BERBERINE AND CURCUMIN
Herbal Superstars

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Financial Disclosure: Consultant to Restorative Formulations
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 HAS NUMEROUS ACTIONS AND CAN BE USED TO TREAT:

- Gastrointestinal Infections
- Familial Adenomatous Polyposis
- Liver Disease
- Elevated Lipids
- Diabetes
- Cancer
- Obesity
- Traumatic Brain Injury
EXPLODING RESEARCH ON BERBERINE

- 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 (BBR) is considered a multi-target drug that has significant advantages. In contrast to its significant pharmacological effects in vivo, the plasma level of BBR is very low. Our previous work revealed that water-soluble berberine (WBBR) could be an absorbable form of BBR in the intestine, and butyrate 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 beagle dogs after oral administration of BBR by single (50 mg/kg) or multiple doses (50 mg/kg/d) for 7 days. GC-MS, GC, LC-MS/MS, and LC-MS²-IT-TOF were used to detect BBR, butyrate and BBR as well as its Phase I and II metabolites, respectively. The results showed that BBR was not detected in dog plasma but was excreted in small amounts in the feces of dogs examined on days 5 and 7. Butyrate was generated by gut bacteria and increased by 1.3- and 1.2-fold in plasma or feces, respectively, after 7 days of BBR treatment compared to the levels before treatment. Changes of intestinal bacterial composition were analyzed by 16S RNA gene analysis. The results presented that dogs treated with BBR for 7 days increased both the abundance of the butyrate- and the norribacteraeae-producing bacteria. We also identified chemical structures of the Phase I and II metabolites and analyzed their contents in beagle dogs. Eleven metabolites were detected in plasma and feces after BBR oral administration (50 mg/kg) to dogs, including 6 metabolites of Phase I and II metabolites of Phase II. The pharmacokinetic profile indicated that the concentration of BBR in plasma was low, with a Cmax value of 36.86 ± 23.45 μg/mL. The relative content of glucuronide conjugates (M1) was higher than those of other metabolites (M1, M2, M12, and M14) in plasma. BBR was detected in feces, with high excreted amounts on day 3 (26.05 ± 17.09 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 BBR, which is beneficial for discovery of drugs with poorly absorbable but good therapeutic efficacy.

Keywords: berberine, gut microbiota, butyrate, metabolites, GC-MS, LC-MS²-IT-TOF, 16S RNA gene analysis

Berberine can help treat Infectious diarrhea and gastroenteritis caused by bacterial and intestinal parasites.

Berberine supports a healthy intestinal microbiome, deterring pathogenic species, yet supporting beneficial flora.
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.

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

Reduces Cholesterol

PlantMedicineNews.com
Berberine offers broad metabolic support, improving lipid and carbohydrate metabolism.
BERBERINE HAS ANTIDIABETIC EFFECTS

Berberine activates fatty acid receptor GPR40 contributing to the antidiabetic action.

Berberine activates thermogenesis in white and brown adipose tissue via AMPK and PGC-1a, 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 protect against inflammatory damage in the vasculature and many tissues.
**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
The AMPK pathway can regulate tumor growth and proliferation.

Berberine activates AMPK and can suppress colon tumor growth in animals.
BERBERINE AGAINST COLON CANCER

- Colorectal cancer, a leading and cause of cancer death, has been linked to inflammation obesity.

- Berberine decreases mutagenesis following exposure to carcinogens, and induces apoptosis in colorectal cancer cell lines.

- Berberine activates AMP-activated protein kinase (AMPK), a major regulator of metabolic pathways.

**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 SW480-83 colon carcinoma cell lines. Remarkably, these active compounds exhibit high fluorescence emission property and ability to induce apoptosis.

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

**Introduction**

Berberine chloride (BBER, C_{30}H_{26}ClNO_7) is a protoberberine alkaloid isolated from many well-known medicinal plants. It has been used as an ayurvedic and Chinese medicine for hundreds of years and shows a wide range of pharmacological and biological effects [1-5]. This alkaloid has a definite potential to be used as drug in a wide spectrum of clinical applications because it is effective against hyperlipidemia, diabetes, metabolic syndrome, polyuria, stress, obesity, fatty liver disease, coronary artery disease, gastrointestinal disorders, dyslipidemia, hyperglycemia, neuropathic pain, and cancer [1-2]. On the contrary, the structure of BBER makes it an attractive natural lead compound for the introduction of novel chemical modifications at appropriate positions of the skeleton [1]. In particular, derivative derivatives of BBER have been designed to have antitumor properties (Lisas).

