BERBERINE AND CURCUMIN
Herbal Superstars

DR JILLIAN STANSBURY

Financial Disclosure: Consultant to Restorative Formulations

THE BROAD MEDICINAL EFFECTS OF BERBERINE

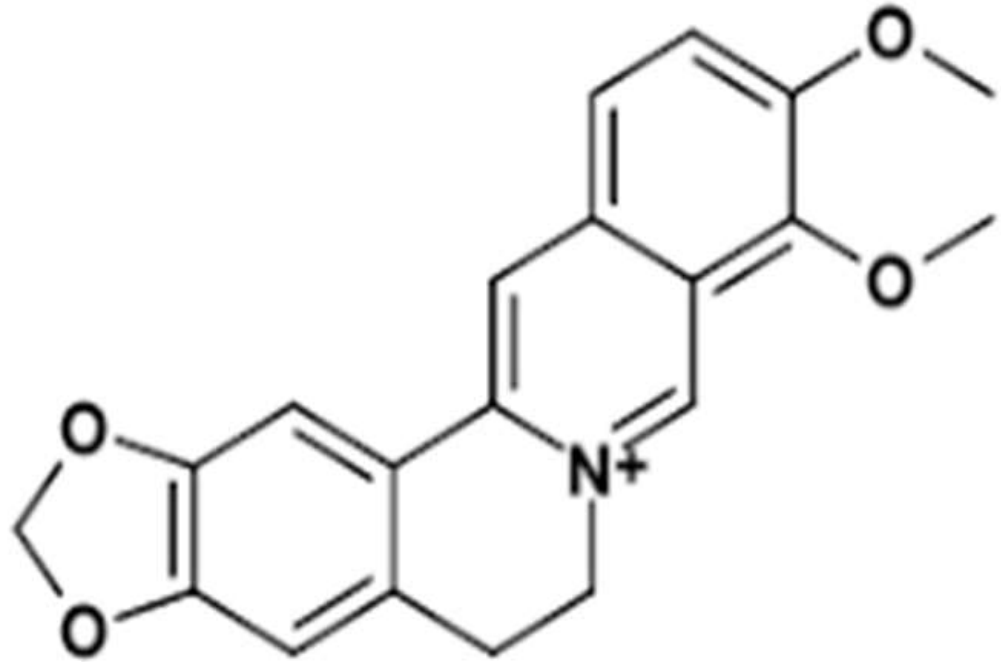
BERBERINE

- 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:

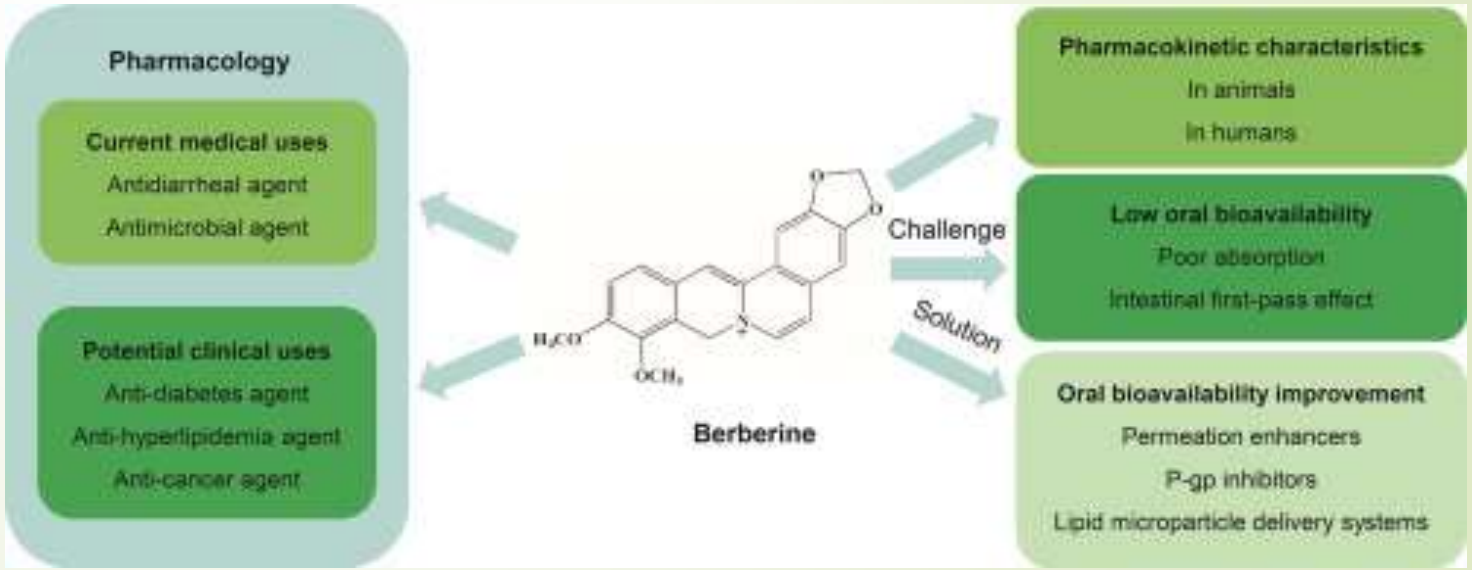
- Gastrointestinal Infections
- Familial Adenomatous Polyposis
- Liver Disease
- Elevated Lipids
- Diabetes
- Cancer
- Obesity
- Traumatic Brain Injury



