VERSITA

Biologia **67**/1: 1—13, 2012
Section Cellular and Molecular Biology
DOI: 10.2478/s11756-011-0155-6

Review

# The role of probiotics and natural bioactive compounds in modulation of the common molecular pathways in pathogenesis of atherosclerosis and cancer

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**Abstract:** Atherosclerosis and cancer are ranked among the most serious health problems in human medicine. Various predictive and etiological factors, biomarkers and molecular pathways of disease development and progression common to atherosclerosis and cancer suggest that the two most common diseases in worldwide dimension are far more closely aligned than previously believed. It is hypothesized that atherosclerosis and cancer are variants of a similar disease process. Shared disease progression in atherosclerosis and cancer is the emergence of similar novel approaches to therapy. On previous knowledge, it may be hypothesized that not only common approaches to therapy but also preventive strategies could be efficacious in both diseases. The results of *in vitro* and *in vivo* animal experiments, clinical and epidemiological studies and also the results of our experiments using animal experimental models of atherosclerosis and carcinogenesis indicate that probiotics, prebiotics, plants and their extracts and poly-unsaturated fatty acids could be effectively used in prevention of both atherosclerosis and colorectal cancer and decrease the disease risk. Future research should answer the question whether probiotic microorganisms and natural bioactive substances could effectively influence the molecular mechanisms in pathogenesis of atherosclerosis and cancer.

**Key words:** probiotics; natural bioactive compounds; atherosclerosis; cancer.

**Abbreviations:** AA, arachidonic acid; ALA, $\alpha$-linolenic acid; CDK, cyclin-dependent kinase; CDKI, cyclin-dependent kinase inhibitor; COX, cyclooxygenase; DHA, docosahexaenoic acid; ECM, extracellular matrix; EGFR, epidermal growth factor receptor; ENG, endoglin; eNOS, endothelial NO synthase; EPA, eicosapentaenoic acid; GPx, glutathione peroxidase; GSH, glutathione; HDL, high-density lipoprotein; IL, interleukin; ILGF, insulin-like growth factor; LDL, low-density lipoprotein; MAPK, mitogen-activated protein kinase; MMP, matrix metalloproteinase; NEC, necrotizing enterocolitis; NF-$\kappa$B, nuclear factor kappa B; oxLDL, oxidized low-density lipoprotein; PDGF, platelet-derived growth factor; PG, prostaglandin; PPAR, peroxisome-proliferator-activated receptor; PUFA, poly-unsaturated fatty acid; ROS, reactive oxygen species; TGF-$\beta$, transforming growth factor-$\beta$; TIMPs, tissue inhibitors of metalloproteinases; TLR, toll-like receptor; TNF-$\alpha$, tumor necrosis factor-$\alpha$; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor; VLDL, very low-density lipoprotein.

## Introduction

In human medicine, chronic diseases represent the most serious health and economic problem. Cancer and coronary heart disease are the most important disorders that cause alarming mortality and morbidity in humans (Giovannini et al. 2007). The cardiovascular diseases are one of the major causes of mortality not only in Western but also in Eastern countries and together with cancer participate in more than 60% of death rate in highly-developed economic countries. Especially in economically developed countries they acquire the character of epidemics, and in mortality they replace infectious diseases (Hughes et al. 2004).

For many years atherosclerosis and cancer were considered to have a completely unrelated pathogenesis and disease progression pathway featuring separate therapeutic strategies. Various predictive and etiological factors, biomarkers and molecular pathways of disease development and progression common to atherosclerosis and cancer suggest that the two most common diseases in worldwide dimension are far more closely aligned than previously believed (Ross et al. 2001). It is hypothesized that atherosclerosis and cancer are variants of a similar disease process. This could lead to the development of common therapeutic strategies. The therapy of atherosclerosis and cancer is complicated and expensive. Synthetic therapeutics used for their therapy are shown to treat some health problems,

but at the same time they induce new ones. For these reasons in the worldwide scale the interest in using alternative and ecological methods of prevention and therapy using substances of biotechnological and natural origin has been increasing (Bengmark 1998; Cavallini et al. 2009). Within the frame of referenced components, probiotics, prebiotics, plants and their extracts and poly-unsaturated fatty acids (PUFA) could be effectively used to decrease chronic disease risk.

It may be hypothesized that not only common approaches to therapy but also preventive strategies could be efficacious in both diseases. The concept that probiotics and natural bioactive compounds could influence the common mechanisms in pathogenesis of both atherosclerosis and cancer and decrease the disease risk is the subject of the present review.

## Common etiological factors of atherosclerosis and cancer

It is hypothesized that atherosclerosis and cancer are variants of a similar disease process. Both diseases share common etiological factors: genetic predisposition, age, sex hormones, cigarette smoking, high dietary fat intake, toxins and mutagens. The consequences of action of above-mentioned etiological factors are cell cycle deregulation, oxidative stress, chronic inflammation, endothelial dysfunction, dysregulation of apoptosis and angiogenesis, DNA instability and impaired DNA repair.

Many epidemiological reports relative to hazard risk assessment evaluations, human genetic studies, experimental investigations, and published review articles have associated a wide variety of inherited genes, proteins, and disease conditions with the development of atherosclerosis. The concept of a genetic predisposition for cancer is now well established for a variety of malignant conditions. Sex hormones have been linked to the development of both diseases but the mechanisms by which the causative and protective effects are mediated are only partially understood. Cigarette smoking is a cause of both atherosclerosis and cancer and broadly supports the common pathway of development hypothesis for both diseases. High dietary fat intake increases diseases incidence. It is suggested that the mechanisms common to atherosclerosis and tumours involve endothelial dysfunction. The endothelial dysfunction leads to an increased production of cytokines, coagulation factors and adhesion molecules favouring progression of both atherosclerosis and cancer. These mechanisms can explain an important relationship between the two diseases: a higher incidence of thromboembolic events in cancer patients, similar laboratory findings and the effect of many drugs on the course of the two diseases (Morganti et al. 2002). Chronic inflammation is a disease mediator. DNA instability and impaired DNA repair have been associated with both atherosclerosis and cancer. Free radical attack upon DNA generates a multiplicity of DNA damage, including modified bases. Some of these modifications have considerable potential to damage the integrity of the genome. Oxidative stress is a major causative mechanism for both atherosclerosis and cancer. There is an evidence that oxidative DNA damage may play a causative role in atherosclerosis. While many details regarding the role of reactive oxygen species-induced DNA damage in the etiology of complex multifactorial diseases like cancer are yet to be discovered, evidence suggests that oxidants act at several stages in the malignant transformation of cells. However, the quantitative relationship between the measured DNA damage and the development of cancer is still lacking (Olinski et al. 2002). Cell proliferation, cell cycle deregulation, clonal cellular expansion and apoptosis are a shared feature and play significant roles in the development of both atherosclerosis and cancer (Ross et al. 2001). Apoptosis represents a protective mechanism against neoplastic transformation and development of tumours by eliminating genetically damaged cells or cells that may be inappropriately induced to proliferate by mitogenic and proliferative stimuli. On the other hand, dysregulated apoptosis of the arterial wall cells is involved in the occurrence of the complex sequence of events responsible for atherogenesis (Olinski et al. 2002).

