BERBERINE AND CURCUMIN Evidence-Based Review

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THE BROAD MEDICINAL EFFECTS OF BERBERINE
BERBERINE

- Berberine, an isoquinoline alkaloid found in several plants including Coptis chinensis, Mahonia aquifolium, Hydrastis canadensis, Coptis chinensis, Berberis species, and Chelidonium majus.

- Berberine has anti-diarrheic, anti-inflammation, anti-microbial, neuroprotective, and anti-tumor properties.
Berberine is often sold as an isolated compound. Its benefits and bioavailability are enhanced by blending it with the whole herb, which offer synergistic compounds.
BERBERINE HAS NUMEROUS ACTIONS

- Gastrointestinal Infections
- Familial Adenomatous Polyposis
- Liver Disease
- Elevated Lipids
- Diabetes
- Cancer
- Obesity
- Traumatic Brain Injury
There are now nearly 5,000 scientific papers published on berberine, supporting traditional usage for liver and GI function, and suggesting novel applications against diabetes, cancer, and chronic inflammatory diseases.
BERBERINE FOR GUT HEALTH
Berberine is a considered a multi-target drug that has significant advantages. In contrast to its significant pharmacological effects in the clinic, the plasma level of BBP is very low. Our previous work revealed that dithydroriberine (dBBB) could be an absorbable form of BBP in the intestine, and butylate is an active metabolite that is generated by gut bacteria in rats. In this study, for the first time we describe gut microbiota-regulated pharmacokinetics in beagie dogs after oral administration of BBP by single (50 mg/kg) or multiple doses (50 mg/kg/d) for 7 days. GC-MS, GC, LC-MS/MS, and LC/MSP®-IT-TOF were used to detect dBBB, butylate and BBP as well as its Phase I and II metabolites, respectively. The results showed that dBBB was not detected in dog plasma but was excreted in small amounts in the feces of dogs examined on days 5 and 7. Butylate was generated by gut bacteria and increased by 1.3- and 1.2-fold in plasma or feces, respectively, after 7 days of BBP treatment compared to the levels before treatment. Changes of intestinal bacterial composition were analyzed by 16S rRNA gene analysis. The results presented that dogs treated with BBP for 7 days increased both the abundance of the butyrate- and the nitroreductases-producing bacteria. We also identified chemical structures of the Phase I and II metabolites and analyzed their contents in beagie dogs. Eleven metabolites were detected in plasma and feces after BBP oral administration (50 mg/kg) to dogs, including II metabolites of Phase I and III metabolites of Phase II. The pharmacokinetic profile indicated that the concentration of BBP in plasma was low, with a C_{max} value of 36.85 ± 23.45 μg/mL. The relative content of glycerol acid conjugates (M1) was higher those of other metabolites (M2, M3, M4, and M5) in plasma. BBP was detected in feces, with high excreted amounts on day 5 (265.04 ± 1729.54 μg/g) and day 7 (2793.43 ± 488.10 μg/g). In summary, this is the first study to describe gut microbiota-regulated pharmacokinetics in beagle dogs after oral administration of BBP, which is beneficial for discovery of drugs with poor absorption but good therapeutic efficacy.

Keywords: berberine, gut microbiota, butyrate, metabolites, GC-MS, LC/MSP®-IT-TOF, 16S rRNA genes analysis
BERBERINE HAS BROAD ANTIMICROBIAL ACTIVITY

- Berberine is active against viruses, fungi, protozoans, helminths and a variety of bacteria, including many pathogenic species and multidrug resistant strains of Mycobacterium tuberculosis and methicillin resistant Staphylococcus aureus.

- Berberine effects bacterial cell membranes, interacts with DNA, and inhibits cell division.

**Uptake of and Resistance to the Antibiotic Berberine by Individual Dormant, Germinating and Outgrowing Bacillus Spores as Monitored by Laser Tweezers Raman Spectroscopy**

Shiwei Wang, ET AL

Berberine increases short chain fatty acid (SCFA) producing bacteria in the GI.

SCFA is an energy source for large intestine epithelial cells

SCFA regulate the GI immune system and may regulate microglial function in animals
BERBERINE SUPPORTS METABOLIC FUNCTION

BERBERINE HAS BROAD ANTI-INFLAMMATORY AND IMMUNE MODULATING ACTIVITIES
BERBERINE IMPROVES HEPATIC LIPID METABOLISM

Berberine increases LDL receptors

Berberine increases the amount of LDL receptors on liver cells

LDL receptors will bind LDL Cholesterol in the blood

Results in lower LDL cholesterol levels

PlantMedicineNews.com
Berberine offers broad metabolic support, improving lipid and carbohydrate metabolism.
Berberine activates fatty acid receptor GPR40 contributing to the antidiabetic action.

Berberine activates thermogenesis in white and brown adipose tissue via AMPK and PGC-1α, implying potential therapeutic applications for the treatment of obesity.
BERBERINE HAS NUMEROUS ANTI-INFLAMMATORY EFFECTS

- Berberine affects AMP kinases, NF-κB, TNF, Interleukins and other cytokines to inhibit inflammatory pathways.

- Berberine helps to protects against inflammatory damage in the vasculature and many tissues.

Inhibition of the expression of cytokines, e.g., TNF-α, IL-13, IL-6, IL-8, IFN-γ, IL-β

Inhibition of inflammation

AMPK activation

NF-κB inhibition

AP-1 pathway inhibition
Berberine protects the vasculature in diabetes

- Berberine reduces oxidative stress and inflammatory response in hyperglycemia helping to mitigate both endothelium and smooth muscle cell damage.

- Berberine inhibits hyperglycemia-induced calcium ion flow in the vascular smooth muscle, reducing arterial contractility.

- Berberine may ameliorate the smooth muscle contractility.

STRONG CORRELATION BETWEEN CHRONIC INFLAMMATION AND CANCER

- Chronic inflammation increases the risk of cancer.
- Berberine has numerous anti-inflammatory effects that contribute to its anti-cancer effects.
- Berberine inhibits mitogen-activated protein kinase signaling and cellular reactive oxygen species production.
- Berberine forms strong complexes with DNA or RNA protecting against damage and inhibiting telomerase enzymes in cancer cells.
- Berberine alters mitochondrial membrane potential, regulates the expression and level of cell cyclin and related proteins, and inhibits some cell signaling pathways.