Berberine

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

frontiers in Pharmacology

ORIGINAL RESEARCH
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Gut Microbiota-Regulated Pharmacokinetics of Berberine and Active Metabolites in Beagle Dogs After Oral Administration

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State Key Laboratory of Bioactive Substance and Function of Natural Medicines, Institute of Materia Medica, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

Berberine (BBR) is considered a multi-target drug that has significant advantages. In contrast to its significant pharmacological effects in clinic, the plasma level of BBR is very low. Our previous work revealed that dihydroberberine (dhBBR) 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/MS^n-IT-TOF were used to detect dhBBR, butyrate and BBR as well as its Phase I and II metabolites, respectively. The results showed that dhBBR was not detected in dog plasma but was excreted in small amounts in the feces of dogs examined on days 3 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 rRNA genes analysis. The results presented that dogs treated with BBR 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 beagle dogs. Eleven metabolites were detected in plasma and feces after BBR oral administration (50 mg/kg) to dogs, including 8 metabolites of Phase I and III metabolites of Phase II. The pharmacokinetic profile indicated that the concentration of BBR in plasma was low, with a C_{max} value of 36.88 ± 23.45 ng/mL. The relative content of glucuronic acid conjugates (M11) 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 (2625.04 ± 1726.94 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 poor absorption but good therapeutic efficacy.

Keywords: berberine, gut microbiota, butyrate, metabolites, GC-MS, LC/MS^n-IT-TOF, 16S rRNA genes analysis

Abbreviations: BBR, berberine; dhBBR, dihydroberberine; GC, gas chromatography; GC-MS, gas chromatography-mass spectrometry, HQC, high concentration of quality control; IS, internal standard; LC/MS^n-IT-TOF, High-performance liquid chromatography-ion trap-time of flight mass spectrometry; LC/MS-MS, liquid chromatography-triple quadrupole mass spectrometry; LDL-c, low-density-lipoprotein cholesterol; LOD, limits of detection; LOQ, limits of quantitation; LQC, low concentration of quality control; MQC, median concentration of quality control; PK, pharmacokinetics; SCFA, short-chain fatty acid; SD, standard deviation; TC, cholesterol; TG, triglyceride; OTU, operational taxonomic unit; QIIME, quantitative insights into microbial ecology.

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BERBERINE BENEFITS THE INTESTINAL MICROBIOME

- 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.

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STUDIES ON ESTIMATION OF BERBERINE AND ANTIMICROBIAL ACTIVITY OF DIFFERENT EXTRACTS OF *BERBERIS ARISTATA* DC

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Key words : *Daruharidra, Berberine, Extraction, Antimicrobial activity, Eye infecting pathogens.*

Abstract - *Berberis aristata* DC, correlated to Daruharidra, is one of the herbal species extensively used in ayurveda for its diverse therapeutic applications. Among its various ingredients, alkaloid berberine is the most active with antimicrobial activities. The present study was carried out to identify an effective strategy for maximum extraction of berberine from *B. aristata* stem samples and to analyse their antimicrobial activity against eye infecting microbes. Different solvents viz., methanol, ethanol, chloroform and water, and various extraction procedures such as hot extraction, cold extraction and centrifugation process were used for analyzing berberine content spectrometrically at 350 nm. Highest yield of 17.32% of berberine was recorded in sample extracted with methanol using soxhlet apparatus for 72 hrs. The antimicrobial activities of the various extracts were tested against the eye infecting pathogens *Staphylococcus aureus* (CoNS) and *Streptococcus* sp. using agar well diffusion method. Though all the solvents showed antimicrobial activity against the tested organisms, highest inhibition was observed in the methanolic extaction against the tested organisms.

INTRODUCTION

Herbal traditional medicine has become popular in recent years due to its advantages over the allopathic system. A number of plant based formulations are being used in Ayurvda, Unani, Siddha and Home remedies (Ramwat and Goyal 2008). In Ayurveda, a plant extract or mixtures of extracts constitute a formulation under the Indian system of medicine. The effect of these preparations is the result of a combined effect of the active molecules in the extracts. Daruharidra, an important ingredient of traditional Indian ayurvedic system of medicine, is continuously used for health care in India and other parts of the globe (Mitra et al., 2011; Balasubramani *et al.*, 2011). Ayurvedic Pharmacopeia of India correlates Daruharidra to *Berberis aristata* DC of family Berberidaceae, a spinous shrub native to mountains of North India and Nepal. It is of trade importance (high volume/high value) and an endemic species of conservation concern (Balasubramani and Venkatasubramanian, 2011). It is used as a tonic to cure ulcers and fevers (Kirtikar and Basu, 2000). It is an important ingredient of several polyherbal formulations for treating diarrhea, cholera and eye diseases (Babbar *et al.*, 1982; Komal *et al.*, 2011).

