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Dairy Probiotic Foods and Coronary Heart Disease: A Review on Mechanism of Action

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1. Introduction

Coronary heart disease (CHD) is one of the major causes of death in adults in the developed and developing countries which is referred to the condition in which the main coronary arteries supplying the heart are no longer able to supply sufficient blood and oxygen to the heart muscle (myocardium). The main cause of the reduced flow is an accumulation of plaques, mainly in the intima of arteries, a disease known as atherosclerosis (Akbarzadeh and Toufan, 2008). A number of risk factors known to affect an individual to CHD have been categorized such as hyperlipidaemia (high levels of lipids in the blood), hypertension (high blood pressure), obesity, cigarette smoking and lack of exercise. Probiotics as a live microbial food supplement beneficially affects the host by improving its intestinal microbial balance and is generally consumed as fermented milk products containing lactic acid bacteria such as bifidobacteria and/or lactobacilli. The supposed health benefits of probiotics include improved resistance to gastrointestinal infections, reduction in total cholesterol and TAG levels and stimulation of the immune system. A number of mechanisms have been proposed to explain their putative lipid-lowering capacity and these include a 'milk factor', which has been thought to inhibit HMG-CoA reductase and the assimilation of cholesterol by certain bacteria. The mechanism of action of probiotics on cholesterol reduction include physiological actions of the end products of fermentation SCFAs, cholesterol assimilation, deconjugation of bile acids and cholesterol binding to bacterial cell walls. It has been well documented that microbial bile acid metabolism is a peculiar probiotic effect involved in the therapeutic role of some bacteria. The deconjugation reaction is catalyzed by conjugated bile acid hydrolase enzyme, which is produced exclusively by bacteria. The mechanism of cholesterol binding to bacterial cell walls has also been suggested as a possible explanation for hypocholesterolaemic effects of probiotics. Probiotics have received attention for their beneficial effects on the gut microflora and links to their systemic

effects on the lowering of lipids known to be risk factors for CHD, notably cholesterol and TAG. The incorporation of probiotics into dairy products such as fermented milk products controlled nutrition studies need to be carried out to determine the beneficial effects of prebiotics, probiotics and synbiotics before substantial health claims can be made (Ranjbar et al., 2007a).

2. Probiotics

Probiotics are distinct as live microorganisms which, when administered in sufficient amounts present a health benefit on the host (FAO/WHO, 2002; Homayouni, 2008a; Homayouni, 2009). In recent years probiotic bacteria have increasingly been incorporated into dairy foods as dietary adjuncts. *Lactobacillus* and *Bifidobacterium* are the most common species of probiotic bacteria that were used in the production of fermented and non-fermented dairy products. Consumption of probiotic bacteria via dairy food products is an ideal way to re-establish the intestinal microflora balance (Homayouni, 2008a).

Probiotics have been shown to be effective against a number of disorders. Some mostly documented effects are relieving diarrhea, improving lactose intolerance and its immunomodulatory, anticarcinogenic, antidiabetic, hypocholesterolemic and hypotensive properties (Shah, 2007; Mai, and Draganov, 2009; Lye, et al., 2009). Probiotic bacteria, by competing with enteric pathogens for available nutrients and binding sites, reducing the pH of the gut, producing a variety of chemicals which inactivate viruses, enhancing specific and non-specific immune responses and increasing mucin production, can reduce incidence, severity and duration of diarrhea (Homayouni, et al., 2007; Allen, et al., 2010; Ejtahed, and Homayouni Rad, 2010). Alleviation of lactose intolerance symptoms by probiotic bacteria is attributed to their intracellular β-galactosidase content (Mustapha, et al., 1997). Studies have revealed that probiotic bacteria can induce many immunological changes and affect both Th1 and Th2 cytokine production and that these effects are strongly strain-specific (Lebeer, et al., 2010). Some major routes through which probiotic bacteria have been assumed to prevent cancer are: binding to mutagenic compounds thus decreasing their absorption, suppression of the growth of bacteria which convert procarcinogens to carcinogens, decreasing the activity of enzymes predictive of neoplasm including β-glucuronidase, nitroreductase and choloylglycine hydrolase as well as enhancing immune responses (Roos, and Katan, 2000). Inflammation plays a major role in both initiation and progression of diabetes (Duncan, et al., 2003; Pickup, and Frcpath, 2004). By reducing inflammatory responses, probiotics have been shown to correct insulin sensitivity and reduce development of diabetes mellitus. This anti-inflammatory effect has been proposed to be rooted in immunomodulatory properties of probiotic bacteria (Lye, et al., 2009). By reducing cholesterol absorption in the gut, incorporation of cholesterol into cell membranes, enzymatically deconjugation of bile salts and conversion of cholesterol to coprostanol, probiotics can reduce blood cholesterol (Lye, et al., 2009; Ooi, and Liong, 2010). Release of angiotensin converting enzyme (ACE) inhibitory peptides from the parent protein through proteolytic action explains how probiotics can exert antihypertensive effects (Lye, et al., 2009).

