. https://doi.org/10.1016/J.METABOL.2009.03.019

Nestel, P. J., Mellett, N., Pally, S., Wong, G., Barlow, C. K., Croft, K., Mori, T. A., & Meikle, P. J. (2013). Effects of low-fat or full-fat fermented and non-fermented dairy foods on selected cardiovascular biomarkers in overweight adults. *The British Journal of Nutrition*, *110*(12), 2242–2249. https://doi.org/10.1017/S0007114513001621

Nestel, P. J., & Mori, T. A. (2022). Dairy Foods: Is Its Cardiovascular Risk Profile Changing? *Current Atherosclerosis Reports*, *24*(1), 33–40. https://doi.org/10.1007/s11883-022-00984-1

Nielsen, E. S., Garnås, E., Jensen, K. J., Hansen, L. H., Olsen, P. S., Ritz, C., Krych, L., & Nielsen, D. S. (2018). Lacto-fermented sauerkraut improves symptoms in IBS patients independent of product pasteurisation - a pilot study. *Food & Function*, *9*(10), 5323–5335. https://doi.org/10.1039/C8FO00968F

Nikooyeh, B., Hollis, B. W., & Neyestani, T. R. (2021). The effect of daily intake of vitamin D-fortified yogurt drink, with and without added calcium, on serum adiponectin and sirtuins 1 and 6 in adult subjects with type 2 diabetes. *Nutrition & Diabetes*, *11*(1). https://doi.org/10.1038/S41387-021-00168-X

Noer, E. R., Dewi, L., & Kuo, C. H. (2021). Fermented soybean enhances post-meal response in appetite-regulating hormones among Indonesian girls with obesity. *Obesity Research & Clinical Practice*, *15*(4), 339–344. https://doi.org/10.1016/J.ORCP.2021.06.005

Oerlemans, M. M. P., Akkerman, R., Ferrari, M., Walvoort, M. T. C., & de Vos, P. (2021). Benefits of bacteria-derived exopolysaccharides on gastrointestinal microbiota, immunity and health. In *Journal of Functional Foods* (Vol. 76, p. 104289). Elsevier Ltd. https://doi.org/10.1016/j.jff.2020.104289

Oh, M. R., Park, S. H., Kim, S. Y., Back, H. I., Kim, M. G., Jeon, J. Y., Ha, K. C., Na, W.

T., Cha, Y. S., Park, B. H., Park, T. sun, & Chae, S. W. (2014). Postprandial glucose-lowering effects of fermented red ginseng in subjects with impaired fasting glucose or type 2 diabetes: a randomized, double-blind, placebo-controlled clinical trial. *BMC Complementary and Alternative Medicine*, *14*. https://doi.org/10.1186/1472-6882-14-237

Pan, R., Xu, T., Bai, J., Xia, S., Liu, Q., Li, J., Xiao, X., & Dong, Y. (2020). Effect of Lactobacillus plantarum fermented barley on plasma glycolipids and insulin sensitivity in subjects with metabolic syndrome. *Journal of Food Biochemistry*, *44*(11). https://doi.org/10.1111/JFBC.13471

Pápai, G., Torres-Maravilla, E., Chain, F., Varga-Visi, É., Antal, O., Naár, Z., Bermúdez-Humarán, L. G., Langella, P., & Martín, R. (2021). The Administration Matrix Modifies the Beneficial Properties of a Probiotic Mix of Bifidobacterium animalis subsp. lactis BB-12 and Lactobacillus acidophilus LA-5. *Probiotics and Antimicrobial Proteins*, *13*(2), 484–494. https://doi.org/10.1007/s12602-020-09702-2

Paparo, L., Bruno, C., Ferrucci, V., Punto, E., Viscardi, M., Fusco, G., Cerino, P., Romano, A., Zollo, M., & Berni Canani, R. (2021). Protective effects elicited by cow milk fermented with L. Paracasei CBAL74 against SARS-CoV-2 infection in human enterocytes. *Journal of Functional Foods*, *87*. https://doi.org/10.1016/j.jff.2021.104787

Park, C., Lee, H., Han, M. H., Jeong, J. W., Kim, S. O., Jeong, S. J., Lee, B. J., Kim, G. Y., Park, E. K., Jeon, Y. J., & Choi, Y. H. (2020). Cytoprotective effects of fermented oyster extracts against oxidative stress-induced dna damage and apoptosis through activation of the nrf2/ho-1 signaling pathway in mc3t3-e1 osteoblasts. *EXCLI Journal*, *19*, 1102–1119. https://doi.org/10.17179/excli2020-2376