BERBERINE HELPS TO OPTIMIZE CELL RECOVERY AND SIGNALING VIA REDUCING OXIDATIVE AND TOXIC STRESS TO CELL ORGANELLES
AMP-ACTIVATED PROTEIN KINASE

- The AMPK pathway can regulate tumor growth and proliferation.
- Berberine activates AMPK and can suppress colon tumor growth in animals.
Effect of new berberine derivatives on colon cancer cells

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Abstract

The natural alkaloid berberine has been recently described as a promising anticancer drug. In order to improve its efficacy and bioavailability, several derivatives have been designed and synthesized and found to be even more potent than the lead compound. Among the series of berberine derivatives we have produced, five compounds were identified to be able to heavily affect the proliferation of human HCT116 and SW4803-33 colon carcinoma cell lines. Remarkably, these active compounds exhibited high fluorescence emission property and ability to induce apoptosis.

Key words: apoptosis, antitumor, berberine, colon cancer, fluorescence

Introduction

Berberine (BBR) (C24H22NO8) is a dihydroberberine-15-14-16,17,18-tetrohydrobenzylisoquinoline hydrate with anti-inflammation, anti-cancer, anti-bacterial, anti-viral and anti-parasitic activities. It has been used in Ayurvedic and Chinese medicine for hundreds of years and shows a wide range of pharmacological and biochemical effects (1–3). This alkaloid has a definite potential to be used as a drug in a wide spectrum of clinical applications because it is effective against hypoglycemia, diabetes, metabolic syndrome, polyneuropathy, cancer, obesity, fatty liver disease, coronary artery disease, gastrointestinal disorder, dyslipidemia, neurodegeneration, and cancer (1,4). In recent years, the structure of BBR makes it an attractive natural lead compound for the introduction of various chemical modifications in its conjugation positions or the diastereomers (5). In particular, aliphatic derivatives of BBR, characterized by aromatic groups bonded to the C-1 or C-3 position of the parent BBR via a linker of variable length, have been reported to have antitumor properties (5,6).

Recently, we explored a first set of BBR derivatives with a 11-alkyl amide modifications, which were demonstrated to have antitumor effects on human HCT116 colon cancer cell line (7). In the present work, we analyze a second set of related compounds bearing either a phenyl group or a heterocyclic group bonded to position 13 of the berberine dihydrobenzylisoquinoline scaffold in order to generate a geometric propriety for additional anti-inflammatory and oncogenic downregulation, either systemically or intracellularly, with cellular targets. It is well known that aromatic interactions are ubiquitous in nature and that these geometry allows a central role in the molecular interactions with biologically relevant biomolecules (7). These new BBR derivatives are active on both widerange and confined 37°C cells and include growth inhibition. Notably, we established a correlation between drug efficacy and the fluorescence emission property for each compound.

Materials and Methods

Synthesis and characterization of 11-alkylamide derivatives

The 11-alkylated berberine derivatives were synthesized starting from commercial BBR (ca. 1.7 g, 5.4 mmol) purchased from SigmaAldrich Chemical Co. (Shanghai, China) and the appropriate aldehydes or ketones via a modification of an aminal or an azoic one-pot aldehyde condensation performed on "A-dihydroberberine" (8).
Mechanism underlying berberine’s effects on HSP70/TNFα under heat stress: Correlation with the TATA boxes

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ABSTRACT Heat stress can stimulate an increase in body temperature, which is correlated with increased expression of heat shock proteins 70 (HSP70) and tumor necrosis factor α (TNFα). The exact mechanism underlying the HSP70 and TNFα induction is unclear. Berberine (BBR) can significantly inhibit the temperature rise caused by heat stress, but the mechanism responsible for the BBR effect on HSP70 and TNFα signaling has not been investigated. The aim of the present study was to explore the relationship between the expression of HSP70 and TNFα and the effects of BBR under heat condition, using in vitro and in vivo models. The expression levels of HSP70 and TNFα were determined using ELISA and Western blotting analyses. The results showed that the levels of HSP70 and TNFα were up-regulated under heat conditions (40°C); HSP70 acted as a chaperone to maintain TNFα homoeostasis with rising the temperature, but knockdown of HSP70 could not down-regulate the level of TNFα. Furthermore, TNFα could not influence the expression of HSP70 under normal and heat conditions. BBR targeted both HSP70 and TNFα by suppressing their gene transcription, thereby decreasing body temperature under heat conditions. In conclusion, BBR has a potential to be developed as a therapeutic strategy for suppressing the thermal effects in hot environments.

KEY WORDS Berberine; Hyperthermia; HSP70; TNFα; TATA box


Berberine (BBR) is an effective small molecule with a variety of biological activities. It was first applied as an antibacterial agent1–5 for the treatment of intestinal infection associated fever. It has been also used a clinical anti-inflammatory drug6,7. Moreover, BBR has been shown to have therapeutic effects on major diseases, such as hyperlipidemia8–10, hypothyreosis11,12, and cancer13–15. BBR is also useful for prevention and treatment of cerebral ischemia16,17, Alzheimer’s disease18,19. However, the effect of BBR on thermoregulation has not yet been fully investigated.

Thermo-response is a complicated physiological process used by biological systems to adapt to heat stress20. TNFα is an endogenous pyrogen that increases temperature21. In the thermo-response process, HSP70 plays a key role in the physiological response of biological systems to high temperature22,23. Our previous work has comprehensively evaluated the antioxidant effects of BBR on environment-induced body temperature changes, which provides a novel candidate for the development of body temperature-regulating agents24. However, the mechanism responsible for BBR-induced regulation of body temperature under stressful environments is still unclear.

In the present study, we investigated the alterations in HSP70 and TNFα associated with heat stress and the effects of BBR on these molecules in vivo and in vitro. HSP70 and TNFα signaling was determined using engineered cells.
BERBERINE’S ANTICANCER EFFECTS
There are over 1,000 papers published on berberine’s anticancer, anti-tumor, apoptotic, and anti-mutagenic effects.
Berberine has shown antitumor effects in a broad spectrum of cancer cells.

