Food and Chemical Toxicology 100 (2017) 103–114

Contents lists available at ScienceDirect

Food and Chemical Toxicology

journal homepage: www.elsevier.com/locate/foodchemtox

Cilostazol and enzymatically modified isoquercitrin attenuate experimental colitis and colon cancer in mice by inhibiting cell proliferation and inflammation

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ARTICLE INFO

Article history:
Received 19 July 2016
Received in revised form
4 December 2016
Accepted 14 December 2016
Available online 15 December 2016

Keywords:
Cilostazol
Enzymatically modified isoquercitrin
Reactive oxygen species
Colorectal cancer
Murine azoxymethane/dextran sodium sulphate-induced colorectal carcinoma model

ABSTRACT

We previously reported the anti-inflammatory effects of cilostazol, a selective inhibitor of phosphodiesterase 3, and two antioxidants, enzymatically modified isoquercitrin and α-lipoic acid in a dextran sodium sulphate-induced colitis mouse model. We further examined the chemopreventive effects of these substances in a murine azoxymethane/dextran sodium sulphate -induced colorectal carcinoma model and compared the effects with those of the well-known anticancer natural plant pigment, anthocyanin. In addition, the effects on cell proliferation activity were evaluated in colon cancer cell lines and mucosal epithelial cells in a model of acute dextran sodium sulphate-induced colitis. Cilostazol and enzymatically modified isoquercitrin improved the outcome of azoxymethane/dextran sodium sulphate-induced colorectal cancer along with anthocyanin though inhibiting inflammation and cell proliferation, but the effect of α-lipoic acid was minimal. Inhibition of cell proliferation by cilostazol was confirmed *in vitro*. In the acute dextran sodium sulphate-induced colitis model, cilostazol and enzymatically modified isoquercitrin prevented the decrease in epithelial proliferative cells. These results indicate that cilostazol and enzymatically modified isoquercitrin first exhibited an anti-dextran sodium sulphate effect at the initial stage of colitis and then showed antitumour effects throughout subsequent inflammation-related cancer developmental stages.

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1. Introduction

The two major clinically defined forms of inflammatory bowel disease (IBD), Crohn's disease (CD) and ulcerative colitis (UC) are chronic remittent or progressive inflammatory conditions that may affect the entire gastrointestinal tract and the colonic mucosa, respectively (Kaser et al., 2010). Epidemiological data indicate that more than 25% of all cancers are related to chronic infection and other types of unresolved inflammation (Hussain and Harris, 2007). Accumulating evidence supports the hypothesis that chronic inflammation is an important risk factor for the development of cancer (Wu et al., 2014). This is because activated inflammatory

Abbreviations: AC, anthocyanin; ACF, aberrant crypt foci; ALA, α-lipoic acid; AOM, azoxymethane; BrdU, 5-bromo-2′-deoxyuridine; CAC, colitis-associated colorectal cancer; CD, Crohn's disease; cAMP, cyclic adenosine monophosphate; CZ, cilostazol; DSS, dextran sodium sulphate; EMIQ, enzymatically-modified isoquercitrin; H&E, haematoxylin and eosin; Iba1, ionized calcium-binding adapter molecule 1; IBD, inflammatory bowel disease; MDF, mucin-depleted foci; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; Nox1, nicotinamide adenine dinucleotide phosphate oxidase 1; PDE, phosphodiesterase; ROS, reactive oxygen species; Tcf, T-cell factor/lymphoid enhancer factor; UC, ulcerative colitis.

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http://dx.doi.org/10.1016/j.fct.2016.12.018
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cells (1) serve as sources of reactive oxygen species (ROS), which are capable of inducing DNA damage and genomic instability, and (2) activate signalling pathways that deregulate the cell cycle in mucosal epithelial cells (Fernandes et al., 2015; Grivennikov et al., 2010). Thus, ROS play an important part in the multiple stages of initiation, promotion, and progression of colitis-associated colorectal cancer (CAC) (Hussain and Harris, 2007; Meier and Sturm, 2011; Wang et al., 2016), which has a unique feature of "inflammation-dysplasia-carcinoma" (Itzkowitz and Yio, 2004).

Animal models of IBD and CAC have been widely used for identifying candidate chemopreventive agents against these inflammation-based disorders. We recently found that cilostazol (CZ), enzymatically modified isoquercitrin (EMIQ), and α-lipoic acid (ALA) attenuated mucosal inflammation in an IBD model of dextran sodium sulphate (DSS)-induced colitis in mice (Kangawa et al., 2014); however, the effects of these substances have not been examined in animal models for CAC best to our knowledge. CZ is a phosphodiesterase (PDE) 3 enzyme inhibitor, which has anti-aggregation, anti-proliferative, anti-inflammatory, and vasodilatatory effects (Ari et al., 2015). Unlike other type-3 PDE inhibitors, CZ has been shown to increase cyclic adenosine monophosphate (cAMP) levels and prevent cardiac mitochondrial dysfunction by attenuating cardiac mitochondrial swelling, ROS production, and mitochondrial membrane potential changes in cardiac mitochondria under oxidative stress (Chattipakorn et al., 2014; Kodama-Takahashi et al., 2003; Watanabe et al., 2003). EMIQ is a quercetin glycoside mixture, consisting of isoquercitrin and its glucosylated derivatives with one or more additional linear glucose moieties produced from rutin by an enzymatic modification (Akiyama et al., 2000). It is an effective antioxidant (Nishimura et al., 2010; Yokohira et al., 2008) and has been noted to have antitumour effects on the liver (Fujii et al., 2013a; Hara et al., 2014; Kimura et al., 2013; Morita et al., 2011) and kidney (Kuwata et al., 2011; Packer et al., 1995; Taniai et al., 2014) *in vivo*. EMIQ has been accorded the generally recognized as safe (GRAS) status and GRAS notice by the Expert Panel of the Flavour and Extract Manufactures Association (FEMA, FEMA No. 4225) (Smith et al., 2005) and the U.S. Food and Drug Administration (FDA, GRAS No. 00220) (FDA, 2007), respectively. EMIQ might be taken by patients as well as healthy individuals and, therefore, its long-term exposure effects require evaluation in appropriate animal models, especially for patients with cancer. ALA, also known as 5-(1,2-dithiolan-3-yl) pentanoic acid or thioctic acid, is a natural metabolic antioxidant (Gruzman et al., 2004). It is known to increase intracellular glutathione levels and regenerate other antioxidants such as vitamins C and E (Jia et al., 2008) and, thereby, has antitumour effects on the liver (Fujii et al., 2013b).