Pothuraju, R., Sharma, R. K., Kavadi, P. K., Chagalamarri, J., Jangra, S., Bhakri, G., & De, S. (2016). Anti-obesity effect of milk fermented by Lactobacillus plantarum NCDC 625 alone and in combination with herbs on high fat diet fed C57BL/6J mice. *Beneficial Microbes*, *7*(3), 375–385. https://doi.org/10.3920/BM2015.0083

Poutanen, K., Flander, L., & Katina, K. (2009). Sourdough and cereal fermentation in a nutritional perspective. *Food Microbiology*, *26*(7), 693–699. https://doi.org/10.1016/j.fm.2009.07.011

Prasetyo, R. V., Surono, I., Soemyarso, N. A., Djojodimedjo, T., Rauf, S., Noer, M. S., & Sudarmo, S. M. (2020). Lactobacillus plantarum IS-10506 promotes renal tubular regeneration in pyelonephritic rats. *Beneficial Microbes*, *11*(1), 59–66. https://doi.org/10.3920/BM2019.0036

Pražnikar, Z. J., Kenig, S., Vardjan, T., Bizjak, M. Č., & Petelin, A. (2020a). Effects of kefir or milk supplementation on zonulin in overweight subjects. *Journal of Dairy Science*, *103*(5), 3961–3970. https://doi.org/10.3168/JDS.2019-17696

Pražnikar, Z. J., Kenig, S., Vardjan, T., Bizjak, M. Č., & Petelin, A. (2020b). Effects of kefir or milk supplementation on zonulin in overweight subjects. *Journal of Dairy Science*, *103*(5), 3961–3970. https://doi.org/10.3168/jds.2019-17696

Qian, Y., Zhang, J., Zhou, X., Yi, R., Mu, J., Long, X., Pan, Y., Zhao, X., & Liu, W. (2018). Lactobacillus plantarum CQPC11 isolated from Sichuan pickled cabbages antagonizes D-galactose-induced oxidation and aging in mice. *Molecules*, *23*(11), 3026. https://doi.org/10.3390/molecules23113026

Rai, A. K., Sanjukta, S., & Jeyaram, K. (2017). Production of angiotensin I converting enzyme inhibitory (ACE-I) peptides during milk fermentation and their role in reducing hypertension. *Critical Reviews in Food Science and Nutrition*, *57*(13), 2789–2800. https://doi.org/10.1080/10408398.2015.1068736

Razmpoosh, E., Zare, S., Fallahzadeh, H., Safi, S., & Nadjarzadeh, A. (2020). Effect of a low energy diet, containing a high protein, probiotic condensed yogurt, on biochemical

and anthropometric measurements among women with overweight/obesity: A randomised controlled trial. *Clinical Nutrition ESPEN*, *35*, 194–200. https://doi.org/10.1016/J.CLNESP.2019.10.001

Rezac, S., Kok, C. R., Heermann, M., & Hutkins, R. (2018). Fermented Foods as a Dietary Source of Live Organisms. *Frontiers in Microbiology*, *9*(AUG). https://doi.org/10.3389/FMICB.2018.01785

Rezazadeh, L., Gargari, B. P., Jafarabadi, M. A., & Alipour, B. (2019). Effects of probiotic yogurt on glycemic indexes and endothelial dysfunction markers in patients with metabolic syndrome. *Nutrition (Burbank, Los Angeles County, Calif.)*, *62*, 162–168. https://doi.org/10.1016/J.NUT.2018.12.011

Rice, B. H., Cifelli, C. J., Pikosky, M. A., & Miller, G. D. (2011). Dairy components and risk factors for cardiometabolic syndrome: Recent evidence and opportunities for future research. *Advances in Nutrition*, *2*(5), 396–407. https://doi.org/10.3945/an.111.000646

Rundblad, A., Holven, K. B., Øyri, L. K. L., Hansson, P., Ivan, I. H., Gjevestad, G. O., Thoresen, M., & Ulven, S. M. (2020). Intake of Fermented Dairy Products Induces a Less Pro-Inflammatory Postprandial Peripheral Blood Mononuclear Cell Gene Expression Response than Non-Fermented Dairy Products: A Randomized Controlled Cross-Over Trial. *Molecular Nutrition & Food Research*, *64*(21). https://doi.org/10.1002/MNFR.202000319

