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Original article

Protective effect of isoquercitrin against acute dextran sulfate sodium-induced rat colitis depends on the severity of tissue damage

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ABSTRACT

Background: Isoquercitrin (quercetin-3-*O*-β-D-glucopyranoside) is a flavonoid that exhibited antioxidant and anti-inflammatory activities in a number of *in vitro* and *in vivo* studies. Experimental evidence from rodent models of inflammatory bowel disease is, however, lacking. This study was designed to examine whether isoquercitrin effectively and dose-dependently attenuates acute dextran sulfate sodium (DSS)-induced rat colitis.

Methods: Wistar rats were divided into negative control group (exposed to vehicle only), positive control group (DSS-induced colitis plus vehicle), low isoquercitrin group (DSS pretreated with isoquercitrin 1 mg/kg/day) and high isoquercitrin group (DSS with isoquercitrin 10 mg/kg/day). Isoquercitrin was administered daily for 14 days, and during the last 7 days rats drank DSS solution. The effect of isoquercitrin on DSS-induced colitis was assessed clinically (e.g. disease activity index), biochemically (tissue myeloperoxidase activity, local cyclooxygenase-2 expression), using histology (standard hematoxylin-eosin-based histomorphometry, immunohistochemical detection of inducible nitric oxide synthase) and hematology (blood count).

Results: Isoquercitrin dose-dependently ameliorated whole colon shortening and mitigated DSS-induced expression of cyclooxygenase-2 and inducible nitric oxide synthase in the descending segment of the organ. However, when different parts of colon were assessed histomorphometrically, the results did not globally support the protective role of this flavonoid. Tissue healing trends observable in the descending colon were not apparent in the rectum, where histological damage was most severe.

Conclusions: We surmise that isoquercitrin may be effective in the prevention of acute colitis. Besides being dose-dependent, the potency of orally administered isoquercitrin may depend on the severity of tissue damage and/or on the site of its action.

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Introduction

Inflammatory bowel disease (IBD) is a chronic, relapsing condition of the gastrointestinal tract. It presents as ulcerative colitis or Crohn's disease and poses a therapeutic challenge [1]. As current conventional management, exemplified by synthetic anti-inflammatory or biological drugs (acetylsalicylic acid, corticosteroids or antibodies against tumor necrosis factor-α [TNF-α]), fails to guarantee long-term remission, patients often resort to alternative and supportive medications with a major share constituted by natural plant products [2].

Over the last few decades, the increasing interest in botanicals, particularly polyphenols, and their complementary role in IBD prevention and healing has been substantiated by studies showing antioxidant and anti-inflammatory properties of these agents [3]. For instance, flavonoids – a group of polyphenols – may attenuate several aspects of acute or chronic intestinal disease including IBD [4]. The mechanisms responsible for the protection include direct radical scavenging, heavy metal chelation and interaction with a number of biomolecules such as enzymes (e.g. phospholipase A2, cyclooxygenase-2 (COX-2), or inducible nitric oxide synthase

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(iNOS)), cell receptors and transcription factors [5]. Extensive attention has been attracted by quercetin and some of its glycosides, including isoquercitrin (quercetin-3-*O*-β-D-glucopyranoside; Fig. 1) [6]. Isoquercitrin occurs in various food sources such as apples and onions, and it is more water-soluble and more bioavailable than its aglycone. Isoquercitrin was found to attenuate the expression of pro-inflammatory enzymes and mediators. In *in vitro* studies, isoquercitrin has been shown to decrease lipopolysaccharide-induced expression of iNOS, to suppress the upregulation of matrix metalloproteinase-9 by phorbol 12-myristate 13-acetate, and to reduce TNF-α-stimulated production of interleukin-6. With regards to *in vivo* biological activity, isoquercitrin exhibited, amongst others, antioxidant, anti-inflammatory, anti-allergic and tumor-suppressing properties [6].

The present work was designed to test the effectiveness of a preventative regime of two selected doses of isoquercitrin on a rat model of acute dextran sulfate sodium (DSS)-induced colitis. We intended to measure large bowel impairment by clinical, biochemical and morphological signs, and hypothesized that isoquercitrin may induce a dose-dependent amelioration in the studied parameters.

Materials and methods

Materials

Sodium salt of dextran sulfate (dextran sulfate sodium, DSS) with average molecular weight of 35,000–55,000 and sulfur substitution of 16–20%, was provided by TdB ConsultancyAB, Uppsala, Sweden. DSS drinking solution (5% DSS, *w/v*) was prepared daily by mixing DSS with fresh tap water. Isoquercitrin (98% purity) was prepared by the enzymatic procedure as described previously [7]. Suspensions of isoquercitrin (0.25 mg/mL for animals receiving the dose of 1 mg/kg and 2.5 mg/mL for animals receiving the dose of 10 mg/kg) were prepared daily by mixing isoquercitrin with distilled water, followed by sonication and deoxygenation by argon.

