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Curcumin, a component of turmeric, efficiently prevents diclofenac sodium-induced gastroenteropathic damage in rats: A step towards translational medicine

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Abbreviations:
DIC
Diclofenac sodium
Hb
Haemoglobin
HCT
Haematocrit
H2RAs
Histamine H2 receptor antagonists
LPO
Lipid peroxidation
NSAIDs
Nonsteroidal anti-inflammatory drugs
PPIs
Proton pump inhibitors
CUR
Curcumin
ROS
Reactive oxygen species

ABSTRACT

There is a need to find/discover novel leads to treat complex and/or multi-factorial disease(s). Curcumin (CUR) is one of the promising lead molecules which need its further evaluation against NSAID-induced gastroenteropathy. Hence, the aim of the present study was to explore the pharmaco-mechanistic efficacy of CUR against NSAID-induced gastroenteropathy. Rats were treated twice daily with CUR (25, 50 and 100 mg kg^{-1} peroral) or vehicle for 10 days. In some experiments, diclofenac sodium (DIC; 9 mg kg^{-1}) was administered orally twice daily for the final 5 days of CUR/vehicle administration. After the last dose on 9th day, rats were fasted. 12 h after the last dose on 10th day, rats were euthanized and their GI tracts were assessed for haemorrhagic lesions, lipid peroxidation, intestinal permeability and GI luminal pH alterations along with haemato-biochemical estimations. The macroscopic, biochemical, haematological and histological evidences suggested that co-administration of CUR resulted in dose dependent attenuation of the NSAID-induced gastroenteropathic damage and the mechanisms may be related to its ability to prevent the NSAID-induced alterations in the GI luminal pH, lipid peroxidation/oxidative stress, GI blood loss and intestinal permeability alteration. Based on these pharmaco-mechanistic results we propose it as a promising lead to treat NSAID-gastroenteropahty.

1. Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) owing to their high efficacy against pain and inflammation are amongst the most frequently prescribed drugs worldwide (Singh et al., 2016a). However, their intake is frequently associated with gastrointestinal

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(GI) side effects (Blackler et al., 2014; Singh et al., 2016b). NSAIDs not only damage the stomach (gastropathy), but, can also exert significant small intestinal damage (enteropathy) including; perforation, ulceration, overt bleeding and diaphragm-like strictures (Adebayo and Bjarnason, 2006; Wallace, 2016). Together, this "NSAID-induced GI toxicity" has been referred as "NSAID-induced gastroenteropathy" (Singh et al., 2016b; Blackler et al., 2014). Management of NSAID-induced gastroenteropathic damage today represents an important medical and socioeconomic problem as there are no approved therapeutic agents for enteropathic damage and currently available gastroprotective drugs such as proton pump inhibitors (PPIs)/histamine H2-receptor antagonists (H2RAs) worsen the small intestinal damage caused by NSAIDs (Abdel-Tawab et al., 2009; Satoh et al., 2012; Wallace et al., 2011; Singh et al., 2016c). In addition, there is mounting evidence from clinical studies that PPIs and/or H2RAs usage may result in hypergastrinemia (Reilly, 1999), enteric infections (Dial et al., 2004), Vitamin B12 deficiency (Lam et al., 2013), increased risk of hip fractures (Corley et al., 2010; Richards and Goltzman, 2008), adverse cardiovascular events (Charlot et al., 2011) and increased mortality rates (Teramura-Grönblad et al., 2012). Thus, the identification of effective and safer therapies for the treatment of NSAID-induced gastric as well as intestinal (i.e. gastroenteropathic) lesions remains an urgent priority.