Salari, A., Ghodrat, S., Gheflati, A., Jarahi, L., Hashemi, M., & Afshari, A. (2021). Effect of kefir beverage consumption on glycemic control: A systematic review and meta-analysis of randomized controlled clinical trials. *Complementary Therapies in Clinical Practice*, *44*. https://doi.org/10.1016/J.CTCP.2021.101443

Salazar, N., Gueimonde, M., de los Reyes-Gavilán, C. G., & Ruas-Madiedo, P. (2016). Exopolysaccharides Produced by Lactic Acid Bacteria and Bifidobacteria as Fermentable Substrates by the Intestinal Microbiota. In *Critical Reviews in Food Science and Nutrition* (Vol. 56, Issue 9, pp. 1440–1453). Taylor and Francis Inc. https://doi.org/10.1080/10408398.2013.770728

Şanlier, N., Gökcen, B. B., & Sezgin, A. C. (2019). Health benefits of fermented foods. In *Critical Reviews in Food Science and Nutrition* (Vol. 59, Issue 3, pp. 506–527). Taylor and Francis Inc. https://doi.org/10.1080/10408398.2017.1383355

Santurino, C., López-Plaza, B., Fontecha, J., Calvo, M. V., Bermejo, L. M., Gómez-Andrés, D., & Gómez-Candela, C. (2020). Consumption of Goat Cheese Naturally Rich in Omega-3 and Conjugated Linoleic Acid Improves the Cardiovascular and Inflammatory Biomarkers of Overweight and Obese Subjects: A Randomized Controlled Trial. *Nutrients*, *12*(5). https://doi.org/10.3390/NU12051315

Schmidt, K. A., Cromer, G., Burhans, M. S., Kuzma, J. N., Hagman, D. K., Fernando, I., Murray, M., Utzschneider, K. M., Holte, S., Kraft, J., & Kratz, M. (2021). The impact of diets rich in low-fat or full-fat dairy on glucose tolerance and its determinants: A randomized controlled trial. *American Journal of Clinical Nutrition*, *113*(3), 534–547. https://doi.org/10.1093/ajcn/nqaa301

Schnorr, S. L., Candela, M., Rampelli, S., Centanni, M., Consolandi, C., Basaglia, G., Turroni, S., Biagi, E., Peano, C., Severgnini, M., Fiori, J., Gotti, R., De Bellis, G., Luiselli, D., Brigidi, P., Mabulla, A., Marlowe, F., Henry, A. G., & Crittenden, A. N. (2014). Gut microbiome of the Hadza hunter-gatherers. *Nature Communications*, *5*. https://doi.org/10.1038/NCOMMS4654

Senger, D. R., Li, D., Jaminet, S. C., & Cao, S. (2016). Activation of the Nrf2 cell defense pathway by ancient foods: Disease prevention by important molecules and microbes lost from the modern western diet. *PLoS ONE*, *11*(2). https://doi.org/10.1371/journal.pone.0148042

Seo, D. B., Jeong, H. W., Kim, Y. J., Kim, S., Kim, J., Lee, J. H., Joo, K., Choi, J. K., Shin, S. S., & Lee, S. J. (2017). Fermented green tea extract exhibits hypolipidaemic effects through the inhibition of pancreatic lipase and promotion of energy expenditure. *The British Journal of Nutrition*, *117*(2), 177–186. https://doi.org/10.1017/S0007114516004621

Sha, J., Song, J., Huang, Y., Zhang, Y., Wang, H., Zhang, Y., & Suo, H. (2022). Inhibitory effect and potential mechanism of lactobacillus plantarum YE4 against dipeptidyl peptidase-4. *Foods*, *11*(1). https://doi.org/10.3390/foods11010080

Shiels, P. G., McGuinness, D., Eriksson, M., Kooman, J. P., & Stenvinkel, P. (2017). The role of epigenetics in renal ageing. *Nature Reviews Nephrology*, *13*(8), 471–482. https://doi.org/10.1038/nrneph.2017.78

Shiels, P. G., Painer, J., Natterson-Horowitz, B., Johnson, R. J., Miranda, J. J., & Stenvinkel, P. (2021a). Manipulating the exposome to enable better ageing. *Biochemical Journal*, *478*(14), 2889–2898. https://doi.org/10.1042/BCJ20200958