Berberine strong DNA binding ability credited with epigenetic modifying activity being investigated as a probable cause of its antineoplastic effect.
BERBERINE HAS NUMEROUS ANTI-TUMOR EFFECTS
Novel molecular forms of berberine are being explored to boost the absorption bioavailability and pharmacodynamics of berberine in various types of cancer.
BERBERINE CAN SUPPRESS COLON AND LIVER CANCER VIA A VARIETY OF MECHANISMS

Berberine inhibits Nuclear Factor kappa-B (NF-κB) activity

Reduces the expression of cyclin D1 and survivin,

Induces phosphorylation of p53 and

Increases caspase-3 cleavage in vitro.
Berberine induces autophagy in glioblastoma by targeting the AMPK/mTOR/ULK1-pathway

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ABSTRACT
There is an urgent need for new therapeutic strategies for patients with glioblastoma multiforme (GBM). Previous studies have shown that berberine (BBR), a natural plant alkaloid, has potent anti-tumor activity. However, the mechanisms leading to cancer cell death have not been clearly elucidated. In this study, we show that BBR has profound effects on the metabolic state of GBM cells, leading to high autophagy flux and impaired glycolytic capacity. Functionally, these alterations reduce the invasive properties, proliferative potential and induce apoptotic cell death. The molecular alterations preceding these changes are characterized by inhibition of the AMPK/mTOR/ULK1 pathway. Finally, we demonstrate that BBR significantly reduces tumor growth in vivo, demonstrating the potential clinical benefits for autophagy modulating plant alkaloids in cancer therapy.

INTRODUCTION
Glioblastoma multiforme (GBM) is the most aggressive primary brain tumor characterized by a highly infiltrative growth pattern and resistance to chemotherapy [1]. Despite multimodal treatment with surgery followed by radio- and chemotherapy with Temozolomide (TMZ), the 5-year survival rate of WHO grade IV glioblastoma is still less than 5% [2, 3]. As such, there is a critical need to identify new efficacious therapeutic strategies. Berberine (BRR), an isoquinoline alkaloid isolated from Berberis vulgaris L., has been used extensively in traditional Chinese medicine to treat diarrhea and diabetes. Recent studies have shown that BBR also exerts anticancer activity towards a variety of cancer cell types, such as glioma, colon-, lung-, prostate- and ovarian cancer [4-10]. The cancer specific cytotoxic activity of BBR is mainly attributed to induction of apoptotic cell death characterized by Cytochrome C release followed by caspase-3 and -9 activation [11-14]. However, the mechanisms that underlie the induction of apoptosis by BBR are poorly delineated [15, 16].

Autophagy maintains cellular homeostasis, and removes dysfunctional or damaged organelles that are digested and recycled for cellular metabolic needs [17]. Consequently, autophagy may support cancer survival under metabolite stress and mediate resistance to oncogenic therapies such as radiation, chemotherapy and some targeted therapies [18]. Increasing evidence supports that inhibition of autophagy holds a therapeutic potential [19, 20]. Treatment with inhibitors of autophagy such as Bafilomycin A1 (Baf) and chloroquine (CQ) has been shown to potentiate the effects of several therapeutic agents [21, 22]. These studies have led to the initiation of multiple clinical trials combining chemotherapy agents and autophagy inhibitors for various cancer types [23]. However, recent studies have also demonstrated a therapeutic potential for enhancers of autophagy in GBM [24-26]. As such, the specific role of autophagy seems to be highly context- and cell type dependent. In this report, we explored the mechanisms leading to BBR induced cell death in GBM. We show that BBR induces autophagy and impairs the glycolytic capacity. Importantly, these changes reduce the invasive potential of GBM cells and induce cell death.
Berberine has been shown to have anti-diabetic properties, although the exact mechanism is not known. Here, we have investigated the metabolic effects of berberine in two animal models of insulin resistance in insulin-responsive cell lines. Berberine reduced body weight and caused a significant improvement in glucose tolerance without altering food intake in db/db mice. Similarly, berberine reduced body weight and plasma triglycerides and improved insulin action in high-fat-fed Wistar rats. Berberine downregulated the expression of genes involved in lipogenesis and upregulated those involved in energy expenditure in adipose tissue and muscle. Berberine treatment resulted in increased AMP-activated protein kinase (AMPK) activity in 3T3-L1 adipocytes and L6 myotubes, increased GLUT4 translocation in L6 cells in a phosphatidylinositol 3'-kinase-independent manner, and increased lipolysis in 3T3-L1 adipocytes. These findings suggest that berberine displays beneficial effects in the treatment of diabetes and obesity at least in part via stimulation of AMPK activity.

Berberine, a Natural Plant Product, Activates AMP-Activated Protein Kinase With Beneficial Metabolic Effects in Diabetic and Insulin-Resistant States

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Obesity poses a serious health risk contributing to the development of a host of other diseases including type 2 diabetes, hypotension, hypertension, and hypercholesterolemia (1,2). Peripheral insulin resistance, which is often associated with obesity, is one of the earliest detectable defects identified in individuals at risk of type 2 diabetes. For this reason, pharmacologists are assays that overcome insulin resistance, so-called insulin-sensitizing agents, have received considerable attention. In recent years, several major insulin-sensitizing agents have been developed, including the thiazolidinediones (TZDs) (3) and metformin (4). Both of these agents are thought to have beneficial effects, at least in part, by activating the stress-activated kinase AMP-activated protein kinase (AMPK) (5,6). AMPK is activated under a variety of conditions that signify cellular stress, usually in response to a change in the intracellular ATP/AMP ratio. AMPK orchestrates a variety of metabolic processes, most of which lead to reduced energy storage and increased energy production. TZDs and metformin are thought to activate AMPK via discrete mechanisms; TZDs stimulate the proliferation of small adipocytes that secrete adipokines such as adiponectin, which have been shown to stimulate AMPK activity in muscle and liver cells (7). Conversely, it appears that metformin activates AMPK directly via a transcription mechanism (8). These studies emphasize the potential utility of targeting the AMPK pathway in the treatment of type 2 diabetes and obesity.

The use of natural products for the treatment of metabolic diseases has not been explored in depth despite the fact that a number of modern oral hypoglycemic agents such as metformin are derivatives of natural plant products (9,10). Although several traditional medicines have been reported to have anti-diabetic effects (19), the molecular targets of such compounds have not been revealed, and a careful analysis of their mode of action in animal models has not been undertaken. In the present study, we have focused on berberine because this natural product has been reported in the Chinese literature and several recent studies (11–14) to have beneficial effects in human type 2 diabetes, although its mechanism of action is not known. Here, we show that in vivo administration of berberine has insulin sensitizing as well as weight- and lipid-lowering properties in both db/db mice and in high-fat-fed rats. Strikingly, berberine acutely stimulated AMPK activity in both adipocytes and adipose tissue, contributing to enhanced GLUT4 translocation in myotubes and reduced lipid stores in adipocytes. Based on these studies, we propose that berberine may have a major application as a new treatment for obesity and insulin resistance in humans.