Table 1. Common molecular pathways of disease progression in atherosclerosis and cancer.

| Common molecular pathways of disease progression in atherosclerosis and cancer |
|---|
| The TGF-$\beta$ signalling pathway |
| Cell adhesion molecules and the $\beta$-catenin pathway |
| The NF-$\kappa$B signalling pathway |
| Angiogenesis and angiogenesis inhibitors |
| Peptide growth factors including EGFR |
| Matrix digestion, proteases and tissue protease inhibitors |
| Cell cycle regulation |

## Some common molecular pathways in pathogenesis of atherosclerosis and cancer

In addition to the aforementioned biological markers and pathogenic factors common to atherosclerosis and cancer disease development, a number of additional genetic pathways have been implicated in the progression of both diseases (Table 1).

The transforming growth factor-$\beta$ (TGF-$\beta$) signal transduction pathway has been the subject of intense research in recent years because of its key role in the pathogenesis of several diseases, including arthritis, diabetes mellitus, inflammatory bowel disease, cancer and atherosclerosis (Blobe et al. 2000). TGF-$\beta$ regulates a range of functions, including cellular proliferation, differentiation, adhesion and apoptosis, production of extracellular matrix components and modulation of the immune system. The pleiotropic effects of TGF-$\beta$ take place through a complex signal transduction. The pathway involves binding TGF-$\beta$ to membrane bound receptor TGF-R-II. After binding to TGF-R-II, the com-

plex TGF-$\beta$/TGF-RII is presented to TGF-R-I. Binding of TGF-$\beta$ to the receptor complex activates the intracellular domain, which leads to the phosphorylation and activation of members of the Smad protein family and subsequent regulation of TGF-$\beta$-dependent gene expression (Redondo et al. 2007). The TGF-$\beta$ pathway has dual roles both positive and negative in development of atherosclerosis and cancer. In normal and premalignant cells, TGF-$\beta$ enforces homeostasis and suppresses tumour progression directly through cell-autonomous tumour-suppressive effects (cytostasis, differentiation, apoptosis) or indirectly through effects on the stroma (suppression of inflammation and stroma-derived mitogens). However, when cancer cells lose TGF-$\beta$ tumour-suppressive responses, they can use TGF-$\beta$ to their advantage to initiate immune evasion, growth factor production, differentiation into an invasive phenotype, and metastatic dissemination or to establish and expand metastatic colonies (Massague 2008). As the tumour progresses genetic and/or biochemical changes allow TGF-$\beta$ to stimulate tumour progression by its pleiotropic activities on both the cancer cells and on non-malignant stromal cell types of the tumour (Akhurst & Derynck 2001). Inhibition of TGF-$\beta$ signalling in animal models, either by the use of neutralizing antibodies or dominant negative receptors leads to accelerated atherosclerosis (Singh & Ramji 2006). In contrast to such a protective role, it is clear that upregulation of TGF-$\beta$ expression is mainly responsible for the excessive intimal fibrocellular proliferation and inward remodelling (restenosis) seen following angioplasty, stenting or atherectomy used to treat obstructive atherosclerotic lesions (Singh & Ramji 2006). In conclusion, TGF-$\beta$ seems to lose its protective role and even to acquire a pathogenic effect within the chronic evolution of cardiovascular disease and cancer (Redondo et al. 2007; Massague 2008).

Cell adhesion molecules, the Wnt-$\beta$-catenin signalling pathway, excess matrix digestion associated with matrix metalloproteases and clotting system disturbances represent other common molecular progression pathways shared by both diseases. Wnt proteins bind to the Frizzled receptors and LRP5/6 co-receptors, and through stabilizing the critical mediator $\beta$-catenin, initiate a complex signalling cascade that plays an important role in regulating cell proliferation and differentiation. $\beta$-Catenin-independent Wnt signalling is also involved in various biological functions, such as vertebral development, cell motility and adhesion and cancer invasiveness (Veeman et al. 2003). Colorectal and many other cancers are caused by hyperactivity of the Wnt/$\beta$-catenin signalling pathway that results in constitutive $\beta$-catenin-mediated transactivation of T cell factor dependent genes. The $\beta$-catenin signalling system mediated by the Wnt or wingles genes and proteins was recently associated with cell proliferation in vascular endothelium during neovascularization after myocardial infarction (Blankesteijn et al. 2000). Wnt/$\beta$-catenin signalling also inhibits adipogenic and enhances chondrogenic differentiation of pericytes (Kirton et al. 2007). The aberrant differentiation of pericytes along the adipogenic, chondrogenic, and osteogenic lineages may contribute to the development and progression of several vascular diseases, including atherosclerosis.

The transcription nuclear factor kappa B (NF-$\kappa$B) plays an important role in physiological processes, such as innate and adaptive immunity, inflammation and regulation of apoptosis (Niederberger & Geisslinger 2010). It is involved in the rapid response to various stimuli, such as viral and bacterial infections, oxidant stress and a number of cytokines. It is composed of homo- and hetero-dimers of different Rel-protein family members (p65, RelB, c-Rel, p52 and p50) that share a Rel homology domain that mediates dimerization, interaction with I-$\kappa$B proteins, nuclear translocation and DNA-binding. A crucial step in the NF-$\kappa$B activation cascade is the phosphorylation of I-$\kappa$B by different I-$\kappa$B kinases. The activation of these kinases can be induced by various pathways (Pahl 1999; Karin et al. 2004; Yamamoto & Gaynor 2004). Consequently, dysregulations in the NF-$\kappa$B activation cascade have been associated with the pathogenesis of several diseases, such as cancer, atherosclerosis and rheumatoid arthritis. The activation of NF-$\kappa$B by circulating cytokines has been linked to atherosclerosis and thrombosis and a number of NF-$\kappa$B-regulated proinflammatory proteins are relevant for initiation and progression of atherosclerosis (Monaco & Paleolog 2004). A number of human cancers including hematologic malignancies (e.g., multiple myeloma, mantle cell lymphoma, different forms of leukemia, etc.) as well as solid tumours (e.g., breast cancer, prostate cancer, melanoma, etc.) have been linked to constitutive NF-$\kappa$B activation, which leads to the transcription of genes responsible for cell proliferation, angiogenesis, metastasis or inhibition of apoptotic cell death (Basseres & Baldwin 2006; Dutta et al. 2006).