Shiels, P. G., Painer, J., Natterson-Horowitz, B., Johnson, R. J., Miranda, J. J., & Stenvinkel, P. (2021b). Manipulating the exposome to enable better ageing. *Biochemical Journal*, *478*(14), 2889–2898. https://doi.org/10.1042/BCJ20200958

Sibbesson, E. (2022). Reclaiming the Rotten: Understanding Food Fermentation in the Neolithic and Beyond. *Environmental Archaeology*, *27*(1), 111–122. https://doi.org/10.1080/14614103.2018.1563374

Silva, F. M., Giatti, L., Diniz, M. de F. H. S., Brant, L. C. C., & Barreto, S. M. (2022). Dairy product consumption reduces cardiovascular mortality: results after 8 year follow-up of ELSA-Brasil. *European Journal of Nutrition*, *61*(2), 859–869. https://doi.org/10.1007/S00394-021-02686-X

Sirilun, S., Chaiyasut, C., Pattananandecha, T., Apichai, S., Sirithunyalug, J., Sirithunyalug, B., & Saenjum, C. (2022). Enhancement of the Colorectal Chemopreventive and Immunization Potential of Northern Thai Purple Rice Anthocyanin Using the Biotransformation by β-Glucosidase-Producing Lactobacillus. *Antioxidants*, *11*(2). https://doi.org/10.3390/antiox11020305

Slattery, C., Cotter, P. D., & O'Toole, P. W. (2019). Analysis of Health Benefits Conferred by Lactobacillus Species from Kefir. *Nutrients*, *11*(6). https://doi.org/10.3390/NU11061252

Snelson, M., Tan, S. M., Clarke, R. E., De Pasquale, C., Thallas-Bonke, V., Nguyen, T. V., Penfold, S. A., Harcourt, B. E., Sourris, K. C., Lindblom, R. S., Ziemann, M., Steer, D., El-Osta, A., Davies, M. J., Donnellan, L., Deo, P., Kellow, N. J., Cooper, M. E., Woodruff, T. M., … Coughlan, M. T. (2021). Processed foods drive intestinal barrier permeability and microvascular diseases. *Science Advances*, *7*(14). https://doi.org/10.1126/sciadv.abe4841

Sonnenburg, J. L., & Sonnenburg, E. D. (2019). Vulnerability of the industrialized microbiota. *Science*, *366*(6464). https://doi.org/10.1126/science.aaw9255

Stenvinkel, P., Meyer, C. J., Block, G. A., Chertow, G. M., & Shiels, P. G. (2020). Understanding the role of the cytoprotective transcription factor nuclear factor erythroid 2-related factor 2-lessons from evolution, the animal kingdom and rare progeroid syndromes. *Nephrology Dialysis Transplantation*, *35*(12), 2036–2045. https://doi.org/10.1093/NDT/GFZ120

Strachan, D. P. (1989). Hay fever, hygiene, and household size. *British Medical Journal*, *299*(6710), 1259–1260. https://doi.org/10.1136/bmj.299.6710.1259

Sun, S., Li, H., Chen, J., & Qian, Q. (2017). Lactic acid: No longer an inert and end-product of glycolysis. In *Physiology* (Vol. 32, Issue 6, pp. 453–463). American Physiological Society. https://doi.org/10.1152/physiol.00016.2017

Suo, H., Feng, X., Zhu, K., Wang, C., Zhao, X., & Kan, J. (2015). Shuidouchi (fermented soybean) fermented in different vessels attenuates HCl/ethanol-induced gastric mucosal injury. *Molecules*, *20*(11), 19748–19763. https://doi.org/10.3390/molecules201119654

Szkudelski, T., & Szkudelska, K. (2011). Anti-diabetic effects of resveratrol. *Annals of the New York Academy of Sciences*, *1215*(1), 34–39. https://doi.org/10.1111/j.1749-6632.2010.05844.x

T, J., N, K., T, M., M, K., L, N., & D, J. (2018). Light wine consumption is associated with a lower odd for cardiovascular disease in chronic kidney disease. *Nutrition, Metabolism, and Cardiovascular Diseases : NMCD*, *28*(11), 1133–1139. https://doi.org/10.1016/J.NUMECD.2018.06.018

T, T., A, G., T, S., S, H., N, S., S, S., & Y, A. (2020). Effects of 12-Week Ingestion of Yogurt Containing Lactobacillus plantarum OLL2712 on Glucose Metabolism and Chronic Inflammation in Prediabetic Adults: A Randomized Placebo-Controlled Trial. *Nutrients*, *12*(2). https://doi.org/10.3390/NU12020374