Ethical issues

All protocols and experimental procedures of the study were approved by the local ethics committee (Approval No. 10405/2010-30). All animals received humane care in compliance with the Experimental Animals Protection Act No. 167/1993L.C.

Animals

Thirty male outbred albino rats of Wistar strain, specific pathogen free (initial age of approximately 6 weeks and body weight 175–199 g) were used. During acclimatization (7–10 days), the animals were housed in the animal house/facilities, in standard plastic cages with dust-free sawdust, 2 rats per cage under standard and controlled environmental conditions with free access to drinking water and standard rat chow.

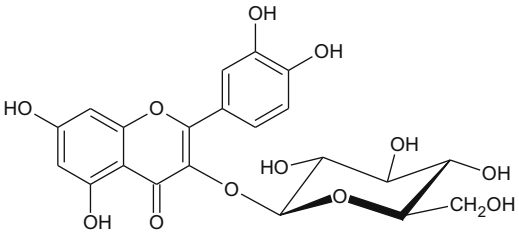

Fig. 1. Structure of isoquercitrin.

Experimental design

A rodent model of DSS-induced colitis [8] was used with some modifications [9,10]. The whole experiment lasted for 14 days, with chow and fluid available *ad libidum*. Rats were randomized into four groups (Fig. 2). Negative control group (group 1, $n = 6$ animals in 3 cages) had free access to drinking water and was daily exposed to vehicle, *i.e.* distilled water (4 mL/kg) by oral gavage. To induce colitis in the positive control group (group 2, $n = 8$ animals in 4 cages), drinking water was replaced with 5% DSS during the last 7 days. These animals were also daily given vehicle (4 mL/kg). As in group 2, low dose isoquercitrin group (group 3, $n = 8$ animals in 4 cages) had free access to 5% DSS. For all 14 days, group 3 animals were daily administered 1 mg/kg isoquercitrin (4 mL/kg). High dose isoquercitrin group (group 4, $n = 8$ animals in 4 cages) was treated identically to group 3 with the exception that the dose of isoquercitrin equaled 10 mg/kg. On day 15, all animals were weighed and intramuscularly injected with a mixture of fentanyl, medetomidin and diazepam (4, 20 and 500 μg per 100 g, respectively). Arterial blood was withdrawn from the aortal bifurcation into ethylenediaminetetraacetate (EDTA)-containing tubes to sacrifice the animals. An aliquot of blood was used for blood count (ABX ABC Vet Hematology Analyzer, Horiba ABX, France). The remaining material was centrifuged (for 15 min at 4000 × *g* and 4 °C) to obtain plasma which was subsequently stored at −80 °C. Following isolation, longitudinal dissection and thorough washing in ice-cold phosphate-buffered saline (PBS, pH 7.4), the large intestine was measured in its length, photographed and sampled. 1 cm long segments were detached from both ends of the organ (ascending colon and rectum, respectively). The residuum was divided into three equal parts and *ca.* 1 cm long segments were cut from both ends of the middle portion (transversal and descending colon, respectively). The remainder of the middle portion (*ca.* 5 cm long and consisting of both transversal and descending colon) was used for the determination of water content. The material of the distal part (*ca.* 1–6 cm from the anus) was considered to be the descending colon and was stored at −80 °C for subsequent biochemical analyses.

Clinical examination

The daily routine included the measurement of body weight, feed consumption and fluid intake (per cage). Following the commencement of DSS exposure, the rats were also examined for stools consistency and rectal bleeding, *i.e.* parameters involved in DAI calculation [11] (Table 1). Color paper test, based on pseudoperoxidase reaction of hemoglobin, was employed to assess the presence of fecal occult blood. DAI was calculated for each cage

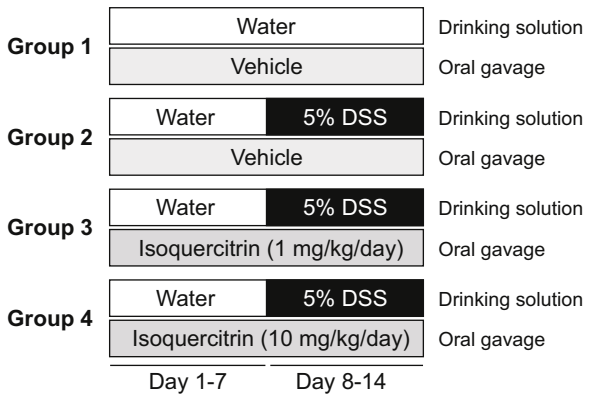

Fig. 2. Experimental design.

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