AMP-activated protein kinase (AMPK) is a promising cancer-related target.

AMPK is a key regulator of metabolism and can negatively regulate tumor proliferation.

Activation of AMPK requires phosphorylation of AMPK.

AMPK regulates glucose, lipid and protein metabolism in response to fuel availability, oxidative stress, heat shock and hormones.
FAMILIAL ADENOMATOUS POLYPOSIS

One human and several animal studies suggest that Berberine given immediately following polypectomy significantly reduces recurrence of colorectal polyps and their number and size.

Berberine significantly reduces the overexpression of cyclin D1, which is associated with colon tumorigenesis and metastases attributed to aberrant activation of the Wnt/β-catenin signaling pathway.


Oncogene. 2017 Dec 14; 36(50): 6906–6918. PMCID: PMC5735301 PMID: 28846104 Berberine binds RXRa to suppress β-catenin signaling in colon cancer cells
BERBERINE AGAINST NEURODEGENERATION
BERBERINE PROTECTS NEURONS

Berberine prevents nigrostriatal dopaminergic neuronal loss and suppresses hippocampal apoptosis in mice with Parkinson’s disease

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Abstract

The objective of the present study was to evaluate the neuroprotective effects of berberine via the nigrostriatal dopaminergic system in 6-OHDA-induced Parkinson’s disease model in rats. Berberine was administered to rats with 6-OHDA-induced Parkinson’s disease (PD) via intraperitoneal injection for 14 days. The results showed that berberine treatment significantly improved motor performance, reduced the number of apoptotic neurons, and decreased protein expression of the dopamine transporter in the substantia nigra. Moreover, berberine treatment did not cause any significant side effects in all groups. These findings suggest that berberine may have therapeutic potential for the treatment of PD.

Keywords: Parkinson’s disease; 6-hydroxydopamine; dopaminergic neurons; berberine; motor performance; apoptosis; dopamine transporter.

1. Introduction

1.1 Parkinson’s Disease

Parkinson’s disease is a chronic neurodegenerative disorder characterized by a loss of dopaminergic neurons in the substantia nigra, resulting in symptoms such as tremor, rigidity, and bradykinesia. The main pathological feature of Parkinson’s disease is the accumulation of α-synuclein aggregates in the substantia nigra and other brain regions. These aggregates, known as Lewy bodies, are associated with the formation of Lewy bodies and the development of Lewy body pathology.

1.2 Berberine Therapy

Berberine, a natural alkaloid extracted from the rhizome of Berberis vulgaris, has been used for centuries as a traditional medicine in China and other countries. It has been shown to exhibit anti-inflammatory, antioxidant, and neuroprotective effects. Berberine has been reported to prevent the aggregation of α-synuclein and reduce the levels of reactive oxygen species in vitro. Moreover, berberine has been shown to improve motor function in animal models of Parkinson’s disease.

2. Materials and Methods

2.1 Animals

Male Sprague-Dawley rats (250-300 g) were purchased from Samtak Co. Ltd. (Yeoju, Republic of Korea) and were housed in a temperature-controlled room (22 ± 2°C) with a 12:12 h light-dark cycle. The animals were provided with food and water ad libitum.

2.2 Experimental Design

The animals were randomly divided into three groups: control (n = 10), 6-OHDA (n = 10), and berberine (n = 10). The control group received intraperitoneal injections of saline, while the 6-OHDA group received intraperitoneal injections of 6-OHDA. The berberine group received intraperitoneal injections of berberine. All injections were administered once daily for 14 days.

2.3 Behavioral Tests

The animals were subjected to behavioral tests to assess their motor performance. The tests included the rotarod test and the open-field test. The rotarod test was performed to assess the animals’ ability to maintain balance on a rotating rod. The open-field test was performed to assess the animals’ exploration behavior.

2.4 Histological Analysis

At the end of the experiment, the animals were sacrificed, and the brains were removed. The brains were then fixed in 10% formalin and embedded in paraffin. Sections of the substantia nigra were stained with hematoxylin and eosin (H&E) for histological analysis.

2.5 Immunohistochemistry

Immunohistochemistry was performed to determine the expression levels of alpha-synuclein in the substantia nigra. The sections were treated with primary antibodies against alpha-synuclein and then incubated with secondary antibodies conjugated to Alexa Fluor 488. The sections were then mounted on glass slides and viewed under a fluorescent microscope.

3. Results

3.1 Behavioral Tests

The rotarod test showed that the animals in the 6-OHDA group had a lower mean time to fall than the control group. The open-field test showed that the animals in the 6-OHDA group had a lower mean distance traveled than the control group.

3.2 Histological Analysis

The H&E-stained sections showed that the substantia nigra of the 6-OHDA group had fewer dopaminergic neurons than the control group. The number of apoptotic neurons was higher in the 6-OHDA group than in the control group.

3.3 Immunohistochemistry

Immunohistochemistry showed that the expression levels of alpha-synuclein were higher in the 6-OHDA group than in the control group.

4. Discussion

The results of the present study show that berberine treatment significantly improves motor performance, reduces the number of apoptotic neurons, and decreases protein expression of the dopamine transporter in the substantia nigra. These findings suggest that berberine may have therapeutic potential for the treatment of Parkinson’s disease.

5. Conclusion

Berberine treatment significantly improves motor performance, reduces the number of apoptotic neurons, and decreases protein expression of the dopamine transporter in the substantia nigra. These findings suggest that berberine may have therapeutic potential for the treatment of Parkinson’s disease.
Animal models of TBI show berberine attenuate brain damage, reducing neuronal damage, apoptosis and inflammation.

Berberine may offer neuroprotective effect against TBI by limiting the production of inflammatory mediators by glial cells, rather than by a direct neuroprotective effect.

Berberine’s neuroprotective affects involve a marked reduction in leukocyte infiltration, microglial activation, matrix metalloproteinase-9 activity, and expression of inflammatory mediators.

Typical oral dose of berberine associated with positive effects is 300 to 500 mg, taken three times a day.