Takahashi, F., Hashimoto, Y., Kaji, A., Sakai, R., Miki, A., Okamura, T., Kitagawa, N., Okada, H., Nakanishi, N., Majima, S., Senmaru, T., Ushigome, E., Hamaguchi, M., Asano, M., Yamazaki, M., & Fukui, M. (2021). Habitual miso (Fermented soybean paste) consumption is associated with glycemic variability in patients with type 2 diabetes: A cross-sectional study. *Nutrients*, *13*(5). https://doi.org/10.3390/nu13051488

Tamang, J. P., & Lama, S. (2022). Probiotic properties of yeasts in traditional fermented foods and beverages. *Journal of Applied Microbiology*. https://doi.org/10.1111/jam.15467

Thorning, T. K., Raziani, F., Bendsen, N. T., Astrup, A., Tholstrup, T., & Raben, A. (2015). Diets with high-fat cheese, high-fat meat, or carbohydrate on cardiovascular risk markers in overweight postmenopausal women: a randomized crossover trial. *The American Journal of Clinical Nutrition*, *102*(3), 573–581. https://doi.org/10.3945/AJCN.115.109116

Tobita, K., & Meguro, R. (2022). Bacillus subtilis BN strain promotes Th1 response via Toll-like receptor 2 in polarized mouse M1 macrophage. *Journal of Food Biochemistry*, *46*(2). https://doi.org/10.1111/jfbc.14046

Tonolo, F., Moretto, L., Grinzato, A., Fiorese, F., Folda, A., Scalcon, V., Ferro, S., Arrigoni, G., Bellamio, M., Feller, E., Bindoli, A., Marin, O., & Rigobello, M. P. (2020). Fermented soy-derived bioactive peptides selected by a molecular docking approach show antioxidant properties involving the keap1/nrf2 pathway. *Antioxidants*, *9*(12), 1–21. https://doi.org/10.3390/antiox9121306

Tonucci, L. B., Olbrich dos Santos, K. M., Licursi de Oliveira, L., Rocha Ribeiro, S. M., & Duarte Martino, H. S. (2017). Clinical application of probiotics in type 2 diabetes mellitus: A randomized, double-blind, placebo-controlled study. *Clinical Nutrition*, *36*(1), 85–92. https://doi.org/10.1016/j.clnu.2015.11.011

Torres, S., Fabersani, E., Marquez, A., & Gauffin-Cano, P. (2019). Adipose tissue inflammation and metabolic syndrome. The proactive role of probiotics. *European Journal of Nutrition*, *58*(1), 27–43. https://doi.org/10.1007/s00394-018-1790-2

Toshimitsu, T., Gotou, A., Sashihara, T., Hachimura, S., Shioya, N., Suzuki, S., & Asami, Y. (2020). Effects of 12-week ingestion of yogurt containing lactobacillus plantarum OLL2712 on glucose metabolism and chronic inflammation in prediabetic adults: A randomized placebo-controlled trial. *Nutrients*, *12*(2). https://doi.org/10.3390/nu12020374

Turroni, S., Fiori, J., Rampelli, S., Schnorr, S. L., Consolandi, C., Barone, M., Biagi, E., Fanelli, F., Mezzullo, M., Crittenden, A. N., Henry, A. G., Brigidi, P., & Candela, M. (2016). Fecal metabolome of the Hadza hunter-gatherers: a host-microbiome

