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Protective effect of lactofermented red beetroot juice against aberrant crypt foci formation, genotoxicity of fecal water and oxidative stress induced by 2-amino-1-methyl-6-phenylimidazo[4,5-*b*] pyridine in rats model

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ABSTRACT

The aim of the study was to investigate the effects of beetroot juice fermented by *Lactobacillus brevis* 0944 and *Lactobacillus paracasei* 0920 (FBJ) on carcinogen induction of aberrant crypt foci (ACF) in rat colon. 2-Amino-1-methyl-6-phenylimidazo[4,5-*b*] pyridine (PhIP) was used as carcinogen, which was administrated intragastrically at a dose of 10 μg/day, every day of the experiment. Additionally, we investigated the cytotoxicity and genotoxicity of fecal water from experimental animals in the Caco-2 cell line, evaluated by MTT test and the comet assay, respectively, as well as by the count of bacteria adhered to colon epithelium assessed by fluorescence *in situ* hybridization. Oxidative stress in rats was expressed by measuring serum antioxidant status and the level of malondialdehyde in the kidneys and liver. The experimental rats were divided into four groups based on diet type: basal diet, basal diet supplemented with FBJ, basal diet and PhIP treatment, and basal diet supplemented with FBJ and PhIP treatment. FBJ significantly reduced the number of ACF in PhIP-treated rats (from 59 ± 18 to 26 ± 4). Moreover, the number of extensive aberrations (more than 4 crypts in a focus) decreased from 52 ± 18 to 18 ± 4. Fecal water obtained from rats fed with a PhIP-containing diet induced pronounced cytotoxic and genotoxic effects in Caco-2 cells, but FBJ supplementation of the diet abolished these effects. In groups fed dietary PhP and FBJ the latter was found to increase the antioxidant status of serum from 40% to 66% depending on the fraction. Reduced concentration of malondialdehyde was found only in the kidneys of rats fed with PhIP and FBJ. FBJ present in the diet of rats causes a reduction of MDA in the kidneys from 118.7 nmol/g tissue to 100 nmol/g tissue. The presence of FBJ in the diet of rats significantly increased the count of bacteria, including *Lactobacillus/Enterococcus* and *Bacteroides–Prevotella* group adhered to colonic epithelium. In conclusion, supplementation

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of the diet with lactofermented beetroot juice may provide protection against precancerous aberrant crypt formation and reduce the cytotoxic and genotoxic effects of fecal water and improve the oxidative status of the organism.

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1. Introduction

A diet rich in animal protein encourages the development of gastrointestinal cancers, in particular the large intestine. One of the reasons of this phenomenon may be the presence of heterocyclic amines (HCAs) in food. U.S. Department of Health and Human Services report from 2005 qualifies as HCA compounds with mutagenic activity and carcinogenic. These compounds are present in small amounts in raw meat, but their concentration increases with thermal treatment (frying, grilling, baking, cooking) (Puangsombat et al., 2011). Of the 19 heterocyclic amines identified, 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine (PhIP) is the most abundant heterocyclic amine produced during the cooking of beef, pork and chicken (Sinha et al., 1995; Vanhaecke et al., 2008). The highest levels of PhIP can be found in grilled or fried meats. In very well-done flame-grilled chicken can be found at levels up to 400 ng/g (Sinha et al., 1995; Vanhaecke et al., 2008). The studies of human PhIP metabolism mainly focused on the activation and detoxification of HCAs by mammalian enzymes. PhIP must first be metabolized *via* Phase I and Phase II enzymes to exert its mutagenic and carcinogenic effect (Vanhaecke et al., 2008). PhIP is enzymatically activated to genotoxic metabolites *via* a two-step process that involves cytochrome P450-dependent monooxygenase (CYP) followed by acetylation or sulfonation (Turesky, 2002; Platt et al., 2010). In addition to these activating enzymes, UDP-glucuronosyltranferase (UGT) and glutathione S-transferase (GST) are two phase-II enzymes able to reduce the genotoxicity of HCA by catalyzing the trapping of their reactive metabolites (Alexander et al., 1991; Stillwell et al., 1999; Platt et al., 2010). The diet rich in vegetables and fruits is a dietary factor in relation to the prevention of gastrointestinal cancer. The phytochemicals contained in vegetables and fruits are able to inhibit the genotoxic action of food-borne carcinogens, *e.g.* HCAs (Kapiszewska, 2006). Red beetroots rank among attractive and worldwide consumed vegetables. They are characterized by high content of betacyanins (red pigments such as betalains: betanine, isobetanine, neobetanine, betanidine, isobetanidine) imparting antioxidant activity. The strongest antioxidants among them are betanine and betanidine. Their intake by humans and animals, even at low concentrations, retards processes of oxidation of lipid cell membranes and prevents redox reactions of "free iron". Participation in these reactions causes degradation of betanidine while the structure of betanine is maintained and it can be further absorbed (Kanner et al., 2001). The anticarcinogenic effect of betacyanins results from lowering the frequency of reactions between carcinogens and cellular DNA. They may bind carcinogens and thereby reduce their transfer through cell membranes into cells. This in turn decreases the intensity of reactions catalyzed by enzymes such as monooxygenases and hydrases (Kapadia et al., 2003). Apart from betalains red beetroots contain also other biologically active compounds such as vitamin C, which also has antioxidant properties, and folic acid, protecting nucleic acids from aberrations of genes responsible for predisposition to certain types of cancer, *e.g.* colorectal cancer or cancers of female reproductive system. Folic acid is also essential for the development and reproduction of cells. The principal bioactive components if red beetroots are betacyanins, which are unstable during thermal processing and storage. To prevent their degradation and maintain biological activity, red beetroots, their juice or pulp should be subjected to lactic acid fermentation by selected strains of *Lactobacills* (Czyżowska et al., 2006). Fermented red beetroot juice maintains its biological and antimutagenic activity during the storage under refrigerated conditions for 30 days (Klewicka and Czyżowska, 2011). Another advantage of fermented juice is the presence of probiotic bacteria of genus *Lactobacillus*, which are characterized by the ability to modulate the intestinal microbiota and their metabolic activity expressed as the fermentation profile, it means the short-chain fatty acid profiles. Furthermore, the modulation of metabolic activity of the intestinal microbiota by probiotic bacteria brings about changes in activities of enzymes responsible for transformations of numerous procarcinogenic compounds to carcinogenic ones (Klewicka et al., 2009). The intestinal microbiota is an important element that plays a key role in the formation and prevention of colorectal cancer. Key physiological functions that might be related to cancer risk include control of epithelial cell proliferation and differentiation, production of essential nutrients and/or bioactive food components, prevention overgrowth of pathogenic organisms and stimulation of intestinal immunity (Tappenden and Deutsch, 2007; O'Keefe, 2008; Davis and Milner, 2009).

The simultaneous presence of biologically active compounds originating from the plant source (red beetroot) and probiotic bacteria in one product enables creation of novel functional foods preventing the development of cancers and degenerative diseases.

In vivo and *in vitro* studies on properties of fermented red beetroot juice in terms of detoxification of toxic compounds and protection from the development of colorectal cancer are necessary to evaluate its potential in treatment of gastrointestinal tract diseases. Presented work aimed at determination of protective properties of the fermented beetroot juice preventing formation of aberrant crypt foci induced by PhIP in the intestine of experimental animals. Both the genotoxicity and cytotoxicity of the intestinal environment (fecal water) and the composition of microflora adhered to colon epithelium of experimental animals were estimated. Also the antioxidant status of blood serum and organs involved in detoxification of xenobiotics such as liver and kidneys was evaluated.

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