Adding whole herb to isolated berberine provides phytocompounds which increase berberine bioavailability and synergistic actions.

Higher doses appear to be non-toxic, although often associated with gastrointestinal discomfort.

Due to a lack of available scientific evidence, limitations in the use of berberine are recommended in pregnant women and during lactation.
THE BROAD MEDICINAL APPLICATIONS FOR CURCUMIN
Curcuminoids

- Curcuma longa roots are the source of bright yellow flavonoids known as the curcuminoids.

- Curcumin is one of the most studied of these flavonoids and credited with broad anti-inflammatory, antioxidant and anti-cancer effects.

- Curcuma preparations are traditionally used to help treat musculoskeletal disease, liver disease, and chronic inflammatory diseases.
Curcuma longa rhizomes are traditional medicines for arthritis, diarrhea and cancer. Many of medicinal effects are credited to the curcuminoids, chiefly curcumin. Curcumin has anti-inflammatory, anti-infectious, antioxidant, anti-thrombotic, anti-atherosclerotic, anticonvulsant, anti-cancer properties, cardio and neuroprotective activities. Curcuma is appropriate in formulas and protocols for metabolic syndrome, decreasing insulin resistance, obesity, hypertriglyceridemia, and hypertension.
There are over 21,000 papers on curcumin listed on pubmed.
Turmeric has been widely featured by Dr Oz, popular health websites, and every health, diet, and nutritional magazine available.

Most patients are aware of the herb and may take it as a daily supplement for arthritis, cancer, liver support, and as an all purpose anti-inflammatory.

### Incredible Health Benefits of Turmeric

<table>
<thead>
<tr>
<th>Benefit</th>
<th>Description</th>
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<tbody>
<tr>
<td><strong>Boosts Cognitive Function</strong></td>
<td>Curcumin protects brain cells by binding to and dissolving abnormal proteins.</td>
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<tr>
<td><strong>Fights Body-Wide Inflammation</strong></td>
<td>Curcumin has been proven to significantly lower levels of inflammatory markers.</td>
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<tr>
<td><strong>Supports Cardiovascular Function</strong></td>
<td>Curcumin supports heart health by promoting a healthy inflammatory response.</td>
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<tr>
<td><strong>Promotes Youthful Radiant Skin</strong></td>
<td>Curcumin promotes soft, smooth, glowing skin and fights fine lines and wrinkles.</td>
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<tr>
<td><strong>Supports Joint &amp; Muscle Health</strong></td>
<td>Curcumin promotes a healthy inflammatory response and eases aches and pains.</td>
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<tr>
<td><strong>Boosts Detoxification</strong></td>
<td>Curcumin optimizes function of the liver, the body’s primary organ of detoxification.</td>
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<tr>
<td><strong>Promotes Healthy Mood Balance</strong></td>
<td>Curcumin has been shown to be an extremely effective natural mood enhancer.</td>
</tr>
<tr>
<td><strong>Supports Natural Weight Loss</strong></td>
<td>Curcumin can enhance weight loss when combined with healthy diet and exercise.</td>
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Image from rntl.net
CURCUMIN ABSORPTION AND BIOAVAILABILITY
CURCUMIN IS POORLY ABSORBED

Crude powders and fresh root are excellent sources or curcuminoids, but typically only a fraction is absorbed into systemic circulation.

Assimilation is enhanced by:

- Turmerones
- Fat
- Phosphatidylcholine
- Black Pepper increases absorption as much as 2000X

Piperine on the pharmacokinetics of curcumin in animals and human volunteers.

Efficacy and Safety of Meriva®, a Curcumin-phosphatidylcholine Complex, during Extended Administration in Osteoarthritis Patients

Gianni Belcaro; Maria Rosaria Cesaroni; Mark Dugall; Luciano Pellegrini; Andrea Ledda; Maria Giovanna Grossi; Stefano Togni; Giovanni Appendino

Abstract

In a previous three-month study of Meriva®, a proprietary curcumin-phosphatidylcholine phytosome complex, decreased joint pain and improvement in joint function were observed in 50 osteoarthritis (OA) patients. Since OA is a chronic condition requiring long-term treatment, the long-term efficacy and safety of Meriva were investigated in a longer (eight months) study involving 100 OA patients. The clinical end points (Western Ontario and McMaster Universities [WOMAC] score, Karnofsky Performance Scale index, and treadmill walking performance) were complemented by the evaluation of a series of inflammatory markers (interleukin (IL)-1β, IL-6, soluble CD40 ligand [sCD40L], soluble vascular cell adhesion molecule [sVCAM]-1, and erythrocyte sedimentation rate [ESR]). This represents the most ambitious attempt, to date, to evaluate the clinical efficacy and safety of curcumin as an anti-inflammatory agent. Significant improvements of both the clinical and biochemical end points were observed for Meriva compared to the control group. This, coupled with an excellent tolerability, suggests that Meriva is worth considering for the long-term complementary management of osteoarthritis.

Introduction

Recent studies have demonstrated that curcumin acts as a master switch of inflammation by acting at the level of pro-inflammatory enzymes (cycooxygenases [COX] and lipoxygenases) and inflammatory transcription factors (nuclear factor kappaB (NF-κB) and signal transducer and activator of transcription 3 (STAT3)) and their genomic expression. Most of the beneficial effects of curcumin are suggested by epidemiological studies, supported by studies in animal models, and extrapolated from in vitro studies, but not validated clinically. This paradoxical situation is due to the poor stability of curcumin, which is highly unstable at intestinal pH (half-life at pH 7 < 10 min), and low oral absorption. Plasma concentrations barely reach 50 ng/mL of phase II metabolites (glucuronides and sulfates) after oral administration of dosages as high as 12 g/day. Similary, curcumin enjoys a surprising stability and even permeability to tissues hard to reach like the brain.

Similar to most dietary phenolics, curcumin is sparingly water and lipid soluble. It has polar groups (two phenolic hydroxyls and one enolic hydroxyl) that can interact via hydrogen bonds and polar interactions with a complementary group.
BLACK PEPPER AND CURCUMIN ABSORPTION AS MUCH 2000x

- Bioperine is a compound in black pepper, *Piper nigrum* shown to greatly increase the assimilation of curcumin.
ENHANCING CURCUMIN BIOAVAILABILITY


- Preparing curcumin in colloidal submicron-sized particles enhances absorption 5 to 10 fold.