3. Dairy probiotic foods

Dairy probiotic foods are scientifically documented as having physiological benefits beyond those of basic nutritional values. Dairy products such as ice cream, cheese, yogurt, acidophilus-bifidus-milk, ayran, kefir, kumis, doogh containing probiotics and milk having omega-3, phytosterols, isoflavins, CLA, minerals, and vitamins have an outstanding position in the development of functional foods (Homayouni, et al., 2008b; Homayouni, et al., 2008c). Dairy beverages (both fermented and non-fermented) have long been considered as important vehicles for the delivery of probiotics. In fermentation process, lactic acid, acetic acid and citric acid are naturally produced which are commonly used organic acids to enhance organoleptic qualities as well as safety of many food products. Lactic acid bacteria are found to be more tolerant to acidity and organic acids than most of the pathogens and spoilage microorganisms (Homayouni, et al., 2008d).

4. Coronary heart disease (CHD)

Coronary heart disease (CHD) is one of the major causes of death in adults in the developed and developing countries which is referred to the condition in which the main coronary arteries supplying the heart are no longer able to supply sufficient blood and oxygen to the heart muscle (myocardium). The main cause of the reduced flow is an accumulation of plaques, mainly in the intima of arteries, a disease known as atherosclerosis (Akbarzadeh etal., 2003; Ranjbar et al., 2007b; Akbarzadeh etal., 2010; Ghaffari etal., 2010).

5. Main risk factors of coronary heart disease

CHD has assumed almost epidemic proportions in wealthy societies, whereas rheumatic heart disease is common in developing countries (Akbarzadeh etal., 2003; Akbarzadeh etal., 2008). Known risk factors of CHD can be classified into those that cannot be modified (being male increasing age, genetic traits including lipid metabolism abnormalities, body build, ethnic origin), those that can be changed (cigarette smoking, hyperlipidaemia, low levels of high density lipoprotein, obesity, hypertension, low physical activity, increased thrombosis, stress, alcohol consumption), those associated with disease states (diabetes and glucose intolerance) and those related to geographic distribution (climate and season, cold weather, soft drinking water) (Lovegrove and Jackson, 2003; Akbarzadeh etal., 2009a). It has been demonstrated that there is a strong and consistent relationship between total plasma cholesterol and CHD risk (Martin et al., 1986). Accumulation of LDL in the plasma leads to a deposition of cholesterol in the arterial wall, a process that involves oxidative modification of the LDL particles. The oxidized LDL is taken up by macrophages, which finally become foam cells and forms the basis of the early atherosclerotic plaque. It has been estimated that every 1% increase in LDL cholesterol level leads to a 2-3% increase in CHD risk (Gensini et al., 1998; Akbarzadeh etal., 2009b). HDL cholesterol levels are higher in women than in men. Factors that may lead to reduced HDL cholesterol levels include smoking, low physical activity and diabetes mellitus; whereas those that increase levels include moderate alcohol consumption (Assmann et al., 1998; Akbarzadeh etal., 2009c).

6. Probiotics and CHD: Mechanism of action

Diet is considered to control the risk of CHD through its effects on certain risk factors including blood lipids, blood pressure and probably also through thrombogenic mechanisms. New evidences suggest a protective role for dietary antioxidants such as vitamins E and C and carotenes, possibly through a mechanism that prevents the oxidation of LDL cholesterol particles (Lovegrove and Jackson, 2003). The diet is one of the adjustable risk factors associated with CHD risk which is recommends to reduce total fat (especially saturated fat), increasing Non-starch polysaccharides (NSP) intake and consumption of fruit and vegetables is advice that is expected to be associated with overall benefits on health.

As a result of low consumer compliance of low-fat diets, attempts have been made to identify other dietary components that can reduce blood cholesterol levels. These have included investigations into the possible hypocholesterolaemic properties of milk products, especially in a fermented form. 18% fall in plasma cholesterol after feeding 4-5 liters of fermented milk per day for three weeks (Mann, and Spoerry, 1974).

