



## Review

## Berberine and inflammatory bowel disease: A concise review

Solomon Habtemariam<sup>a,b</sup><sup>a</sup> Pharmacognosy Research Laboratories, University of Greenwich, Chatham-Maritime, Kent ME4 4TB, UK<sup>b</sup> Herbal Analysis Services, UK

## ARTICLE INFO

## Article history:

Received 28 June 2016

Received in revised form 27 August 2016

Accepted 29 September 2016

Available online 30 September 2016

## Keywords:

Berberine

Inflammatory bowel disease

Anti-inflammatory mechanisms

Antinociceptive

Epithelial barrier protection

Anti-diarrhoeal

## ABSTRACT

Berberine is the principal component of many popular medicinal plants (e.g. the genus *Berberis*, *Coptis* and *Hydrastis* among others) with a history of thousands of years of usage in traditional medicine. The numerous pharmacological activities of berberine reported in the last two decades have been attracting high level interests both within the scientific community, clinicians and the public at large. Despite enormous amount of efforts have been placed to show its therapeutic value for inflammatory bowel diseases (IBD), however, comprehensive up-to-date review article in this field is not yet available. In this communication, literature data from *in vitro* and *in vivo* experiments were scrutinised and concisely presented to demonstrate its anti-IBD potential. Beyond the known general antioxidant and anti-inflammatory effects of berberine, IBD-specific effects including gut epithelial barrier pathology, T cells as emerging targets, antinociceptive and other effects are discussed.

© 2016 Elsevier Ltd. All rights reserved.

## Contents

1. Introduction .....	592
2. Berberine and IBD .....	593
3. Antibacterial and anti-diarrhoeal activity .....	593
4. Berberine and the intestinal epithelial barrier .....	594
5. Berberine and oxidative stress .....	595
6. Beyond anti-inflammatory effect .....	595
6.1. T cells as emerging targets for berberine .....	595
6.2. Antinociceptive mechanism .....	596
7. Conclusion .....	597
Competing interests .....	597
References .....	597

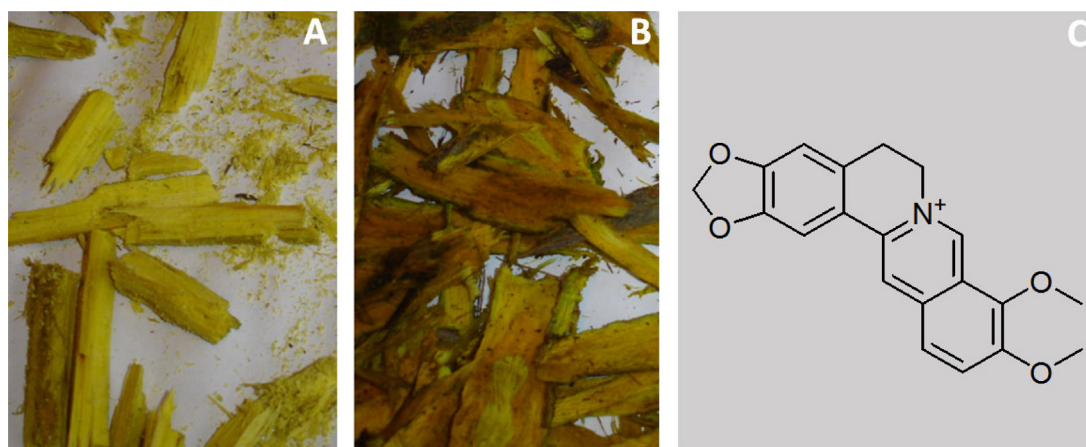
**Abbreviations:** AP1, activator protein 1; ATF, activating transcription factor; COX-2, cyclooxygenase-2; ERK1/2, extracellular signal-regulated protein kinases 1 and 2; H<sub>2</sub>O<sub>2</sub>, hydrogen peroxide; HO-1, heme oxygenase; iNOS, inducible nitric oxide synthase; IBD, inflammatory bowel disease; ICAM-1, intercellular adhesion molecule-1; IFN- $\gamma$ , interferon gamma; IL, interleukin; IBS, irritable bowel syndrome; JAK, Janus kinase; JNK, c-Jun N-terminal kinase; LPS, lipopolysaccharide;  $\delta$ -DOR,  $\delta$ -opioid receptors;  $\mu$ -MOR,  $\mu$ -opioid receptors; MAPK, mitogen-activated protein kinases; NF- $\kappa$ B, nuclear factor- $\kappa$ B; NSAID, non-steroidal anti-inflammatory drugs; Nrf2, (erythroid-derived-2)-related factor-2; PI3K/Akt, phosphatidylinositol 3-kinases/Protein Kinase B; PPAR $\gamma$ , proliferator-activated receptor- $\gamma$ ; ROR- $\gamma$ , tRAR-related orphan receptor- $\gamma$ ; ROS/RNS, reactive oxygen/nitrogenous species; STAT, signal transducer and activator of transcription; TAK1, TGF-activated kinase 1; Th, T helper cells; TGF- $\beta$ , transforming growth factor- $\beta$ ; Treg, regulatory T cells; TNF- $\alpha$ , tumour necrosis factor- $\alpha$ .

E-mail address: [s.habtemariam@herbalanalysis.co.uk](mailto:s.habtemariam@herbalanalysis.co.uk)<http://dx.doi.org/10.1016/j.phrs.2016.09.041>

1043-6618/© 2016 Elsevier Ltd. All rights reserved.