Angiogenesis plays a crucial role in both diseases development and progression. Numerous genes and gene products have been associated with proangiogenic and antiangiogenic effects. In atherosclerosis, the development of angiogenesis appears to have both beneficial and deleterious effects. Whereas increased angiogenesis may be a favourable sign in the healing of the ischemic tissues, such as myocardial infarctions and necrosis of the lower extremities, progressive angiogenesis in a primary atherosclerotic lesion has been considered to be a cause of plaque expansion, plaque vulnerability, and the risk of significant disease complications, such as plaque rupture and vascular thrombosis. Tumour angiogenesis is regarded as a negative prognostic variable for several malignancies (Ross et al. 2001). At the molecular level, common targets of therapeutic angiogenesis inhibitors and stimulators are the ligands and receptors of the vascular endothelial growth factor (VEGF) system, in which the ligand VEGF transduces pro-angiogenic signals through receptor tyrosine kinases, such as VEGF receptor 2 (VEGFR2), while the soluble receptor VEGFR1 is inhibitory to angiogenic signalling, partially through VEGF sequestration (Wu et al. 2010).

Matrix metalloproteinases (MMPs), zinc dependent proteolytic enzymes, cleave extracellular matrix (ECM, collagen, laminin, fibronectin, etc.) as well as non-matrix substrates (growth factors, cell surface receptors, etc.) (Yoon et al. 2003). In normal physiology, MMPs are involved in embryonic development, wound repair, ovulation, bone remodelling, macrophage and neutrophil function. MMPs also have important functions in pathologic conditions that are characterized by the excessive degradation of ECM, such as tumour metastasis, rheumatoid arthritis, atherosclerosis, periodontal disease, osteoarthritis and gastric ulcer (Westermarck & Kahari 1999). A number of cytokines and growth factors have been shown to induce or stimulate the synthesis of MMPs, including interleukin-1 (IL-1), platelet-derived growth factor (PDGF), and tumour necrosis factor-$\alpha$ (TNF-$\alpha$), whereas others, such as TGF-$\beta$, heparin, and corticosteroids, have an inhibitory effect (Dollery et al. 1995). MMPs have long been associated with cancer-cell invasion and metastasis. This provided the rationale for clinical trials of MMP inhibitors. The pathological effects of MMPs and tissue inhibitors of MMPs in cardiovascular disease processes involve vascular remodelling and atherosclerotic plaque instability (Visse & Nagase 2003). Part of the influence of MMPs and tissue inhibitors of metalloproteinases (TIMPs) on angiogenesis is mediated by their effects on pro-angiogenic molecules (members of the VEGF family) and anti-angiogenic molecules (angiostatin). Bergers et al. (2000) demonstrated that the switch from vascular quiescence to angiogenesis involved MMP-9, which was up-regulated in angiogenic islets and tumours, releasing VEGF-A from an extracellular reservoir. VEGF-A is well established as an inducer of angiogenesis (Yoon 2003).

Cyclooxygenase-2 (COX-2) is the rate-limiting enzyme in the synthesis of pro-inflammatory and angiogenic prostaglandins (PG) such as PGE2, which induces MMPs and VEGF. COX-2 is an inducible form of the enzyme and is barely detectable in most tissues under normal physiological conditions. COX-2, PGs, and TGF-$\beta$ are involved in vascular development and vascular pathology from vasculogenesis and angiogenesis, to atherosclerosis and cancer. Lack of the TGF-$\beta$ receptor component endoglin (ENG) prevents proper angiogenesis (Dickson et al. 1995). COX-2 and TGF-$\beta$ co-localize in atherosclerotic lesions and in carcinogen-induced colon carcinomas, suggesting coordinated expression. In the cancer, COX-2 induces new vessel formation via PGE2 that induces VEGF (Fosslien 2001).

In atherosclerosis and cancer, there are persistent periods of DNA synthesis within the respective lesions. Many of these lesions are caused by exogenous and endogenous factors that damage DNA via cellular stress, such as the uncontrolled production of oxygen radicals. The unregulated production of reactive oxygen species (ROS) has been linked to mutations and altered gene expression in many cell types (Klaunig & Kamendulis 2004). An example of the role of oxidative stress in both atherosclerosis and cancer lies in the p38 mitogen-activated protein kinase (MAPK) cascade. p38 MAPK is involved in cellular migration, growth, and apoptosis (Zarubin & Han 2005). Oxidative stress can induce p38 MAPK and lead to the activation of several signalling pathways detrimental to vascular cells and to other cell types (Lim et al. 2004).

Adiponectin might be the important signal protein from the adipocyte to the vascular wall in the pathogenesis of atherosclerosis. Adiponectin inhibits several processes which play a role in atherogenesis like smooth muscle cell proliferation and foam cell formation. Adiponectin is positively related to high-density lipoprotein (HDL) levels and inversely related to several obesity-associated cancers. Adiponectin inhibits carcinogenesis directly via stimulation of apoptosis and indirectly via inhibition of insulin-like growth factors (ILGF) and ILGF-1 and the inhibition of angiogenesis. Measuring plasma adiponectin levels may be worthwhile in the future for detecting subjects with an increased risk for the development of cancer and atherosclerosis. Mechanisms to increase plasma levels of adiponectin and its action via two adiponectin receptors Adipo R1 and Adipo R2 may lead to new therapeutic interventions. Stimulation of these receptors is followed by activation of intracellular signalling molecules like AMP kinase and peroxisome-proliferator activated receptor $\alpha$ (PPAR$\alpha$) (Jazet & Meinders 2007).

A major common pathway of progression for both atherosclerotic plaques and malignant neoplasms centres on cell proliferation with increasing DNA synthesis and shortened cell cycles. Cell cycle progression is a tightly controlled series of events that are positively regulated by cyclin-dependent kinases (CDKs) and their cyclin-regulatory subunits (Sherr 1996), and negatively regulated by CDK inhibitors (CDKIs) and tumour suppressor genes (Grana & Reddy 1995). At the centre of cellular proliferation is the cell division cycle, the process by which a cell grows, replicates its DNA and then divides to give two daughter cells. This process is divided into four sequential phases (Garrett 2001). Cell proliferation regulatory pathways including genes involved in the G1S checkpoint (p53, pRb, p15, p16, and cyclins A, D, E, and cdk 2,4) have been associated with plaque progression, stenosis and restenosis after angioplasty as well as in cancer progression. Alterations in cell adhesion molecules (integrins, cadherin-catenins) have been linked to plaque formation and thrombosis as well as to tumour invasion and metastasis. Altered expression of proteases associated with thrombolysis has been implicated in atherosclerotic plaque expansion and hemorrhage and in the invasion and metastasis of malignancy. Ligand-growth factor receptor interactions (tyrosine kinases) have been associated with early atherosclerotic lesions as well as cancer development and spread (Ross et al. 2001).