NSAID-induced gastroenteropathy is caused by perturbations of multiple signalling pathways and hence has multi-factorial pathogenesis (Singh et al., 2016a; Scarpignato and Hunt, 2010; Scarpignato, 2008; Blackler et al., 2014). Thus, targeting only one of these multiple pathways with singly-targeted drugs is highly unlikely to be effective and would prove to be highly expensive. Here lies the importance of multi-targeted, innocuous, inexpensive, and readily available dietary agents or nutraceuticals such as flavonoids (Hu, 2007; Farzaei et al., 2015; Gonzalez et al., 2011; Kawaguchi et al., 2011). In our previous studies, we proposed flavonoids as therapeutic agents for NSAID-induced GI toxicity owing to their potent multimodal actions (like antioxidant, anti-Inflammatory, imunomodulatory, cytoprotective and antisecretory effects) and the ability of these molecules like Curcumin (CUR) to elicit their pharmacological effects through MTDD approach (Fig. 1) (Gupta et al., 2012a; Prasad et al., 2014a, 2014b; Goel et al., 2008; Teiten et al., 2010; Balogun et al., 2003; Motterlini et al., 2000; Swarnakar et al., 2005; Gu et al., 2015; Sivalingam et al., 2008; Singh and Aggarwal, 1995; Wang et al., 2012; Mei et al., 2012; Sadashiva Reddy et al., 2014, Devendra Pratap Singh et al., 2012). We stressed on the need for testing the efficacy of these agents at preclinical level in a clinically simulated animal model based on the multi-factorial pathogenesis of NSAID-induced gastroenteropathy (Kawaguchi et al., 2011; Gonzalez et al., 2011; Farzaei et al., 2015; Singh et al., 2016a, 2016b, 2017b; Devendra Pratap Singh et al., 2016a, 2016b, 2016c, 2016d). The discovery of CUR dates back to around two centuries ago when two Harvard College laboratory scientists Vogel and Pelletier reported its isolation from the *Curcuma longa* (turmeric) rhizomes (Prasad et al., 2014a). CUR is a highly pleiotropic molecule which has been shown to possess anti-inflammatory, hypoglycemic, antioxidant, wound-healing and antimicrobial activities etc (Gupta et al., 2012a; Prasad et al., 2014a, 2014b; Teiten et al., 2010) (Fig. 1). Multiple randomized, double blind, placebo-controlled trials have established its therapeutic efficacy, tolerability and safety in various diseases *viz.* ulcerative colitis, rheumatoid arthritis, peptic ulcer and colorectal cancer (Hanai et al., 2006; Chandran and Goel, 2012a; He et al., 2011; Prucksunand et al., 2001). The safety, tolerability, and non-toxicity of CUR are well established by clinical trials at doses as high as 2–8 g/day (Gupta et al., 2012b; Kanai et al., 2011; Dhillon et al., 2008; James et al., 2015; Irving et al., 2015). Fig. 1 illustrates the anti-gastroenteropathic potential of CUR. We recently reviewed the anti-gastroenteropathic/therapeutic potential of CUR (Singh et al., 2017a).

Importantly, there is increasing interest in using CUR in conjunction with NSAIDs for reducing the dosage of NSAIDs and enhancing the pharmacological effects of NSAIDs and/or CUR as well (Banerjee et al., 2003; Jain et al., 2014). Synergism between CUR and conventional NSAIDs is an interesting concept and may pave the way for a novel combination treatment in osteoarthritis/other rheumatologic disorders (Lev-Ari et al., 2006; Jain et al., 2014; Chandran and Goel, 2012b). However, CUR although appears to be a promising candidate, but, there is no data on the effects of CUR on commonly used NSAIDs such as diclofenac sodium (DIC)-induced GI injury and underlying mechanisms are poorly defined. Importantly, the effects of CUR on DIC-induced generation of reactive oxygen species (ROS)/lipid peroxidation in GI tissues, intestinal permeability alteration, both gastric and intestinal luminal pH alterations and alterations in the levels of haematological (haemoglobin etc) and biochemical parameters (albumin and total protein) remains to be determined as these factors have been identified as some of the important players in the etiopathogenesis of NSAID-induced gastroenteropathic lesions (Boelsterli et al., 2013; Blackler et al., 2014; Wallace, 2012; Singh et al., 2016a, 2016c; Reuter et al., 1997). In previous studies, researchers demonstrated the efficacy of CUR against indomemethacin-induced gastropathy and enteropathy using different dosage of indomethacin in separate animal models (Menozzi et al., 2009, Swarnakar et al., 2005). Though, previous studies were informative, however, it is imperative to study and assess the effects of CUR at gastric as well as intestinal level in a clinically simulated animal model because assessing only gastro-protective or entero-protective activity may prove to be problematic in the long run just like what is happening with PPIs today (emerging evidence for worsening of NSAID enteropathy with PPIs) (Abdel-Tawab et al., 2009; Satoh et al., 2012; Wallace et al., 2011; Singh et al., 2016c).

Thus, in the present study, we have examined the effects of oral administration of CUR in our recently developed translational and novel rat model for NSAID-induced gastroenteropathy simulating the clinical situation during NSAID therapy (Singh et al., 2016b). It is expected that the current study would aid in understanding the mechanisms underlying the various effects of CUR on the DIC-induced gastroenteropathic lesions.

2. Materials and methods

2.1. Chemicals and assay kits

DIC and CUR were purchased from Sigma Aldrich, St. Louis, Missouri, United States. The assay kits for total protein, albumin, alanine transaminase (ALT) and bilirubin (both total and direct) were products of ERBA Diagnostics Mannheim GmbH, Mannheim, Germany. Heparin was purchased from Biological E. Ltd., Hyderabad, India. Heparinized capillaries and carboxymethyl cellulose (CMC) were purchased from Himedia, Mumbai, India. Rodent diet was purchased from VRK nutrition, Pune, India. Deionised water was prepared in-house using a Milli-Q water purifier system (Millipore Elix, Germany). All other reagents used in this study were procured from Qualigens Fine chemicals, India.

2.2. Animals

Male, Wistar rats (n = 45), 4–6 months old, weighing 200–250 g were obtained from the animal house of B. V. Patel PERD Centre, Ahmedabad, India. All animals were housed in clean, polypropylene cages (3 animals per cage) and were allowed to