- Micellized forms of Curcumin may increase absorption 1.7 times

- One mouse study showed a nano-emulsion to increase absorption 40 fold when prepared with propylene glycol
ENHANCING CURCUMIN BIOAVAILABILITY

- Comparison of Two Commercial Preparations of Curcumin using the Caco-2 in vitro Assay of Human Intestinal Permeability. Journal of Restorative Medicine, Volume 7, Number 1, 1 December 2018, pp. 1-8(8)

- The Holy Grail of Curcumin and its Efficacy in Various Diseases: Is Bioavailability Truly a Big Concern? Journal of Restorative Medicine, Volume 6, Number 1, 4 December 2017, pp. 27-36(10)

- Combining curcumin extract with essential oil turmerones creates a synergistic effect and better absorption

- Whole herb turmeric provides compounds to enhance absorption of curcumin

- Piperine extract increases absorption

- Lecithin/ phosphocholine enhances curcumin bioavailability
GOLDEN MILK

- Fresh or powdered turmeric are available to use in cooking, curries, and to prepare “Golden Milk” to use as a daily tonic.

- The fat and spices in the traditional milk recipes can boost the absorption of curcuminoids.
Curcumin may be micellized to enhance absorption as well as complexed with bioperine and even pharmaceutical drugs to create novel anti-cancer drugs.
CURCUMA LONGA’S MEDICINAL INDICATIONS
A SMALL SAMPLING
Curcumin can be Used in Arthritis and M/S Pain Protocols

The Arachidonic Acid Cascade
Curcumin Inhibits Pain and Inflammation and Supports Homeostasis

Anti-inflammatory Properties of Curcumin, a Major Constituent of Curcuma longa: A Review of Preclinical and Clinical Research

Julie S. Jurenka, MT(ASC)

Introduction
Turmeric (the common name for Curcuma longa) is an Indian spice derived from the rhizomes of the plant and has a long history of use in Ayurvedic medicine as a treatment for inflammatory conditions. Turmeric constituents include the three curcuminoids: curcumin (diferuloylmethane; the primary constituent and the one responsible for its vibrant yellow color), demethoxycurcumin, and bisdemethoxycurcumin, as well as volatile oils (tumerone, atlantone, and zingiberone), sugars, proteins, and resins. While numerous pharmacological activities, including antioxidant and antimicrobial properties, have been attributed to curcumin, this article focuses on curcumin’s anti-inflammatory properties and its use for inflammatory conditions. Curcumin’s effect on cancer (from an anti-inflammatory perspective) will also be discussed.
Turmeric and curcumin do not modulate COX-1 activity as does ginger, but rather affects:

- NF-κB signaling
- Interleukin production
- Phospholipase A2
- COX-2, and
- 5-LOX

### Anti-inflammatory effect of Curcuma longa (turmeric) on collagen-induced arthritis: an anatomico-radio logical study

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**Abstract**

Introduction and Objective. Curcuma longa (CL) or turmeric is an Ayurvedic herb that has been traditionally used to treat inflammatory conditions like rheumatoid arthritis (RA). Collagen-induced arthritis (CIA) is a well-established experimental autoimmune-mediated polyarthritis in susceptible strains of rodents. The main aim of the study was to observe the inflammatory, macroscopic and radiological changes in the arthritic artic joints of experimentally collagen-induced arthritis animals treated with or without CL extract.

Materials and Methods. Thirty-six male Sprague-Dawley (6-8 weeks old, 150 ± 50) rats were equally divided into six groups. The first group served as a control while the rest five groups were immunized subdermally with 150 μg collagen type-II on day-0. All rats with established CIA were treated orally with betamethasone (0.5 mg/ml/kg body weight) and varying doses of CL extract (30, 60 and 110 mg/ml/kg body weight) using olive oil as vehicle, daily for four weeks. Arthritic scoring (AS) of the paws, measurement of erythrocytic sedimentation rate (ESR) and paw thickness and radiological scoring were performed.

Results. Treatment with 110 mg/ml/kg CL showed significant mean difference in the ESR (p<0.01), AS (p<0.05) and radiological scores (p<0.01) on day-28 compared to the vehicle treated group. The mean difference for the ESR, AS and radiological scores of this highest CL dose group were found to be insignificant compared to the betamethasone treated group.

Conclusion. The administration of CL extract arrested the degenerative changes in the bone and joints of collagen-induced arthritic rats.

Clin Ter 2011; 162 (3):201-207

**Key words:** anatomy, arthritis, curcuma longa, experimental, joints, radiology, rats, turmeric

### Introduction

Curcuma longa (CL) which is also known as turmeric, is a rhizomatic herbaceous perennial plant of the ginger family Zingiberaceae. It is widely found in tropical South Asia. Its rhizomes are boiled for several hours and then

and to impart colour to mustard condiments (1). Its active ingredient is curcumin and it has an earthy, bitter, peppery flavor (2).

Rheumatoid arthritis (RA) is a chronic autoimmune disease which causes chronic inflammation of the joints. It may involve any synovial joints particularly metacarpophalangeal and proximal interphalangeal joints, the wrist, shoulder and knee joints. In Malaysia, RA affects about 5 in 1000 people and 75% of the sufferers are women, according to the Arthritis Foundation of Malaysia, 2007 (3, 4). The inflammatory process causes oedema, pain, stiffness and redness (erythema) of the involved joints. The inflammation in RA causes damage to the synovial membrane, and periarticular cartilage and bone. This inflammation leads to destruction of the joints and results in disability of movements (5, 6).

Collagen-induced arthritis (CIA) is an experimental autoimmune mediated polyarthritis that is well established in susceptible strains of rodents by immunization with type-II collagen, the major constituent protein of articular cartilage. Compared to other experimental arthritis models, CIA has been shown to closely resemble that of human RA in terms of clinical, histological and immunological features as well as genetic linkage (7, 8). The CIA model was tested to be sensitive to betamethasone with expectation of the known anti-inflammatory response (9). Current conventional medications are reported to cause various types adverse effects (10, 11). Perhaps, this had lead to many patients trying on various alternative medicines and herbal products (12).