Shared disease progression in atherosclerosis and cancer is the emergence of similar novel approaches to therapy. Therapeutic approaches common to both diseases include: (i) reducing oxidative stress by eliminating cigarette smoking, reducing dietary fat intake and

administering antioxidant therapeutics; (ii) using anti-inflammatory agents to reduce chemokine, cytokine, and growth factor cell signalling; (iii) employing antiproliferative drugs targeting growth factor receptors to reduce cell proliferation; (iv) reducing excess matrix digestion caused by excessive metalloprotease stromal digestion; (v) reducing NF-$\kappa$B signalling with proteasome inhibitors; (vi) restoring cell cycle regulation; and (vii) antiangiogenesis strategies designed to delay atherosclerotic plaque expansion and cancer invasion and metastasis (Ross et al. 2001; Ramos & Partridge 2005; Hull & Kant 2010).

On previous knowledge, it may be hypothesized that not only common approaches to therapy but also preventive strategies could be efficacious in both diseases. Nowadays, medical research is focused on finding new strategies in prevention of chronic diseases, such as atherosclerosis and cancer. Probiotics and substances of natural origin can represent such a preventive approach. Although their exact mechanisms of action are not completely known, there is a lot of evidence confirming their effects on the aforementioned common molecular pathways of atherosclerosis and cancer.

## The modulatory effect of probiotics and natural bioactive compounds on the molecular pathways in disease development and progression of both cancer and atherosclerosis

Current knowledge indicates that probiotics, prebiotics, plants and their extracts and PUFA may modulate the common mechanisms in pathogenesis of both atherosclerosis and cancer and decrease the disease risk.

### Probiotics

Identification of components of the microbiota and elucidation of the molecular mechanisms of their action in inducing pathological changes or exerting beneficial, disease-protective activities could aid in our ability to influence the composition of the microbiota and to find bacterial strains and components (e.g., probiotics and prebiotics), whose administration may aid in disease prevention and treatment. Just as homeostasis of our body systems is the product of many complex, redundant mechanisms, multigenic disease development is also dependent on both missing and over-activated pathways. The goal to find a common factor in the disease pathogenesis is difficult, genetic and pathophysiological data are incomplete, and the individual variability is enormous. Examination of the role of the microbiota in human illnesses using animal models of human diseases reared in defined (gnotobiotic) conditions could allow insight into the unusual complexity of the mechanisms involved in the initiation and maintenance of chronic diseases. Although the most important findings in this fascinating field are still to come, it is clear that our bacterial companions affect our fates more than previously assumed (Tlaskalová-Hogenová et al. 2011).

According to Fuller (1992) probiotics are biopreparations containing living cells or metabolites of stabilised autochthonous microorganisms that optimise the colonisation and composition of gut microflora in both animals and humans, and have a stimulatory effect on digestive processes and the immunity of the host. Food and Agriculture Organization and World Health Organization (2001) defined probiotics as "Live microorganisms which when administered in adequate amounts confer a health benefit on the host". From the viewpoint of the practical use of probiotics, it is of particular importance that probiotics have both local and general biomedical effects, an inhibitory effect against pathogens, an optimising effects on digestive processes, an immunostimulative effect, anti-tumour and cholesterol-reducing activities (Bomba et al. 2006; Rafter et al. 2007).

In recent years, there have been many studies using animal models which have clearly demonstrated a protective effect of dietary supplements of lactic acid bacteria against colon tumour development (Hirayama & Rafter 2000; Wollowski et al. 2001). The dosage of the probiotic directly resulted in suppressed development of aberrant crypt (Brady et al. 2000). A slight, non-significant effect of probiotics in reducing azoxymetane-induced malignant tumours was also observed in rats (Femia et al. 2002). Dietary supplementation with a strain of *Lactobacillus acidophilus* significantly suppressed the total number of colon cancer cells in rats in a dose-dependent manner (De Santis et al. 2000) and application of *Lactobacillus* GG reduced the incidence and number of tumours in animals artificially induced with colon cancer (Goldin et al. 1996). The application of probiotic microorganisms (*Lactobacillus plantarum*) significantly decreased the activity of $\beta$-glucuronidase ($p < 0.001$) and the faecal bile acids concentration ($p < 0.01$; $p < 0.001$) in the colon content and significantly increased serum TNF$\alpha$ level ($p < 0.001$) in comparison to the control rats. The results of a previous study indicate that probiotic microorganisms could exert a preventive effect on chemically induced colon carcinogenesis in rats. The application of *Lactobacillus plantarum* in combination with bioactive compounds was more effective in comparison to the administration of probiotic alone (Bertková et al. 2010).

The studies conducted on volunteers confirmed the protective importance of probiotics only indirectly through the decreasing of excretal faeces mutagens (Lindbeck et al. 1992), activity of bacterial enzymes inducing the conversion of pro-carcinogens to carcinogens (Benno & Mitsuoha 1992) and by stimulation of immunity (Ling-Amster et al. 1994; Ferenčík et al. 1999). Intervention studies have shown a shift of intermediate markers of colorectal cancer risk in human subjects from a high- to low-risk pattern after ingestion of fermented milks or probiotics (Saikali et al. 2004). The intervention with probiotic yoghurt, which included the strains of *Lactobacillus acidophilus* 145 and *Bifidobacterium longum* 913, significantly lowered faecal water genotoxicity compared

with standard yoghurt (Oberreuther-Moschner et al. 2004).

The precise mechanisms by which lactic acid bacteria may inhibit colon cancer are presently unknown. However, mechanisms may include: (i) alteration of the metabolic activities of intestinal microflora; (ii) alteration of physico-chemical conditions in the colon; (iii) binding and degrading potential carcinogens; (iv) modulation of the intestinal microflora incriminated in producing putative carcinogens and promoters (e.g., bile acid-metabolising bacteria); (v) production of antitumourigenic or antimutagenic compounds; and (vi) enhancing the host's immune response and effects on physiology of the host (Rafter 2002).

It is suggested that a preventive effect of probiotic bacteria on the cancer process is based mainly on its antagonism against other intestinal bacteria. The probiotics in such a way suppress the growth of bacteria, which convert pro-carcinogens into carcinogens. Besides that, the lactic acid bacteria have a lower activity of enzymes metabolizing xenobiotics as enterobacteria, clostridia, bacteroides and other commensal bacteria and beneficial modulation of the intestinal microflora could decrease the colorectal cancer risk (Limdi et al. 2006; Rafter et al. 2007).