Recently, we synthesized a first set of BBER derivatives with 13-side alkyl modified, which were demonstrated to exert antitumor effects in human PC-3 prostate cancer cell lines [2]. In the present work, we analyzed a second set of related compounds bearing either a phenyl group or a 4-hydroxyphenyl group linked to position 13 of the berberine skeleton through a short carbon linker of variable length (Fig. 1), trying to generate a geometric predisposition for additional binding to covalent or noncovalent aromatic interactions, with consideration both electronically or sterically, with cellular targets. It is well known that aromatic interactions are ubiquitous in nature and that their geometry does a central role in the molecular interactions with biologic macromolecules [5]. These new BBER derivatives are active on both与否and xenografts of colon cell lines and induce apoptosis. Remarkably, we established a correlation between drug efficacy and the fluorescence emission property for each compound.

**Materials and Methods**

- Synthesis and characterization of 13-(alkylaryl) derivatives

The 13-(alkylaryl) berberine derivatives were synthesized starting from commercial BBER by various chemical methods. The 4-(4-chlorophenyl) compound was purchased from Shunshi Chen TKK Pharmaceutical Co., Shanghai, China, and the appropriate alkylchlorobenzenesubstituted via a modification of an annelated synthesis-alkylation condensation performed on 4-A dibromoketenate [6].

Berberine affects on Heat Shock proteins and TNF alpha reducing inflammatory damage and offering possible anti-mutagenic affects.
BERBERINE’S ANTICANCER EFFECTS
GROWING ANTICANCER RESEARCH ON BERBERINE

- 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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Keywords: berberine, glioblastoma, autophagy, apoptosis, metabolism

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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, colorectal-, 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 metabolic stress and mediate resistance to anticancer 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 chemotherapeutic 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 impacts 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 risk of side effects is not known. Here, we have investigated the metabolic effects of berberine in two animal models of insulin resistance and in insulin-responsive cell lines. Berberine reduced body weight and caused a significant improvement in glucose tolerance without altering food intake in ob/ob 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 STZ-Li adipocytes and L6 myoblasts, increased GLUT4 translocation in L6 cells in a phosphorylatable form of AMPK-independent pathway and increased lipid accumulation in STZ-Li 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. Diabetes 55:2228–2234, 2006

Obesity poses a serious health risk contributing to the development of a host of other diseases including type 2 diabetes, hyperlipidemia, hypercholesterolemia, and hypertension (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, pharmacologic agents 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. Active 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 distinct 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 an undefined 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 disorders 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 ob/ob mice and in high-fat-fed rats. Strikingly, berberine acutely stimulated AMPK activity in both adipocytes and adipocytes in vitro, contributing to enhanced GLUT4 translocation in myoblasts and reduced lipid mass in adipocytes. Based on these studies, we propose that berberine may have a major application as a new treatment for obesity and/or insulin resistance in humans.
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.


Berberine potently attenuates intestinal polyps growth in ApcMin mice and familial adenomatous polyposis patients through inhibition of Wnt signalling.

Oncogene. 2017 Dec 14; 36(50): 6906–6918. PMCID: PMC5735301 PMID: 28346104 Berberine binds RXRa to suppress β-catenin signaling in colon cancer cells
BERBERINE AGAINST NEURODEGENERATION
BERBERINE PROTECTS NEURONS

INTERNATIONAL JOURNAL OF MOLECULAR MEDICINE 33: 870-878, 2014

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

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Neurotoxic effects of berberine on long-term L-DOPA administration in 6-hydroxydopamine-lesioned rat model of Parkinson’s disease

Koan Magong Shin1, Hyun Sook Choi1, Wonyoung Shim2, Bo Young Lee3, Hyun Eun Kwon1, Suin Ok Choi1 and Myung Koo Lee1