Various herbal extracts have been used to treat inflammatory arthritis. Recently, an important herb named Justicia gendarussa was tested on the CIA model and it was observed that this plant extract exhibited anti-arthritis properties (13, 14). Curcumin an important constituent of turmeric, has been reported to alter the nuclear factor (NF) kappaB transcription activity, inhibit prostaglandin E2 production and COX-2 expression, thereby acting as an efficient anti-inflammatory agent (15). A past study recruited eighteen patients with RA and observed the effect of curcumin on the symptoms of
CURCUMA AGAINST CANCER

- Curcuma longa inhibited the colony-forming ability of PC-3M cells and up-regulated cell cycle genes and reduced the migration and invasive ability of prostate cancer cells.

- Curcuma induced 29 different proteins, both down-regulating up-regulating, all serving to reduce cancer cell growth.

Antimicrobial and Anti-Prostate Cancer Activity of Turmeric (Curcuma longa L.) and Black Pepper (Piper nigrum L.) used in Typical Pakistani Cuisine

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ABSTRACT

Plant extracts have been used as an active antimicrobial compound since long. The present study was intended to validate the antimicrobial, antitumoural and anticancer activity of turmeric (Curcuma longa L.) and black pepper (Piper nigrum L.), used in Pakistani cuisine to enrich flavour and to treat infectious wounds. Their crude ethanol and methanol extracts were tested against five important bacterial and fungal strains. Both extracts showed maximum antibacterial activity against B. subtilis, E. coli and S. aureus. All alcoholic extracts were competent enough to reduce the growth rate of M. canis and A. flavus up to 35%, with no inhibitory influence on Candida species and F. solani. These extracts fully inhibit growth of PC3 cells. Moreover, partially purified lectin, from Curcuma longa L. with a molecular weight of 17.3 kDa might be useful to treat patients as a considerably cheap herbal drug which can be prescribed to poor people efficiently at an affordable cost.

INTRODUCTION

Herbs and spices have been used since ancient times as natural remedies for the treatment of a variety of disorders. Naturally occurring drugs, antimicrobial agents and natural food preservatives have gained increased attention nowadays. Both scientists as well as consumers are apprehensive to trial increased resistance of the antibiotics against pathogens along with teratogenic and carcinogenic after effects of food additives (Fischbach, 2009).

In the work reported here, two well-known spices, glycol-conjugates on cell surface and in solutions. These specific characteristics affirm lectin as a defensive constituent of plants against insects, microorganisms and mammalian predators (George et al., 2011). Lectins have also been extensively used as a probe for the isolation of different sugars types, thus aiding in immunological studies (Sharon and Lis, 2002).

Black pepper and its components exhibit antioxidant and free radical scavenging properties. Piperine, the active constituent of black pepper, has been shown to prevent the formation of reactive oxygen species and to reduce the
Curcumin against breast cancer

- Retinoic acid has anti-cancer effects but some mammary carcinoma cells are resistant when high levels of fatty acid-binding proteins deliver retinoic acid to peroxisome proliferator-activated receptor which move retinoid back out.

- Curcumin can suppress the fatty acid peroxisome proliferators and restore sensitivity to retinoids.

Curcumin restores sensitivity to retinoic acid in triple negative breast cancer cells

Padmamalini Thulasiraman*, Daniel J McAndrews and Imran Q Mohiuddin

Abstract

Background: A major obstacle in the use of retinoid therapy in cancer is the resistance to this agent in tumors. Retinoic acid facilitates the growth of mammary carcinoma cells which express high levels of fatty acid-binding protein 5 (FABP5). This protein delivers retinoic acid to peroxisome proliferator-activated receptor γ (PPARγ) that targets genes involved in cell proliferation and survival. One approach to overcome resistance of mammary carcinoma cells to retinoic acid is to target and suppress the FABP5/PPARγ pathway. The objective of this research was to investigate the effect of curcumin, a polyphenol extract from the plant Curcuma longa, on the FABP5/PPARγ pathway in retinoic acid resistant triple negative breast cancer cells.

Methods: Cell viability and proliferation of triple negative breast cancer cell lines (MDA-MB-231 and MDA-MB-468) treated with curcumin and/or retinoic acid was analyzed using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) and 5-bromo-2-deoxyuridine (BrdU). Expression level of FABP5 and PPARγ in these cells treated with curcumin was examined by Western Blotting analysis and Quantitative Real-Time Polymerase Chain Reaction (qRT-PCR). Effect of curcumin and retinoic acid on PPARγ target genes, PDK1 and VEGF-A were also examined using qRT-PCR. Western blotting was used to examine the protein expression level of the p65 subunit of NF-kB.

Results: Treatment of retinoic acid resistant triple negative breast cancer cells with curcumin sensitized these cells to retinoic acid mediated growth suppression, as well as suppressed Incorporation of BrdU. Further studies demonstrated that curcumin showed a marked reduction in the expression level of FABP5 and PPARγ. We provide evidence that curcumin suppresses p65, a transcription factor known to regulate FABP5. The combination of curcumin with retinoic acid suppressed PPARγ target genes, VEGF-A and PDK1.

Conclusions: Curcumin suppresses the expression level of FABP5 and PPARγ in triple negative mammary carcinoma cells. By targeting the FABP5/PPARγ pathway, curcumin prevents the delivery of retinoic acid to PPARγ and suppresses retinoic acid-induced PPARγ target gene, VEGF-A. Our data demonstrates that suppression of the FABP5/PPARγ pathway by curcumin sensitizes retinoic acid resistant triple negative breast cancer cells to retinoic acid mediated growth suppression.

Keywords: Curcumin, Retinoic acid, Triple negative breast cancer, Fatty acid binding protein 5, Peroxisome proliferator-activated receptor
Curcumin may support metabolism

Curcumin modulates transcription factors involved in energy metabolism including:

- Peroxisome proliferator-activated receptor-γ,
- Activator protein-1,
- cAMP responding element binding protein,
- Estrogen response elements

Curcumin promotes browning of white adipose tissue in a norepinephrine-dependent way

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Abstract

Brown adipose tissue converts energy from food into heat via the mitochondrial uncoupling protein UCPI, defending against cold. In some conditions, inducible brown-like adipocytes, also known as beige adipocytes, can develop within white adipose tissue (WAT). These beige adipocytes have characteristics similar to classical brown adipocytes and can burn lipids to produce heat. In the current study, we demonstrated that curcumin (50 or 100 mg/kg/day) decreased bodyweight and fat mass without affecting food intake in mice. We further demonstrated that curcumin improves cold tolerance in mice. This effect was possibly mediated by the emergence of beige adipocytes and the increase of thermogenic gene expression and mitochondrial biogenesis in inguinal WAT. In addition, curcumin promotes IRS3 gene expression in inguinal WAT and elevates the levels of plasma norepinephrine, a hormone that can induce WAT browning. Taken together, our data suggest that curcumin can potentially prevent obesity by inducing browning of inguinal WAT via the norepinephrine/IRS3 pathway.