Also an immuno-modulatory effect of lactic acid bacteria could significantly contribute to its anticarcinogenic activity. These effects are believed to be mediated through activating macrophages, increasing levels of cytokines (IL-6, TNF$\alpha$, interferon $\gamma$), which constrain cancer development, increasing natural killer cell activity and/or increasing levels of immunoglobulins (Raitano & Korc 1993; Takeuchi et al. 2001; Ouwehand et al. 2002; Commane et al. 2005; Parvez et al. 2006).

Probiotics have been shown to amplify the gut mucosal barrier functions, in increasing the expression of intestinal mucins, reversing increased intestinal permeability and dampening inflammation in the gut. The mechanisms here may involve the anti-inflammatory mediators generated in the interactions of the gut mucosal barrier with the intraluminal bacteria (Isolauri et al. 2008).

For the past 20 years, the focuses of public health strategies for reducing the risk of cardiovascular disease have been aimed at lowering cholesterol levels. However, recent findings have highlighted not only cholesterol but also triacylglycerol as a lipid risk factor for cardiovascular disease. Among the beneficial effects attributed to probiotics and probiotic-containing food products, the reduction of blood cholesterol is of particular interest. This effect can be produced by lactic acid bacteria, such as lactobacilli, bifidobacteria and enterococci. The results of experiments in cholesterol-fed rabbits indicated that probiotic microorganism *Enterobacterium faecium* CRL 183 could be used to improve the lipid profile as an alternative or an adjuvant for drug therapy. The cholesterol-fed rabbits that received the suspension of *E. faecium* showed an increase of 46.3% in HDL cholesterol and significantly lower concentration of triglycerides ($p < 0.05$) compared to cholesterol-fed rabbits without any treatments (Cavallini et al. 2009). Insignificant differences were observed in the concentration of total cholesterol and triacylglycerols in rats fed with a high-fat diet administered with *Lactobacillus plantarum*, while the combination of this probiotic strain with bioactive compounds (inulin enriched with oligofructose, plant extract of *Aesculus hippocastanum*, *Lini oleum virginale*) significantly decreased ($p < 0.001$) the serum concentration of total cholesterol and triacylglycerols (Koprovičová et al. 2010).

Probiotics in the form of fermented milk products have been shown to have cholesterol-lowering properties, whereas non-digestible fermentable prebiotics have been shown to reduce triacylglycerol levels in animal studies. However, in human studies, there have been inconsistent findings within respect to changes in lipid levels with both probiotics and prebiotics although on the whole there have been favourable outcomes (Jackson & Lovegrove 2004; Lovegrove & Jackson 2004). It is hypothesized that probiotics may influence the blood cholesterol level by the inhibition of cholesterol synthesis, or decreases its level directly by assimilation (Zacconi et al. 1992).

Despite a lot of knowledge obtained, the mode of action of probiotics has not been explained yet. From the viewpoint of chronic diseases prevention, it is of great importance to detect whether probiotics could influence the common molecular pathways in cancer and atherosclerosis pathogenesis.

Administration of *Lactobacillus plantarum* was associated with a complex genetic response in the jejunal Peyer's patches. The microarray data revealed that, among approximately 14,000 genes, 420 were expressed in *Lactobacillus plantarum* administration group at two-fold or higher levels compared to the control group. These included genes involved in immune response, and cell differentiation, cell-cell signalling, cell adhesion, signal transcription, and transduction (Chang et al. 2009).

It was shown that lactobacilli may modulate human cellular pathways (Van Baarlen et al. 2010). In the mucosa of the proximal small intestine of healthy volunteers, probiotic strains from the species *Lactobacillus acidophilus*, *Lactobacillus casei* and *Lactobacillus rhamnosus* each induced differential gene-regulatory networks and pathways in the human mucosa (including NF-$\kappa$B cascade activation, apoptosis and angiogenesis). Consumption of different probiotic lactobacilli led to markedly different gene expression *in vivo* human mucosa, corroborating the notion that specific probiotics strains induce specific responses in humans. Comprehensive analyses revealed that transcriptional networks induced by probiotic intervention regulate major basal mucosal processes and uncovered remarkable similarity to response profiles obtained for specific bioactive molecules and drugs. The large person-to-person variation in response transcriptomes helps to explain why probiotic supplementation may lead to measurable effects in some persons but not in others. Authors anticipate that responsiveness to probiotics is not only

Table 2. Summary of the effects of probiotics and biological active substances on common cellular and molecular pathways of disease progression in atherosclerosis and cancer.

| Probiotics and biological active substances | Molecular mechanism | References |
|---|---|---|
| Probiotics | | |
| Lactic acid bacteria | Production of cytokines | Takeuchi et al. (2001) |
| *Lactobacillus acidophilus* | NF-$\kappa$B cascade activation | Van Baarlen et al. (2010) |
| *Lactobacillus casei* | Apoptosis induction | Takagi et al. (2001) |
| *Lactobacillus plantarum* | Reduction of oxidative stress | Sun et al. (2005); Parvez et al. (2006); Isolauri et al. (2008) |
| Prebiotic | | |
| Oligofructose | Reduction of oxidative stress | Busserolles et al. (2003) |
| Synbiotic | | |
| Oligofructose-enriched inulin + *Lactobacillus rhamnosus* GG and *Bifidobacterium lactis* Bb | Decrease colonic cell proliferation | Femia et al. (2002) |
| Plant extracts | | |
| Polyphenols | Protection of LDL against oxidation | Moon et al. (2006) |
| Flavonoids | Apoptosis induction | Catapano (1997) |
| Phytoestrogens | Inhibition of cell proliferation | Mojžišová & Mojžiš (2008) |
| Organosulphur compounds | Angiogenesis inhibition | Higdon & Frei (2003) |
| | The modulation of nuclear factor NF-$\kappa$B | Gong et al. (2003) |
| | The prevention of endothelial dysfunction | Cavallini et al. (2009) |
| | Reducing the expression of adhesion molecules; modulation effects on pro-inflammatory cytokines; inhibition of platelet aggregation | Giovannini et al. (2007) |
| Poly-unsaturated fatty acids | | |
| $\omega$-3 PUFA | Inhibition of cell proliferation | Olsen & Lien (2008) |
| | Anti-inflammatory effects; angiogenesis inhibition; metastasis inhibition; reduction of oxidative stress | Dupertuis et al. (2007) |

determined by characteristic of the consumed bacterial strain but also by genetic background, resident microflora, diet and lifestyle. It was shown that both NF-$\kappa$B and p38 MAPK signalling pathways play important roles in the augmentation of innate immunity by the probiotic *L. casei* (Kim et al. 2006).