integrative view. *Scientific Reports*, *6*. https://doi.org/10.1038/SREP32826
Udenigwe, C. C., & Mohan, A. (2014). Mechanisms of food protein-derived antihypertensive peptides other than ACE inhibition. *Journal of Functional Foods*, *8*(1), 45–52. https://doi.org/10.1016/j.jff.2014.03.002
Usinger, L., Jensen, L. T., Flambard, B., Linneberg, A., & Ibsen, H. (2010). The antihypertensive effect of fermented milk in individuals with prehypertension or borderline hypertension. *Journal of Human Hypertension*, *24*(10), 678–683. https://doi.org/10.1038/jhh.2010.4
Voidarou, C., Antoniadou, M., Rozos, G., Tzora, A., Skoufos, I., Varzakas, T., Lagiou, A., & Bezirtzoglou, E. (2021). Fermentative foods: Microbiology, biochemistry, potential human health benefits and public health issues. *Foods*, *10*(1), 69. https://doi.org/10.3390/foods10010069
Wang, P., Feng, Z., Sang, X., Chen, W., Zhang, X., Xiao, J., Chen, Y., Chen, Q., Yang, M., & Su, J. (2021). Kombucha ameliorates LPS-induced sepsis in a mouse model. *Food and Function*, *12*(20), 10263–10280. https://doi.org/10.1039/d1fo01839f
Wang, R., Sun, J., Li, G., Zhang, M., Niu, T., Kang, X., Zhao, H., Chen, J., Sun, E., & Li, Y. (2021). Effect of Bifidobacterium animalis subsp. lactis MN-Gup on constipation and the composition of gut microbiota. *Beneficial Microbes*, *12*(1), 31–42. https://doi.org/10.3920/BM2020.0023
Wastyk, H. C., Fragiadakis, G. K., Perelman, D., Dahan, D., Merrill, B. D., Yu, F. B., Topf, M., Gonzalez, C. G., Van Treuren, W., Han, S., Robinson, J. L., Elias, J. E., Sonnenburg, E. D., Gardner, C. D., & Sonnenburg, J. L. (2021). Gut-microbiota-targeted diets modulate human immune status. *Cell*, *184*(16), 4137-4153.e14. https://doi.org/10.1016/j.cell.2021.06.019
Welman, A. D., & Maddox, I. S. (2003). Exopolysaccharides from lactic acid bacteria: Perspectives and challenges. In *Trends in Biotechnology* (Vol. 21, Issue 6, pp. 269–274). Elsevier Ltd. https://doi.org/10.1016/S0167-7799(03)00107-0
Wu, H., Liu, H. N., Liu, C. Q., Zhou, J. Z., Liu, X. L., & Zhang, H. Z. (2022). Hulless Black Barley as a Carrier of Probiotics and a Supplement Rich in Phenolics Targeting Against H2O2-Induced Oxidative Injuries in Human Hepatocarcinoma Cells. *Frontiers in Nutrition*, *8*. https://doi.org/10.3389/fnut.2021.790765
Wu, P. S., Ding, H. Y., Yen, J. H., Chen, S. F., Lee, K. H., & Wu, M. J. (2018). Anti-inflammatory Activity of 8-Hydroxydaidzein in LPS-Stimulated BV2 Microglial Cells via Activation of Nrf2-Antioxidant and Attenuation of Akt/NF-κB-Inflammatory Signaling Pathways, as Well As Inhibition of COX-2 Activity. *Journal of Agricultural and Food Chemistry*, *66*(23), 5790–5801. https://doi.org/10.1021/acs.jafc.8b00437
Xi, Y., Huang, Y., Li, Y., Yan, J., & Shi, Z. (2020). Fermented feed supplement relieves caecal microbiota dysbiosis and kidney injury caused by high-protein diet in the development of gosling gout. *Animals*, *10*(11), 1–18. https://doi.org/10.3390/ani10112139
Xia, T., Zhang, J., Yao, J., Zhang, B., Duan, W., Zhao, C., Du, P., Song, J., Zheng, Y., & Wang, M. (2018). Shanxi aged vinegar protects against alcohol-induced liver injury via activating NRF2-mediated antioxidant and inhibiting TLR4-induced inflammatory response. *Nutrients*, *10*(7), 805. https://doi.org/10.3390/nu10070805
Xiao, Y., Zhang, C., Zeng, X., & Yuan, Z. (2020). Microecological treatment of hyperuricemia using Lactobacillus from pickles. *BMC Microbiology*, *20*(1). https://doi.org/10.1186/s12866-020-01874-9
Yacoub, R., Kaji, D., Patel, S. N., Simoes, P. K., Busayavalasa, D., Nadkarni, G. N., He, J. C., Coca, S. G., & Uribarri, J. (2016). Association between probiotic and yogurt consumption and kidney disease: Insights from NHANES. *Nutrition Journal*, *15*(1).