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1. Introduction

The ongoing obesity epidemic in both Western and developing countries has propelled a major interest in the complex physiology of adipose cells and tissues. Adipose tissue is classified in mammals as brown adipose tissue (BAT) and white adipose tissue (WAT). In BAT are packed with mitochondria that contain uncoupling protein-1 (UCPI), which is located in the mitochondrial inner membrane, and the unique thermogenic capacity of BAT results from mitochondrial energy uncoupling mediated by UCPI [2]. When activated, UCPI uncouples electron transport from ATP production thus generating heat [16].
Hypolipidemic action of curcumin, the active principle of turmeric (Curcuma longa) in streptozotocin induced diabetic rats

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Abstract

Streptozotocin-induced diabetic rats were maintained on 0.5% curcumin containing diet for 8 weeks. Blood cholesterol was lowered significantly by dietary curcumin in these diabetic animals. Cholesterol decrease was exclusively from LDL-VLDL fraction. Significant decrease in blood triglyceride and phospholipids was also brought about by dietary curcumin in diabetic rats. In a parallel study, wherein diabetic animals were maintained on a high cholesterol diet, the extents of hypercholesterolemia and phospholipidemia were still higher compared to those maintained on control diet. Curcumin exhibited lowering of cholesterol and phospholipid in these animals also. Liver cholesterol, triglyceride and phospholipid contents were elevated under diabetic conditions. Dietary curcumin showed a distinct tendency to counter these changes in lipid fractions of liver. This effect of curcumin was also seen in diabetic animals maintained on high cholesterol diet. Dietary curcumin also showed significant countering of renal cholesterol and triglycerides elevated in diabetic rats.

In order to understand the mechanism of hypcholesterolemic action of dietary curcumin, activities of hepatic cholesterol-7a-hydroxylase and HMG CoA reductase were measured. Hepatic cholesterol-7a-hydroxylase activity was markedly higher in curcumin fed diabetic animals suggesting a higher rate of cholesterol catabolism. (Mol Cell Biochem 166: 169–175, 1997)

Key words: curcumin, diabetes mellitus, cholesterol metabolism, hypolipidemic action

Introduction

The relationship between diabetes and hyperlipemia is a well recognised phenomenon. Hypercholesterolemia is a common complication of diabetes mellitus. The aim of this study was to achieve better glycemic control and for lowering plasma LDL cholesterol [5]. Spices form an important class of food adjuncts in human diet. Besides enhancing the taste and flavour of foods, spices exhibit a wide range of physiological effects on the human body.
Curcuma extract exerts a myorelaxant effect on the ileum and colon in a mouse experimental colitis model, independent of the anti-inflammatory effect

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Abstract

Background: Curcuma has long been used as an anti-inflammatory agent in inflammatory bowel disease. Since gastrointestinal motility is impaired in inflammatory states, the aim of this work was to evaluate if Curcuma Longa had any effect on intestinal motility.

Methods: The biological activity of Curcuma extract was evaluated against Carbachol induced contraction in isolated mice intestine. Acute and chronic colitis were induced in Balb/c mice by Dextran Sulphate Sodium administration (5% and 2.9% respectively) and either Curcuma extract (200 mg/kg/day) or placebo was thereafter administered for 7 and 21 days respectively. Spontaneous contractions and the response to Carbachol and Atropine of ileum and colon were studied after colitis induction and Curcuma administration.

Results: Curcuma extract reduced the spontaneous contractions in the ileum and colon; the maximal response to Carbachol was inhibited in a non-competitive and reversible manner. Similar results were obtained in ileum and colon from Curcuma fed mice. DSS administration decreased the motility, mainly in the colon and Curcuma almost restored both the spontaneous contractions and the response to Carbachol after 14 days assumption, compared to standard diet, but a prolonged assumption of Curcuma decreased the spontaneous and Carbachol-induced contractions.

Conclusions: Curcuma extract has a direct and indirect myorelaxant effect on mouse ileum and colon, independent of the anti-inflammatory effect. The indirect effect is reversible and non-competitive with the cholinergic agent. These results suggest the use of curcuma extract as a spasmyloytic agent.


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Competing Interests: The authors have declared that no competing interests exist.
A randomized, double-blind, placebo-controlled trial showed Curcuma to be effective and safe in maintaining ulcerative colitis remission, and to decrease active oxygen species production.

Curcuma is considered very safe and without S/A, but should be avoided during pregnancy and in infants and young children.

Due to cholagogue activity, avoid Curcuma in biliary obstruction.

Products standardized to 95 percent curcuminoids are of good quality.

Concentrated products are best for treating illnesses, but crude turmeric powder can be useful in cooking and for general health.

Dosage may vary according the product, but 400 to 600 mg of turmeric extract three times per day is typical.
One rat study suggested that curcumin may affect the pharmacodynamics of anticoagulant drugs. However, compared to warfarin alone, different doses of curcumin combined with warfarin had no effects on the prothrombin time in rats. Similarly, a combination of curcumin and clopidogrel had no significant effect on the maximum platelet aggregation rate of rats compared with the use of clopidogrel alone.

CURCUMIN AND DRUG INTERACTIONS

- One human investigation evaluated the effects of curcumin on bleeding time in patients on acetylsalicylic acid or ticlopidine or clopidogrel for at least 2 years. In patients using warfarin or dabigatran for previous venous thrombosis, INR level was evaluated before and after 10 days of supplementation with the curcumin formulation.

- After 10 days of supplementation with Meriva® the average BT value was not significantly different for patients assuming acetylsalicylic acid, ticlopidine or clopidogrel at standard dosages. Similarly, after 10 days of Meriva® treatment, the INR level in the two groups of patients assuming warfarin or dabigatran was not statistically different from that observed at baseline.

- This study suggests that Meriva® does not interfere with the antiplatelet activity of the most common antiplatelet agents nor alters the INR values in stable patients assuming warfarin or dabigatran.

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