It was demonstrated *in vivo* that peptidoglycan from a lactobacillus species was able to dose-dependently reduce the growth of CT26 colon cancer cells in BALB/c mice via an increased level of apoptosis (Sun et al. 2005). Interestingly, peptidoglycan had no effect on tumour cell apoptosis *in vitro*, implying that the *in vivo* anti-tumourigenic effect may have been mediated by the immune response. Oral administration of *Bifidobacterium bifidum* activates toll-like receptor-2 (TLR-2) in the intestinal epithelium. *B. bifidum* increases expression of COX-2, which leads to higher production of PGE2 in the ileum and protects against intestinal apoptosis associated with necrotizing enterocolitis (NEC). This study indicates the ability of *B. bifidum* to down-regulate apoptosis in the rat NEC model and in intestinal epithelial cell lines by a COX-2–dependent matter and suggests a molecular mechanism by which this probiotic reduces mucosal injury and preserves intestinal integrity (Khailova et al. 2010). Table 2 shows the effects of probiotics and biological active substances on common cellular and molecular pathways of disease progression in atherosclerosis and cancer.

The results of *in vivo* animal experiments using animal experimental models of atherosclerosis and carcinogenesis and clinical studies indicate that probiotics could influence the common molecular pathways of both cancer and atherosclerosis pathogenesis. From that point of view, we suggest new definition of probiotics as follows: "Probiotics are live microorganisms which modulate the specific function of organism by activation of specific molecular pathways".

## Prebiotics

A prebiotic is a non-digestible food ingredient that beneficially affects the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon (Gibson & Roberfroid 1995). Some oligosaccharides comply with all the criteria for prebiotics. It has been demonstrated that dietary oligofructose, a short-chain fructo-oligosaccharides, and other fructans such as inulin, reduce the number of aberrant crypt foci, purported preneoplastic lesions in the colon of rats and mice (Reddy et al. 1997; Femia et al. 2002). The application of inulin type fructans decreased the intestinal activity of bacterial enzymes involved in the conversion of pre-carcinogens to carcinogens and bile acids concentration in rats (Hijová et al. 2009). Evidence suggests that synbiotics (combinations of probiotics and prebiotics) are more effective than are either probiotics or prebiotics alone (Rowland et al. 1998). It was shown that the symbiotic intervention (oligofructose-enriched inulin + *Lactobacillus rhamnosus* GG and *Bifidobacterium lactis* Bb 12) can

favourably alter several colorectal cancer biomarkers in human (Rafter et al. 2007).

The mechanisms by which prebiotics act in cancer development are less clear. It can be suggested that they may act through a combination of mechanisms including molecular mechanisms in cancer development. Application of prebiotics can beneficially affect the colon microflora (Gibson & Roberfroid 1995) and in this manner can decrease the colorectal cancer risk. Administration of prebiotics increases short-chain fatty acids production, decreases proliferative activity and the expression of some enzymes involved in the pathogenesis of colon cancer (Femia et al. 2002; Liong 2008). Butyrate and propionate inhibit growth of colon tumour cells and histone deacetylases. Butyrate also causes apoptosis, reduces metastasis in colon cell lines, and protects from genotoxic carcinogens. The synbiotic intervention resulted in significant alterations in the composition of the colonic bacterial ecosystem, which presumably have consequences for the metabolic activity of this organ. The results also provided indirect evidence that some of the consequences of the synbiotic intervention might be decreased exposure of the epithelium to cytotoxic and genotoxic agents, decreased colonic cell proliferation, and improved mucosa structure.

Several findings have pointed out the possibilities of using oligosaccharides in prevention of cardiovascular diseases. Studies in animals and human subjects have proven hypolipidaemic effects of inulin supplemented to the diet (Beylot 2005). The effects of different inulin-type fructan fractions on atherosclerotic plaque formation in male apo E-deficient mice have been studied. The apo E-deficient mice fed long-chain inulin or an oligofructose-enriched inulin had about 35% and 25% less atherosclerotic lesion area compared with the control group, respectively. Feeding long-chain inulin significantly reduced plasma cholesterol concentrations, and the three inulin-type fructans reduced triacylglycerol concentrations compared with the control group. Both the long-chain inulin and an oligofructose-enriched inulin significantly lowered hepatic cholesterol concentrations compared with the control diet. Hepatic triacylglycerol concentrations were significantly lower in all three groups fed the fructan-supplemented diets in comparison with the control group. The study demonstrates that long-chain inulin in the diet reduces the development of atherosclerotic plaque. The inhibition of atherosclerotic plaque formation is more potent in the presence of long-chain inulin, either alone or in combination with oligofructose (an oligofructose-enriched inulin) (Rault-Nania et al. 2006).

Based on the present results, it is hypothesized that inulin acts mainly by modulating lipid metabolism. Inulin-type fructans with different degrees of polymerization, long-chain inulin and oligofructose (short chain) have other effects including molecular mechanisms that might contribute to the anti-atherogenic action. It was shown that oligofructose is protective against the pro-oxidative effects of fructose-rich diets in rats (Busserolles et al. 2003). In addition, end-products of dietary fibre fermentation, such as short-chain fatty acids, can modulate the expression of multiple genes involved in the process of atherosclerosis (Ranganna et al. 2000). Based on these data it can be hypothesized that the addition of inulin-type fructans to diets may reduce the atherosclerosis process, similar to the anti-atherosclerotic effect described for some dietary fibres (Wu et al. 2003). Future studies will determine the contribution of the different mechanisms to the anti-atherogenic action of inulin including molecular pathways in atherosclerosis pathogenesis.

***Plants and their extracts***

Numerous plant bioactive compounds appear to have beneficial health effects. The epidemiologic studies evaluating associations between intake of a variety of plant-based foods indicate a protective effect, both on cardiovascular disease and certain cancers. Many bioactive compounds have been discovered. These compounds vary widely in chemical structure and function and are grouped accordingly. Current interest is focused on beneficial health effects of dietary polyphenols, because these compounds have many biological activities including antioxidative (Moon et al. 2006), cardioprotective (Zern & Fernandez 2005) and anticancer effects (Ren et al. 2003). It seems that plant bioactive compounds can influence different molecular pathways in atherosclerosis and cancer development.

