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Micellar solubilisation enhances the antiinflammatory activities of curcumin and boswellic acids in rats with adjuvant-induced arthritis

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ABSTRACT

Objective: Native extracts of curcumin and boswellia are known to exert antiinflammatory properties but have poor bioavailability when given orally. Using advanced micellation technology, it has been possible to produce stable solubilisates of these extracts with markedly enhanced bioavailability. In the present study, we compared the chronic antiinflammatory activities of native and micellar curcumin in the rat adjuvant arthritis model, using diclofenac as a reference drug.
Methods and procedures: Adjuvant arthritis was induced by injecting Freund's complete adjuvant (FCA) into the right hind paw of rats and monitoring paw volume over 3 wk. The drugs were given daily for 3 wk, starting from the day of adjuvant inoculation. The serum was collected at end of the experiment for the assay of inflammatory and oxidative stress parameters. Statistical comparisons between different groups were carried out by one-way analysis of variance followed by Tukey-Kramer multiple comparison test.
Results: Solubilized curcumin showed better antiinflammatory activity than its native form. The reduction in paw volume was reflected in corresponding changes in relevant mediators of inflammation like tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), C-reactive protein (CRP), myeloperoxidase (MPO), and lipid peroxidation markers. The combination of curcumin and boswellia solubilisates synergistically produced an even more potent therapeutic effect.
Conclusion: The findings confirm that micellar solubilisation of curcumin and boswellia not only increases their bioavailability, but also enhances their biological activity. Micellar curcumin, in particular in combination with micellar boswellia, may thus represent a promising concomitant tool for antiinflammatory treatment and a potential antiinflammatory alternative to synthetic drugs.
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Introduction

Inflammation is one of the major causes of the development of various diseases like arthritis, cancer, cardiovascular disease, diabetes, obesity, osteoporosis, inflammatory bowel disease, asthma, and even central nervous system (CNS)-related diseases such as depression and Parkinson's disease [1]. Reports in the literature suggest that almost 90% of synthetic antiinflammatory drugs produce drug-related toxicities, iatrogenic reactions, and adverse effects compromising the treatment process [2,3]. Consequently, an immense interest has reemerged in herbs exerting antiinflammatory activity as potential alternative or concomitant tools for antiinflammatory treatment with much less side effects. The most promising and widely used herbs in this context are *Boswellia* serrata Roxb. ex Colebr. (Burseraceae) and *Curcuma longa* L. (Zingiberaceae).

Conflict of interest statement: Jan Frank is a consultant at AQUANOVA AG, the company manufacturing micellar curcumin and boswellia. Dariush Behnam is the inventor of curcumin and boswellia micellization, founder and CEO of AQUANOVA AG. All other authors have claimed to have no conflict of interest.

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Curcuma has been used in Ayurvedic medicine to treat inflammatory conditions [4,5]. The three major curcuminoids isolated from C. longa are curcumin, demethoxycurcumin, and bisdemethoxycurcumin, with curcumin being the primary component. Numerous studies have demonstrated the antioxidant, antimicrobial, antiinflammatory, anticarcinogenic, and proapoptotic properties of curcumin [6] particularly for exhibiting therapeutic effects against arthritis [7] and various neurologic [8] and pulmonary conditions [9].

Curcumin exerts its antiinflammatory activity at least partly through modulation of pro-inflammatory signaling molecules and enzymes such as cytokines (tumor necrosis factor (TNF)-α, interleukin-1 beta (IL-1 β), interleukin-6 (IL-6)), nuclear factor kappa B (NF–κB), C-reactive protein (CRP), cyclooxygenase (COX)-2, 5-lipoxygenase (5-LO), and prostaglandin E_2 [10,11]. Often curcumin is combined with boswellia to enhance its antiinflammatory effect, especially because a number of pivotal enzymes involved in inflammation, like 5-LO, cathepsin G (catG), and microsomal prostaglandin E synthase (mPGES)-1 as well as NF-κB and several pro-inflammatory cytokines like TNFα, IL-1 β, interleukin-2 (IL-2), and IL-6 are also inhibited by boswellic acids, which have been shown to inhibit inflammatory mediators in experimentally induced arthritis [12] and to have potential in pilot clinical trials to treat a variety of chronic inflammatory diseases like rheumatoid arthritis, osteoarthritis, chronic colitis, ulcerative colitis, collagenous colitis, Crohn's disease, and bronchial asthma [13,14].