https://doi.org/10.1186/s12937-016-0127-3
Yang, H. J., Kim, M. J., Hur, H. J., Lee, B. K., Kim, M.-S., & Park, S. (2022). Association Between Korean-Style Balanced Diet and Risk of Abdominal Obesity in Korean Adults: An Analysis Using KNHANES-VI (2013-2016). *Frontiers in Nutrition*, *8*. https://doi.org/10.3389/FNUT.2021.772347
Yanni, A. E., Kokkinos, A., Psychogiou, G., Binou, P., Kartsioti, K., Chatzigeorgiou, A., Konstantopoulos, P., Perrea, D., Tentolouris, N., & Karathanos, V. T. (2019). Daily consumption of fruit-flavored yoghurt enriched with vitamins B contributes to lower energy intake and body weight reduction, in type 2 diabetic patients: a randomized clinical trial. *Food & Function*, *10*(11), 7435–7443. https://doi.org/10.1039/C9FO01796H
Yao, K., Zeng, L., He, Q., Wang, W., Lei, J., & Zou, X. (2017). Effect of probiotics on glucose and lipid metabolism in type 2 diabetes mellitus: A meta-analysis of 12 randomized controlled trials. *Medical Science Monitor*, *23*, 3044–30453. https://doi.org/10.12659/MSM.902600
Yılmaz, İ., Enver Dolar, M., & Özpınar, H. (2019). Effect of administering kefir on the changes in fecal microbiota and symptoms of inflammatory bowel disease: A randomized controlled trial. *Turkish Journal of Gastroenterology*, *30*(3), 242–253. https://doi.org/10.5152/tjg.2018.18227
Yoo, J. H., Park, E. J., Kim, S. H., & Lee, H. J. (2020). Gastroprotective effects of fermented lotus root against ethanol/HCL-induced gastric mucosal acute toxicity in rats. *Nutrients*, *12*(3), 808. https://doi.org/10.3390/nu12030808
Yu, S., Liu, L., Bu, T., Zheng, J., Wang, W., Wu, J., & Liu, D. (2022). Purification and characterization of hypoglycemic peptides from traditional Chinese soy-fermented douchi . *Food & Function*, *13*(6), 3343–3352. https://doi.org/10.1039/d1fo03941e
Zareian, M., Oskoueian, E., Majdinasab, M., & Forghani, B. (2020). Production of GABA-enriched: Idli with ACE inhibitory and antioxidant properties using Aspergillus oryzae: The antihypertensive effects in spontaneously hypertensive rats. *Food and Function*, *11*(5), 4304–4313. https://doi.org/10.1039/c9fo02854d
Zarrati, M., Raji Lahiji, M., Salehi, E., Yazdani, B., Razmpoosh, E., Shokouhi Shoormasti, R., & Shidfar, F. (2019). Effects of Probiotic Yogurt on Serum Omentin-1, Adropin, and Nesfatin-1 Concentrations in Overweight and Obese Participants Under Low-Calorie Diet. *Probiotics and Antimicrobial Proteins*, *11*(4), 1202–1209. https://doi.org/10.1007/S12602-018-9470-3
Zeng, X., Jia, H., Zhang, X., Wang, X., Wang, Z., Gao, Z., Yuan, Y., & Yue, T. (2021). Supplementation of kefir ameliorates azoxymethane/dextran sulfate sodium induced colorectal cancer by modulating the gut microbiota. *Food and Function*, *12*(22), 11641–11655. https://doi.org/10.1039/d1fo01729b
Zhang, X., Chen, S., Zhang, M., Ren, F., Ren, Y., Li, Y., Liu, N., Zhang, Y., Zhang, Q., & Wang, R. (2021). Effects of fermented milk containing lacticaseibacillus paracasei strain shirota on constipation in patients with depression: A randomized, double-blind, placebo-controlled trial. *Nutrients*, *13*(7). https://doi.org/10.3390/nu13072238
Zhao, D., & Shah, N. P. (2016). Concomitant ingestion of lactic acid bacteria and black tea synergistically enhances flavonoid bioavailability and attenuates D-galactose-induced oxidative stress in mice via modulating glutathione antioxidant system. *Journal of Nutritional Biochemistry*, *38*, 116–124. https://doi.org/10.1016/j.jnutbio.2016.09.005
Zhou, F., Li, Y. L., Zhang, X., Wang, K. B., Huang, J. A., Liu, Z. H., & Zhu, M. Z. (2021). Polyphenols from Fu Brick Tea Reduce Obesity via Modulation of Gut Microbiota and Gut Microbiota-Related Intestinal Oxidative Stress and Barrier Function. *Journal of Agricultural and Food Chemistry*, *69*(48), 14530–14543.

https://doi.org/10.1021/ACS.JAFC.1C04553