Free radicals play an important role in pathogenesis of many chronic diseases. Many plants possess the antioxidant properties (Catapano 1997) what makes it possible to use them in cardiovascular disease and cancer prevention (Al-Sereiti et al. 1999). Polyphenols are considered to be major constituents of plants, fruits and vegetables and responsible for many of their positive health effects (Bingham 2006). Phenolic compounds, including their subcategory, flavonoids, are present in all plants and have been studied extensively in cereals, legumes, nuts, olive oil, vegetables, fruits, tea, and red wine. Many phenolic compounds have antioxidant properties, and some studies have demonstrated favourable effects on thrombosis and tumourigenesis and promotion. Epidemiological and *in vivo* studies in humans have shown an inverse association between the consumption of polyphenols, or polyphenol-rich food, and the risk of cardiovascular diseases, suggesting protective effects of phenolic compounds. In particular, epidemiologic studies suggest a protective effect of fruit and vegetables against ischemic heart disease (Law & Morris 1998; Peters et al. 2001).

Various phytoestrogens are present in soy, but also in flaxseed oil, whole grains, fruits, and vegetables. They have antioxidant properties, and some studies demonstrated favourable effects on other cardiovascular risk factors, and in animal and cell culture models of cancer. However, because phytoestrogens act both as partial estrogen agonists and antagonists, their effects on cancer are likely complex. Hydroxytyrosol, one of many phenolics in olives and olive oil, is a potent antioxidant. Resveratrol, found in nuts and red wine, has an-

tioxidant, antithrombotic, and anti-inflammatory properties, and inhibits carcinogenesis. Lycopene, a potent antioxidant carotenoid in tomatoes and other fruits, is thought to protect against prostate and other cancers, and inhibits tumour cell growth in animals. Organosulphur compounds in garlic and onions, isothiocyanates in cruciferous vegetables, and monoterpenes in citrus fruits, cherries, and herbs have anticarcinogenic actions in experimental models, as well as cardioprotective effects (Kris-Etherton et al. 2002). In addition to antioxidant properties, polyphenols show a number of interesting activities in animal models and within *in vitro* systems. These effects include scavenging free radicals, nitric oxide regulation, apoptosis induction, inhibition of cell proliferation and angiogenesis and phytoestrogenic activity (Higdon & Frei 2003).

Polyphenols can affect the overall process of carcinogenesis by several mechanisms. First of all, exogenous polyphenols supplied with the diet, contribute to counteract oxidative stress occurrence and thus could contribute to the prevention of cancer onset and development. In fact they can modulate oxidative stress in cancer cells, thereby affecting signal transduction, activation of redox-sensitive transcription factors and expression of specific genes that influence cell proliferation and apoptosis. In addition, a growing body of evidence indicates that polyphenols can directly interact with specific steps and/or proteins responsible for the regulation of apoptotic process, such as the release of cytochrome c with subsequent activation of caspases-9 and caspases-3, the increase of caspases-8 and t-Bid levels, the down-regulation of Bcl-2 and Bcl-XL expression, the enhanced expression of Bax and Bak and the modulation of NF-$\kappa$B (Gong et al. 2003; Giovannini et al. 2007; Mojžišová & Mojžiš 2008).

Several mechanisms by which polyphenols may reduce risk for cardiovascular diseases have been proposed. They affect plasma lipids and lipoproteins reducing plasma cholesterol and triglycerides. They also exert a protective effect on platelet function and haemostasis inhibiting platelet aggregation. Furthermore they control blood pressure and vascular reactivity promoting nitric oxide-induced endothelial relaxation. In conclusion, they may opposite to the growth of atherosclerotic plaque by reducing the expression of adhesion molecules, exerting anti-inflammatory action and counteracting the macrophage-mediated oxidation of low-density lipoproteins (LDLs). In particular, there is substantial evidence that polyphenols can exert their protective effects by blocking early events which lead to atherosclerosis such as LDL peroxidation and oxidized LDL (oxLDL)-induced apoptosis. Several phenolic compounds, e.g., those contained in green tea, red wine, extra virgin olive oil and liquorice root, have been demonstrated *in vitro* to inhibit macrophage cell-mediated oxidation of LDL and increase endogenous antioxidant defences. However, while many studies have pointed out the anti-atherogenic effects exerted by polyphenols in protecting the vascular wall from oxidation, inflammation, platelet aggregation and thrombus formation, few data are available for their anti-apoptotic activity, which can play an important role in preventing the onset and progression of atherosclerosis. There is *in vitro* evidence that polyphenols exert further protective effects against apoptosis mediated by oxLDL and hydrogen peroxide in different cell systems, by affecting several proteins and signalling factors. It has been demonstrated that polyphenols can affect apoptosis by modulating the level of expression of anti-apoptotic (Bcl-2, Bcl-xL) or pro-apoptotic (Bax, Bid, Bak) proteins. On the other hand, some polyphenols are able to inhibit the release of cytocrome c from mitochondria in endothelial cells by increasing endothelial NO synthase (eNOS) expression via MAPK inhibitor-sensitive pathway (Tinhofer et al. 2001; Martin et al. 2003; Nam et al. 2003; Curin & Andriantsitohaina 2005). Some phenolic compounds have been shown to counteract the oxLDL-induced cytotoxicity and apoptosis in murine macrophage J774A.1 cells by strengthening the endogenous antioxidant cell defences. This effect seems to be related more to the capability in inducing gene expression for glutathione (GSH)-related antioxidant enzymes, such as glutathione peroxidase (GPx) and glutathione reductase, than to the antioxidant power of the compounds (Masella et al. 2004).

Flavonoids are the most important class of polyphenols in plants that have numerous biological effects. Data from laboratory studies, epidemiological investigations, and human clinical trials indicate that there is a relationship between flavonoids and risk of chronic diseases including cardiovascular diseases and cancer. They are serious candidates in explanation of the protective effects of vegetables and fruits against both cancer and cardiovascular diseases (Mojžišová & Mojžiš 2008). There is an increasing evidence that flavonoids have cardio-protective effects. The antioxidant effects are supposed to participate in the favourable effect of flavonoids to a great extent, thereby they become an important element in the defence of the organism against the effect of free radicals (Hussain et al. 2003). Flavonoids can influence the effect of bioreactive forms of oxygen on different levels: (i) flavonoids as effective suppressor of free radicals inhibit lipid peroxidation; (ii) they have chelatation effects since they produce complexes with metals that in free form could create bioreactive forms of oxygen in higher rate; (iii) flavonoids inhibit enzymes of arachidonic acid cascade and thus decrease the production of bioreactive forms of oxygen; and (iv) flavonoids cooperate with antioxidative vitamins (A, E, $\beta$-carotene), i.e. they increase their effectiveness and decrease their degradation (Mojžiš & Mojžišová 2001). It was shown that soy and soy isoflavones may protect against cardiovascular diseases through their modulation effects on pro-inflammatory cytokines, cell adhesion proteins and NO formation, improve the serum lipid profile, protect the LDL against oxidation, inhibit the platelet aggregation and improve the vascular reactivity contributing to the prevention of endothelial dysfunction known to play a central role in the pathogenesis of cardiovascular diseases. Soy isoflavones

reduced by 19.5% the total cholesterol and non-HDL cholesterol (after 30 days) and tended also to reduce the atherosclerotic lesions (effect was not significant) in cholesterol-fed rabbits compared to cholesterol-fed rabbits without any treatments (Cavallini et al. 2009).