Neuroscience Letters

Effects of berberine on 6-hydroxydopamine-induced neurotoxicity in PC12 cells and a rat model of Parkinson’s disease

Hyun Eun Kwon1, Hyun Soo Choi1, Kwon Seong Shin2, Byung Koo Lee3, Chong Ki Lee4, Bang Yeon Kwana5, Sung Gil Lim5 and Myung Koo Lee1

To determine the Effect of Berberine on 6-OHDA induced memory impairment in Parkinson’s disease in rodents

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Abstract:

The present study of berberine administration in preclinical models confirms neuroprotective potential of berberine in 6-hydroxydopamine (6-OHDA) induced Parkinson’s disease (PD). The data is a chronic and progressive neurological disease with loss of motor function accompanied with preference loss, dystonia, tremors and rigidity of the extremities. This disease is characterized by impaired dopamine (DA) production and presynaptic nigrostriatal dopaminergic neurons. This study aimed at investigating the protective effects of berberine on nigrostriatal dopaminergic neurons in 6-OHDA-induced PD model in rats. The results showed that berberine treatment prevented the development of behavioral changes, significantly reduced motor impairment and improved motor function in Parkinson’s disease rats. The present results confirm the potential of berberine in the treatment of PD.
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.

Berberine is well tolerated in rodents (100 to 300 mg/kg).

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

Higher doses appear to be non-toxic, although often associated with gastrointestinal discomfort.8

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, antithrombotic, antiatherosclerotic, anticonvulsant, anticancer 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.
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:
  - Fat
  - Phosphatidylcholine
  - Black Pepper increases absorption as much as 2000X


Influence of piperine on the pharmacokinetics of curcumin in animals and human volunteers.

Shoba G¹, Joy D, Joseph T, Majeed M, Rajendran R, Srinivas PS.

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

Gianni Belcaro; Maria Rosaria Cesarone; 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 prolonged 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 (VCAM)-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
Curcumin is a sesquiterpene lactone that is derived from the rhizomes of the Zingiber officinale Roscoe (Ginger family) plant and has been used in traditional Ayurvedic medicine for more than 2000 years. It is known to have multiple beneficial properties including anti-inflammatory, antioxidant, and chemopreventive effects. However, its bioavailability is limited due to its poor water solubility and rapid metabolism. This limits its therapeutic potential. Meriva® is a proprietary curcumin-phosphatidylcholine phytosome complex that has been developed to enhance the bioavailability and efficacy of curcumin. In previous studies, Meriva® has demonstrated that curcumin acts as a master switch of inflammation by acting at the level of pro-inflammatory enzymes (cyclooxygenases (COX) and lipooxygenases) 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. Once in the plasma, however, 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.
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
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.

- Stimulus
- Phospholipids
- Phospholipase A-2
- Arachidonic Acid

**Lipoxygenase**

Curcumin inhibits both selectively.

- Leukotrienes: LTB4, LTC4, LTD4
- Prostaglandins: LTE4, 5-HETE, 5-HETE
- Thromboxanes

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

Julie S. Jurenka, MT(ASCP)

**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.
Curcuma 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
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, antifungal and anticancer activity of turmeric (Curcuma longa L.) and black pepper (Piper nigrum L.), used in Pakistani cuisine to enrich flavour and to treat infections 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. luteus 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 Lif, 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 oxidative damage (Shakir et al., 2002).
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

Padmalalini 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/6 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/6 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 retinoid 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/6 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 retinoid on PPARγ/6 target genes, PDK1 and VEGF-A were also examined using qRT-PCR. Western Blotting was utilized to examine the protein expression level of the p65 subunit of NF-κB.

Results: Treatment of retinoid acid resistant triple negative breast cancer cells with curcumin sensitized these cells to retinoid 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/6. We provide evidence that curcumin suppresses p65, a transcription factor known to regulate FABP5. The combination of curcumin with retinoic acid suppressed PPARγ/6 target genes, VEGF-A and PDK1.

Conclusions: Curcumin suppresses the expression level of FABP5 and PPARγ/6 in triple negative mammary carcinoma cells. By targeting the FABP5/PPARγ/6 pathway, curcumin prevents the delivery of retinoic acid to PPARγ/6 and suppresses retinoid acid-induced PPARγ/6 target gene, VEGF-A. Our data demonstrates that suppression of the FABP5/PPARγ/6 pathway by curcumin sensitizes retinoid acid resistant triple negative breast cancer cells to retinoid acid mediated growth suppression.