Although curcumin has exhibited much therapeutic promise, its use has been limited by its poor intestinal absorption, rapid metabolism, and limited systemic bioavailability [15]. To increase its water solubility, stability, bioavailability, and potential applications various strategies have been proposed and investigated, including its formulation in the form of nanoparticles, liposomes, solid dispersions, microemulsions, and complexation with phospholipids and cyclodextrins [16–18]. Although each of these novel delivery strategies offers promise, there are still limitations to their potential use. Most of these technologies are not able to accommodate high loading of curcumin, thus limiting the bioactivity of the finished products, and some of the delivery systems are not readily suitable for food, drug, and related applications. The present study involves an advanced micellation technology based on micellar solubilisation of curcumin with Tween 80, which has been shown to result in the largest increase of curcumin bioavailability reported to date [19–21]. Thus, a 3.5-fold increase in the apparent permeability coefficient for micellar over native curcumin was observed in the Caco-2 in vitro model, demonstrating a much better absorption of the micellar formulation in the small intestine [22]. This was confirmed in a human trial, where an up to 185-fold larger AUC and a 455-fold higher maximum total curcumin plasma concentration (Cmax) were observed for micellar curcumin compared to the native form [19]. Encouraged by this tremendous increase in the oral bioavailability observed for curcumin, micellar solubilization was also applied to boswellia extracts in a recent pharmacokinetic study carried out in rats; showing an enormous increase in the absorption of boswellic acids (unpublished results). Based on this, the present study pursued the question whether micellar solubilization would also result in an increased antiinflammatory activity of curcumin, boswellia, and their combination compared to their respective native forms in the rat adjuvant arthritis model. This is the first study setting great value on choosing oral doses in the rat adjuvant arthritis model that correspond to applicable doses in human subjects.

Materials and methods

Chemicals

Native and solubilized extracts of curcumin (82% curcumin, 16% demethoxycurcumin, and 2% bis-demethoxycurcumin) and boswellia extract (standardized to 80% total boswellic acids) were kindly provided by AQUANOVA AG, Darmstadt, Germany. The liquid curcumin and boswellia micelles (NovaSOL Curcumin and NovaSOL Boswellia) were composed of 7% curcumin powder (equivalent to 6% curcumin) and 15% Boswellia serrata extract (equivalent to 12% total boswellic acids). All percentages refer to weight. Diclofenac sodium was obtained from Novartis (Egypt) and Freund's complete adjuvant (FCA) from Sigma-Aldrich (St. Louis, Missouri).

Animals

Female Wistar rats, each weighing 150–200 g were obtained from the animal breeding unit of the National Research Centre, Giza, Egypt. Rats were acclimatized in the animal facility of the National Centre for Radiation Research and Technology (NCRRT), Atomic Energy Authority, Cairo, Egypt for 1 wk before experimentation. Rats were housed at an ambient temperature of 25 ± 2 ° C, relative humidity of 60% to 70% and a 12-h light/12-h dark cycle. They were fed standard laboratory chow and water ad libitum. The study was conducted in accordance with the guidelines set by the European Economic Community (EEC) regulations (revised Directive 86/609/EEC) and was approved by the Ethical Committee at the Faculty of Pharmacy, Cairo University, Egypt (Approval 24/17).

Induction of adjuvant arthritis

Adjuvant arthritis was induced in the rats according to the method described by Pearson [23]. Briefly, the animals were inoculated with a subplantar injection of 0.1 mL FCA into the right hind paw at day 0 and were randomly allocated to six groups of eight rats each ($n = 8$) as follows: **Control:** Served as control arthritic rats (untreated); **Diclofenac:** Received diclofenac as a reference drug (3 mg/kg); **Native curcumin 5:** Received native curcumin extract (5 mg/kg); **Solubilized curcumin 5:** Received solubilized curcumin (5 mg/kg); **Native curcumin and boswellia:** Received mixture of native curcumin (5 mg/kg) and native boswellia (10 mg/kg); **Solubilized curcumin and boswellia:** Received mixture of solubilized curcumin (5 mg/kg) and solubilized boswellia (10 mg/kg).

All extracts were given orally 1 h before adjuvant inoculation and continued once daily for 21 d (from day 0 to day 20). Arthritis was assessed by measuring the paw volume every 4 d at days 0, 4, 8, 12, 16, and 20 after adjuvant injection using a water displacement plethysmometer, LE 7500 (Panlab, HARVARD Apparatus, Barcelona, Spain). Twenty-four hours after the last treatment, the animals were sacrificed and serum samples were prepared and stored at -80°C until analyzed for TNF-α, IL-6, myeloperoxidase (MPO), CRP, total antioxidant capacity (TAC) and thiobarbituric acid reactive substances (TBARS).

Assessment of inflammatory cytokines

Both TNF-α and IL-6 levels in the serum were assessed using rat specific Quantikine ELISA kits (R&D systems, Inc., Minneapolis, Minnesota, USA) according to manufacturer's instructions. The optical density of each sample was measured using an ELISA plate reader (Dynatech R MR 5000, Guernsey, Channel Islands, UK) set at 450 nm. Values were expressed as pg/mL.

Assessment of myeloperoxidase (MPO) activity

MPO activity was assessed in the serum using a colorimetric activity assay kit (Sigma-Aldrich, St. Louis, Missouri, USA) according to manufacturer's instructions. The absorbance of each sample was measured using an ELISA plate reader set at 412 nm. Values were expressed as mU/mL.

Assessment of C-reactive protein (CRP)

Serum CRP was measured using a DuoSet ELISA kit (R&D systems, Inc., Minneapolis, Minnesota, USA) according to manufacturer's instructions. The optical density of each sample was measured using an ELISA plate reader set at 450 nm. Values were expressed as pg/mL.

Assessment of lipid peroxidation

Lipid peroxides were determined in serum as described by Uchiyama and Mihara [24]. The method depends on the colorimetric determination of a pink

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