The mechanisms of action of probiotics on cholesterol reduction are physiological actions of the end products of fermentation SCFAs, cholesterol assimilation, deconjugation of bile acids and cholesterol binding to bacterial cell walls. The SCFAs that are produced by the bacterial anaerobic breakdown of carbohydrate are acetic, propionic and butyric. It has been well documented that microbial bile acid metabolism is a irregular probiotic effect involved in the therapeutic role of some bacteria. The deconjugation reaction is catalyzed by conjugated bile acid hydrolase enzyme, which is produced exclusively by bacteria. Deconjugation ability is widely found in many intestinal bacteria including genera Enterococcus, Peptostreptococcus, Bifidobacterium, Fusobacterium, Clostridium, Bacteroides and Lactobacillus (Hylemond, 1985). This reaction releases the amino acid moiety and the deconjugated bile acid, thereby reducing cholesterol reabsorption, by increasing faecal excretion of the deconjugated bile acids. Many in vitro studies have investigated the ability of various bacteria to deconjugate a variety of different bile acids. Grill et al. (1995) reported Bifidobacterium longum as the most efficient bacterium when tested against six different bile salts. Another study reported that Lactobacillus species had varying abilities to deconjugate glycocholate and taurocholate (Gilliland et al., 1985). Studies performed on in vitro responses are useful but in vivo studies in animals and humans are required to determine the full contribution of bile acid deconjugation to cholesterol reduction. Intervention studies on animals and ileostomy patients have shown that oral administration of certain bacterial species led to an increased excretion of free and secondary bile salts (De Smet, et al., 1998; Marteau, et al., 1995).

There is also some in vitro evidence to support the hypothesis that certain bacteria can assimilate (take up) cholesterol. It was reported that L. acidophilus and B. bifidum had the ability to assimilate cholesterol in in vitro studies, but only in the presence of bile and under anaerobic conditions (Gilliland, et al., 1985; Rasic, et al., 1992). However, despite these reports there is uncertainty whether the bacteria are assimilating cholesterol or whether the cholesterol is co-precipitating with the bile salts. Studies have been performed to address

this question. Klaver and Meer (1993) concluded that the removal of cholesterol from the growth medium in which L. acidophilus and a Bifidobacterium sp. were growing was not due to assimilation, but due to bacterial bile salt deconjugase activity. The same question was addressed by Tahri et al., (1995) with conflicting results, and they concluded that part of the removed cholesterol was found in the cell extracts and that cholesterol assimilation and bile acid deconjugase activity could occur simultaneously.

The mechanism of cholesterol binding to bacterial cell walls has also been suggested as a possible explanation for hypocholesterolaemic effects of probiotics. Hosona and Tono-oka (1995) reported Lactococcus lactis subsp. biovar had the highest binding capacity for cholesterol of bacteria tested in the study. It was speculated that the binding differences were due to chemical and structural properties of the cell walls, and that even killed cells may have the ability to bind cholesterol in the intestine. The mechanism of action of probiotics on cholesterol reduction could be one or all of the above mechanisms with the ability of different bacterial species to have varying effects on cholesterol lowering. However, more research is required to elucidate fully the effect and mechanism of probiotics and their possible hypocholesterolaemic action.

It has been demonstrated that microbial bile acid metabolism is a main effect in the therapeutic role of probiotic bacteria. The deconjugation reaction is catalysed by conjugated bile acid hydrolase enzyme, which is produced by Bifidobacterium and Lactobacillus. This reaction releases the amino acid and deconjugated bile acid, which is reducing cholesterol reabsorption, by increasing faecal elimination of the deconjugated bile acids.

7. Conclusions and future trends

Risk factors known to affect an individual to CHD have been categorized such as hyperlipidaemia, hypertension, obesity, cigarette smoking and lack of exercise. Probiotics may prevent coronary heart disease by cholesterol reduction and microbial bile acid metabolism. The mechanism of action of probiotics on cholesterol reduction include physiological actions of the end products of fermentation SCFAs, cholesterol assimilation, deconjugation of bile acids and cholesterol binding to bacterial cell walls. It has been demonstrated that microbial bile acid metabolism is a peculiar probiotic effect involved in the therapeutic role of some bacteria. Deconjugation reaction is catalyzed by conjugated bile acid hydrolase enzyme, which is produced exclusively by bacteria. The mechanism of cholesterol binding to bacterial cell walls has also been suggested as a possible explanation for hypocholesterolaemic effects of probiotics. Probiotics have beneficial effects on the gut microflora and links to their systemic effects on the lowering of lipids known to be risk factors for CHD, notably cholesterol and TAG. In recent years, several probiotic foods were produced industrially. These foods have received attention for their beneficial effects on the gut microflora and links to their systemic effects on the lowering of lipids known to be risk factors for CHD. For progress to be made, the consumers need to be educated about the various health benefits and how they will be able to use these products in their own diet without adverse consequences. Also to make these foods

attractive to the consumer, the products need to be priced in such a way that they are accessible to the general public.

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