Keywords: Curcumin, Retinoic acid, Triple negative breast cancer, Fatty acid binding protein 5, Peroxisome proliferator-activated receptor γ.
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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crossMark

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 thus 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 cAMP response element-binding protein (CREB)-mediated gene expression in inguinal WAT and elevates the levels of plasma noradrenaline, 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 noradrenaline/CREB 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). Brown adipose tissue (BAT) is a specialized form of adipose tissue that is primarily located in the interscapular region (BAT) and plays a critical role in energy dissipation during cold exposure through non-shivering thermogenesis. In contrast, white adipose tissue (WAT) is a large general depot of energy storage and is the major source of circulating triacylglycerols and plasma apolipoproteins. In addition, WAT is an endocrine organ that secretes a variety of hormones and cytokines that are involved in the regulation of energy balance, metabolism, and inflammation.

In BAT, uncoupling protein-1 (UCPI) is localized in the mitochondrial inner membrane and drives the production of heat from the oxidation of fatty acids. UCPI dissipates the electrochemical gradient across the mitochondrial inner membrane by transferring protons back into the mitochondrial matrix, thus reducing the efficiency of ATP synthesis and promoting heat dissipation. However, UCPI expression is downregulated in BAT from obese individuals, and this results in a reduction in energy dissipation and increased energy storage in WAT. Therefore, strategies to increase UCPI expression or to induce UCPI-mediated thermogenesis in WAT are of great importance in the treatment of obesity and associated diseases.

In recent years, the discovery of WAT browning has provided a new perspective for the treatment of obesity. WAT browning refers to the conversion of WAT into BAT-like tissue, which can increase energy dissipation and improve metabolic health. Several factors, including exercise, cold exposure, and certain medications, have been shown to promote WAT browning.

Curcumin is a natural dietary constituent of turmeric, a spice commonly used in traditional medicine. It has been shown to possess various health benefits, including anti-inflammatory, antioxidant, and anti-carcinogenic properties. In particular, curcumin has been reported to promote WAT browning in animal models. The current study investigated the potential of curcumin to promote WAT browning in mice and to decrease bodyweight and fat mass.
CURCUMA SUPPORTS METABOLISM AND IMPROVES LIPID PROFILES

- Curcumin ameliorates IR and increases the uptake and oxidation of fatty acids and glucose in skeletal muscle

_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 extent of hypercholesterolemia and hyperlipidemia 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 counter- ing 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-7α-hydroxylase and HMG COA reductase were measured. Hepatic cholesterol-7α-hydroxylase activity was markedly higher in curcumin fed diabetic animals suggesting a higher rate of cholesterol catabolism. (Mol Cell Biochem 166: 169–175, 1997)

Keywords: curcumin, diabetes mellitus, cholesterol metabolism, hypolipidemic action

Introduction

The relationship between diabetes and hyperlipemias is a well recognised phenomenon. Hypercholesterolemia is a common feature of diabetes mellitus. It is also observed that dietary polyunsaturated fatty acids are also associated with better glycemic control and for lowering plasma LDL cholesterol [5]. Spices form an important class of food adjuvants in human diet. Besides enhancing the taste and flavour of foods, spices exhibit a wide range of physiological activities.
Curcuma longa 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 mouse intestine. Acute and chronic colitis were induced in Balb/c mice by Dextran Sulfate Sodium administration (5% and 2.5% respectively) and either Curcuma extract (100 mg/kg/day) or placebo was 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 spasmylytic agent.


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Compliance with Ethics Guidelines: 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.

Planta Med. 2013 Jul;79(11):971-7. doi: 10.1055/s-0032-1328652.. Curcumin alters the pharmacokinetics of warfarin and clopidogrel in Wistar rats but has no effect on anticoagulation or antiplatelet aggregation. Liu AC1, Zhao LX, Lou HX.
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.

Herbal Compendium Books

Sales and Book Signing at Restorative Formulations booth after presentation

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