## 1. Introduction

Berberine is the principal isoquinoline alkaloidal constituent of the stems and roots of various *Berberis* species such as *B. aristata* [1], *B. Petiolaris* [2] and *B. vulgaris* [3]. While *B. aristata* is acclaimed to contain berberine in about 5% in the roots and 4.2% in the stem [4], a high yielding *B. darwinii* has also been reported [5,6]. Other berberine containing plants of pharmacological significance are *Argemone mexicana* (prickly poppy), *Coptis chinensis* (Chinese goldthread), *C. japonica*, *C. teeta* (rhizome 8–9%), *Eschscholzia californica* (California poppy) and *Hydrastis Canadensis* or goldenseal, *Mahonia aquifolium*, *Tinospora cordifolia*, *Xanthorhiza simplicissima* (yellowroot), *Phellodendron amurense*. Unusually high level of berberine



**Fig. 1.** The structure of berberine and its appearance in medicinal plants.

The yellowish colour of berberine containing medicinal plants as exemplified by the stem wood (A) and bark (B) of *B. darwinii* plant. The structure of the isoquinoline alkaloid berberine (C) is also shown (for interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

content in these plants, particularly in *P. amurense* (up to 4%) and *C. chinensis* (up to 8%) have been reported [7]. With a characteristic bright yellow colour, plant materials containing berberine in high yield usually appear as yellow or orange colour (Fig. 1).

Berberine, both in its pure form and as principal constituent in medicinal plants, has been shown to display numerous pharmacological activities including analgesic [8], anti-inflammatory [9], anticancer [10], antidiabetic [11], anti-hyperlipidemic [12], cardioprotective [13] and memory enhancement and antidepressant [14–16] effects. The antinociceptive and antidepressant-like activity of berberine has been shown to serve as a mechanism of action for its therapeutic use in treating inflammatory bowel disease (IBD) [17,18] though numerous other mechanisms ranging from general anti-inflammatory and antioxidant to IBD-specific immunological effects are implicated. Some of the key findings gathered from the literature in the last two decades are scrutinised in this communication.

## 2. Berberine and IBD

Ulcerative colitis and Crohn's disease are the two most common forms of chronic inflammatory disorders of the gut and are collectively known as IBD. While both ulcerative colitis and Crohn's disease share an exaggerated immune response and some common symptoms as their pathological markers, differences in their location within the gastrointestinal tract, disease severity and response to drug treatment have been well documented. For example, ulcerative colitis is usually confined to the colon and primarily affects the top layers in almost an even distribution while Crohn's disease usually affects any part of the gastrointestinal tract from the mouth to the anus, and even other organs such as the, eyes, joints, liver, etc. [19]. The prevalence of IBD in the western societies is staggeringly high with an estimated 1–1.3 million in the US [20] and 2.2 million Europeans [21] are known to be affected. An accurate figure on the epidemiological significance of IBD is not yet available but some estimates put the general prevalence of the disease in the developed countries at about 0.1% [22]. Of the various potential causes implicated in the IBD pathology include genetic susceptibility coupled with environmental risk factors attributed to lifestyle changes such as dietary habits, smoking, stress and lack of exercise, as well as other changes associated with medications/surgery or those leading to alteration of the bacterial flora of the gut [23–25]. IBD is a classical progressive immunological disorder with a peak

prevalence at the young adulthood age (15 to 30 years) and characteristic feature of remission and relapse.

The main classes of drugs used to treat IBD include the aminosalicylates (e.g. sulfasalazine) which often serve as the first line therapy option, corticosteroids, immunosuppressives (e.g. azathioprine) and anti-tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ) antibodies as classical representatives of biological agents [25,26]. To date, there is no drug of cure for IBD, however, and all drug treatment approaches are designed to minimize the inflammation that triggers the symptoms, limit complications and try to induce long-term remission. Hence, it remains the case that about 20% of ulcerative colitis and 60–75% for Crohn's disease patients who don't respond to medication require surgical intervention [19]. While unwanted side effects and poor efficacy are inherent problems associated with all anti-IBD drugs, the high cost of the newer biological agents-based therapies are among the major drawbacks. The utilisation of natural products as a safer and better efficacy IBD treatment option is therefore of paramount importance. Apart from the numerous pharmacological effects of berberine reported in recent years, specific potential IBD therapeutic potential from *in vivo* studies employing experimental colitis induced by a variety of agents (e.g. acetic acid, indomethacin, trinitrobenzene sulfonic acid or dextran sulfate sodium in rodents) have been documented [27–33]. Numerous other *in vitro* studies suggesting the barrier protective effects in various cell types including epithelial cells of the gut have also been reported [e.g.,34–37]. Besides the general anti-inflammatory and antioxidative effects of berberine that possibly contribute to its IBD efficacy, more and more specific mechanisms have been highlighted in the last decade (Fig. 2).

## 3. Antibacterial and anti-diarrhoeal activity

The potential benefit of berberine in IBD therapy could arise from its widely known antibacterial effects including activity against *E. coli* [38,39]. Most of the studies however appear to show antimicrobial effect at rather high IC<sub>50</sub> values and hence direct antibacterial effect may not be the major mechanism for its observed anti-IBD effects. Berberine being a positively charged compound with direct interaction to bacterial cell wall components, lipopolysaccharide (LPS) and cell surface proteins [40,41], its antibacterial effect at a reasonably high concentrations is not surprising. Clinically, the anti-diarrhoeal effect of berberine has been demonstrated very recently in human patients suffering from irritable bowel syndrome (IBS). Patients receiving berberine

Download English Version:

<https://daneshyari.com/en/article/5557640>

Download Persian Version:

<https://daneshyari.com/article/5557640>

[Daneshyari.com](https://daneshyari.com)