***Poly-unsaturated fatty acids***

PUFAs and their derivatives, eicosanoids, are biologically active substances of lipidic character. They act as local hormones which control important processes in an organism (Lamacka & Sajbidor 1995). Omega-3 fatty acids are polyunsaturated, with various numbers of double bonds. The ones that are nutritionally important have 18, 20 or 22 carbon atoms and three to six double bonds. In $\omega$-6 fatty acids, the first double bond is located at the sixth carbon from the end of the chain. Many studies have shown that $\omega$-3 fatty acids are essential (Olsen & Lien 2008). The effects of these two groups of PUFA on lipid metabolism and the immune system are different. The $\omega$-3 PUFA exhibit both anti-inflammatory and anti-proliferative influences on cells of the immune system. Contrary to that, $\omega$-6 PUFA, through arachidonic acid, have pro-inflammatory and immunoregulative effects (Calder 1998). Omega-3 PUFA positively affect the metabolism of fatty acids and synthesis of PGs. An increased supply of $\omega$-3 PUFA to germ-free piglets decreased the level of triacylglycerols and cholesterol in blood plasma of experimental animals and increased concentrations of $\alpha$-linolenic acid (ALA), eicosapentaenoic (EPA) and docosahexaenoic (DHA) acids ($\omega$-3 PUFA) and in parallel decreased the level of arachidonic acid (AA) ($\omega$-6 PUFA). Comparable results were obtained in conventional piglets (Kašteľ et al. 1999, 2007; Bomba et al. 2003). The mechanism of action of $\omega$-3 PUFA on plasma lipids has not been explained sufficiently. It has been assumed that $\omega$-3 PUFA decrease either the synthesis rate of apoprotein B (Nestel 1986) or the production of very low-density lipoproteins (VLDL) (Harris et al. 1984). EPA and other $\omega$-3 PUFA displace AA from membrane phospholipids and thus affect the metabolism of lipids. This fact was described in some species of mammals (cats, rodents, rats and some higher species) including humans (Fritsche et al. 1993; Das 2002).

In the last 50 years, many experiments and clinical studies focused on the influence of diet with high content of $\omega$-3 PUFA on occurrence of tumours have been carried out. The results of these studies are contradictory. Fatty acid composition of dietary fat plays a vital role in colon tumour development in animal models. Fats containing $\omega$-6 PUFA (e.g., corn oil) enhanced and $\omega$-3 PUFA (e.g., flaxseed oil) reduced chemically induced colon tumour development in rats. Dietary flaxseed is high in lignans content. Lignans are phytoestrogens, good sources of dietary fibre, proteins, antioxidants, and other nutritional elements also showing to prevent colon cancer development in experimental animals and humans (Bommareddy et al. 2006; Theodoratou et al. 2007). It was shown that *Lini oleum virginale* significantly decreased the activity of bacterial enzymes in intestine and bile acids concentrations in serum during N,N-dimethylhydrazine-induced carcinogenesis in rats (Hijová et al. 2009).

Some authors have recorded positive effect of $\omega$-3 PUFA in the food in the prevention of tumour diseases. $\omega$-3 PUFA may protect against the development of certain types of cancer. Fish and fish-oil consumption has been shown to protect against the later promotional stages of colorectal carcinogenesis. In rodents fed with long-chain $\omega$-3 PUFA, both initial and promotional stages of colon carcinogenesis decreased. $\omega$-3 PUFA have also been shown to inhibit initiation, growth and metastasis of various malignant cells, including lines with breast, prostate and white blood cells (Olsen & Lien 2008). It was suggested that $\omega$-3 PUFA may play an important role not only in cancer prevention, but also in cancer therapy. They may act synergistically with radio/chemo-therapy to kill tumour cells by increasing oxidative stress, while reducing angiogenesis, inflammation and metastasis induction (Dupertuis et al. 2007). Others did not confirmed these results, but on the other hand even higher occurrence of tumour diseases at excessive intake of $\omega$-3 PUFA were suggested.

Omega-3 fatty acids can be provided by eating fat fish, functional foods with marine $\omega$-3, or fish oil supplements. Many studies have shown that 1–2 meals of fish per week are associated with a 50% decrease in risk of developing coronary heart diseases (Olsen & Lien 2008). A review of 97 clinical trials noted that $\omega$-3 PUFA gave lower risk ratios than statins did. Studies of individual heart cells showed that fatty acids blocked excessive sodium and calcium currents in the heart, which could otherwise cause dangerous, unpredictable changes in its rhythm (Studer et al. 2005). Consuming oily fish twice per week may also help prevent sudden death due to myocardial infarction by preventing cardiac arrhythmia (Leaf et al. 2003). Long-chain $\omega$-3 fatty acids may also prevent restenosis after trans-luminal coronary angioplasty and significantly decrease the all-cause mortality in myocardial infarction survivors (Olsen & Lien 2008).

## Conclusion

Current knowledge suggests that atherosclerosis and carcinogenesis shared a lot of common features including predisposing and etiological factors and molecular pathways in pathogenesis. Future research is needed to elucidate the precise common mechanisms in diseases development and progression, both atherosclerosis and cancer. It may lead to development of common strategies for prevention as well as for therapy of both diseases. Current knowledge shows that probiotics and natural bioactive compounds could effectively modulate the common cellular and molecular mechanisms in disease development and progression. Future research should be aimed at the enhancement of the effectiveness of cancer and atherosclerosis prevention using substances of natural and biotechnological origin. It will be important to search for ways to improve the efficacy of probiotic microorganisms and natural bioactive

compounds by their adequate combination in order to maximise their preventive effect and decreasing the disease risk.

**Acknowledgements**

This work was partially supported by the Agency of the Slovak Ministry of Education for the Structural Funds of the EU, under project ITMS: 26220220104 (60%) and by the project of Scientific Grant Agency of the Ministry of Education of Slovak Republic and the Academy of Sciences VEGA 1/0372/10 "Modulation of the gastrointestinal ecosystem and metabolic status using probiotic microorganisms and bioactive substances in the chronic diseases prevention" (40%).

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Received July 29, 2011
Accepted November 5, 2011