The azoxymethane (AOM)/DSS model is useful for the evaluation of inflammation-associated colon carcinogenesis in rodents and reflects the pathogenesis of human CAC. Numerous studies on the chemopreventive effects of several natural and synthetic compounds against inflammation-associated colorectal carcinogenesis have been reported using this model in mice (Tanaka, 2009, 2012). We hypothesized that CZ, EMIQ, and ALA could prevent colon cancer in the AOM/DSS model through their anti-inflammatory effects. Therefore, to clarify the anticancer effects in short- and long-term colon cancer studies, BALB/c mice were administered a single intraperitoneal injection of AOM and one or two cycles of DSS in drinking water and were concomitantly treated with CZ, EMIQ, ALA, or anthocyanin (AC) derived from purple sweet potato color in their basal diet. AC is water-soluble pigments that mainly occur as the glycosides of their aglycones derived from anthocyanidin (Wang and Stoner, 2008). In this study, they were used as a control antioxidant to prevent colon cancer (Lim et al., 2013; Nimptsch et al., 2016; Sehitoglu et al., 2014; Shi et al., 2015; Thomasset et al., 2009). We determined the direct anticancer properties of the test substances by analysing their effects on proliferation of several human colon cancer cell lines. In addition, we analysed the effects of these substances on inflammation and cell proliferation activity in DSS-induced acute colitis.

2. Materials and methods

2.1. Chemical and reagents

EMIQ and AC were supplied by San-Ei Gen F.F.I., Inc. (Osaka, Japan). CZ, ALA, and 5-bromo-2′-deoxyuridine (BrdU) were purchased from Tokyo Chemical Industry Co., Ltd. (Tokyo, Japan). AOM and DSS were purchased from Sigma-Aldrich (St Louis, MO, USA) and MP Biomedicals (Santa Ana, CA, USA) respectively. Purities, molecular weights, and Chemical Abstracts Service (CAS) numbers of chemicals and reagents (AC, CZ, ALA, BrdU, and AOM) are as follows: AC as cyanidin-3-glucoside, 35.0%, 779.093, 16727-02-9; CZ, >98.0%, 369.47, 73963-72-1; ALA, >99.0%, 206.32, 1077-28-7; BrdU, >98.0, 307.10, 59-14-3; and AOM, >98%, 74.08, 25843-45-2. The purity of EMIQ was >97%. The molecular weight and CAS number of DSS were 36,000–50,000 and 9011-18-1, respectively.

2.2. Animals

Ethical Considerations: The animals received appropriate care in accordance with the Guide for Animal Experimentation of Kaken Pharmaceutical Co., Ltd. (Fujieda, Shizuoka, Japan). The facility has been certified by the Japan Health Science Foundation (Certification No. 15-047). Four-week-old female BALB/cAnNCrlCrlj mice were purchased from Charles River Japan Inc., (Atsugi Breeding Center, Kanagawa, Japan) and acclimated to the testing environment at least for 7 days. The mice were maintained in an air-conditioned room (temperature: 23 ± 3 °C, relative humidity: 50 ± 20%, and fresh air ventilation circulation rate: > 17 times/h) with a 12-h light/dark cycle (lights on and off at 07:00 and 19:00 respectively). Three to four mice were housed in a single bedding cage (W160 mm × D300 mm × H140 mm) and given free access to a basal diet (Oriental MF, Oriental Yeast, Tokyo, Japan) and tap water (Fujieda, Shizuoka, Japan). During the experimental period, clinical observations including status of stool consistency, rectal bleeding, fur coat, and abdomen staining were carried out daily. In addition, the body weight and food consumption were measured on the intervention days (AOM injection, the start of DSS challenge, and necropsy) or at other times to observe the general condition of the animals. Mice were subdivided into groups based on their latest body weight by using a stratified randomization method.

2.3. AOM/DSS cancer study

Mice (n = 8 for the short- and long-term evaluations) were treated with CZ, EMIQ, ALA, and AC (0.3, 1.5, 0.2, and 5.0 w/w%, respectively, in their feed from 1 week prior to and until the end of the experimentation period. Mice received a single intraperitoneal injection of AOM (10 mg/kg) at the beginning of the experiment. One week after the AOM injections, recurrent colitis was induced by administering DSS (3 w/v%) in drinking water for 1 week. For the short-term evaluation, the mice received one DSS administration cycle and were euthanised 3 weeks after the end of the DSS administration. For the long-term evaluation, mice received two DSS administration cycles with a 2-week interval of normal water access in between. During the short-term evaluation, one mouse with poor general condition died in the AOM + DSS + CZ group while the other mice survived to the end of the study. The mice were euthanised 4 weeks after the end of the second DSS

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