Berberine, one of the main constituents of plant, is known to contain a wide range of pharmacological activities including antimicrobial, antihypersensitive, antiinflammatory, antioxidant, antidepressant, anticancer and hepatoprotective (Kulkarni and Dhir, 2007; Singh *et al.* 2010; Anubhuti *et al.*, 2011).

Considering the aforesaid importance of the compound berberine, the objective of the study was to identify an effective methodology and solvent for berberine extraction, apart from testing antimicrobial activity of the extracts against eye infecting microorganisms.

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BERBERINE HAS BROAD ANTIMICROBIAL ACTIVITY

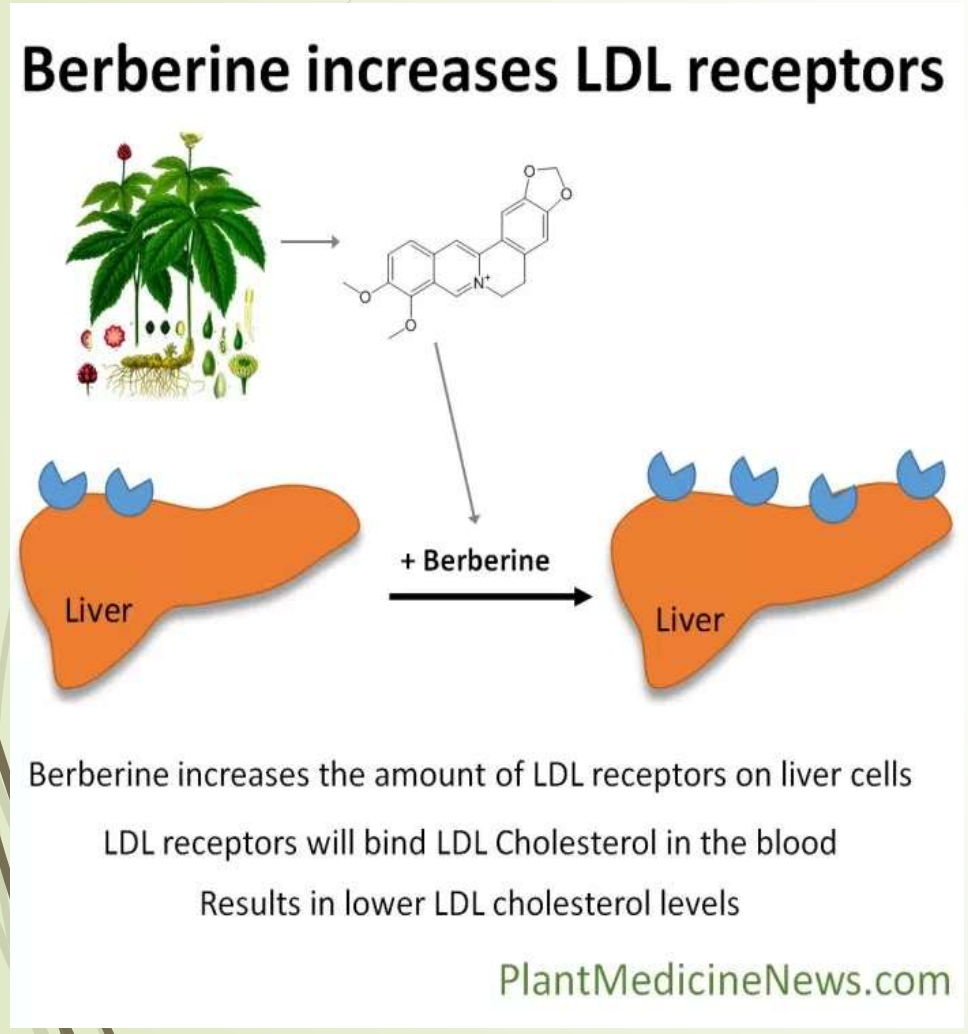
- Berberine is active against viruses, fungi, protozoans, helminths and a variety of bacteria, including many pathogenic species and multidrug resistant strains of *Mycobacterium tuberculosis* and methicillin resistant *Staphylococcus aureus*.
- Berberine effects bacterial cell membranes, interacts with DNA, and inhibits cell division.

PLoS One. 2015; 10(12): e0144183. PMCID: PMC4670213 PMID: 26636757
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 SUPPORTS METABOLIC FUNCTION

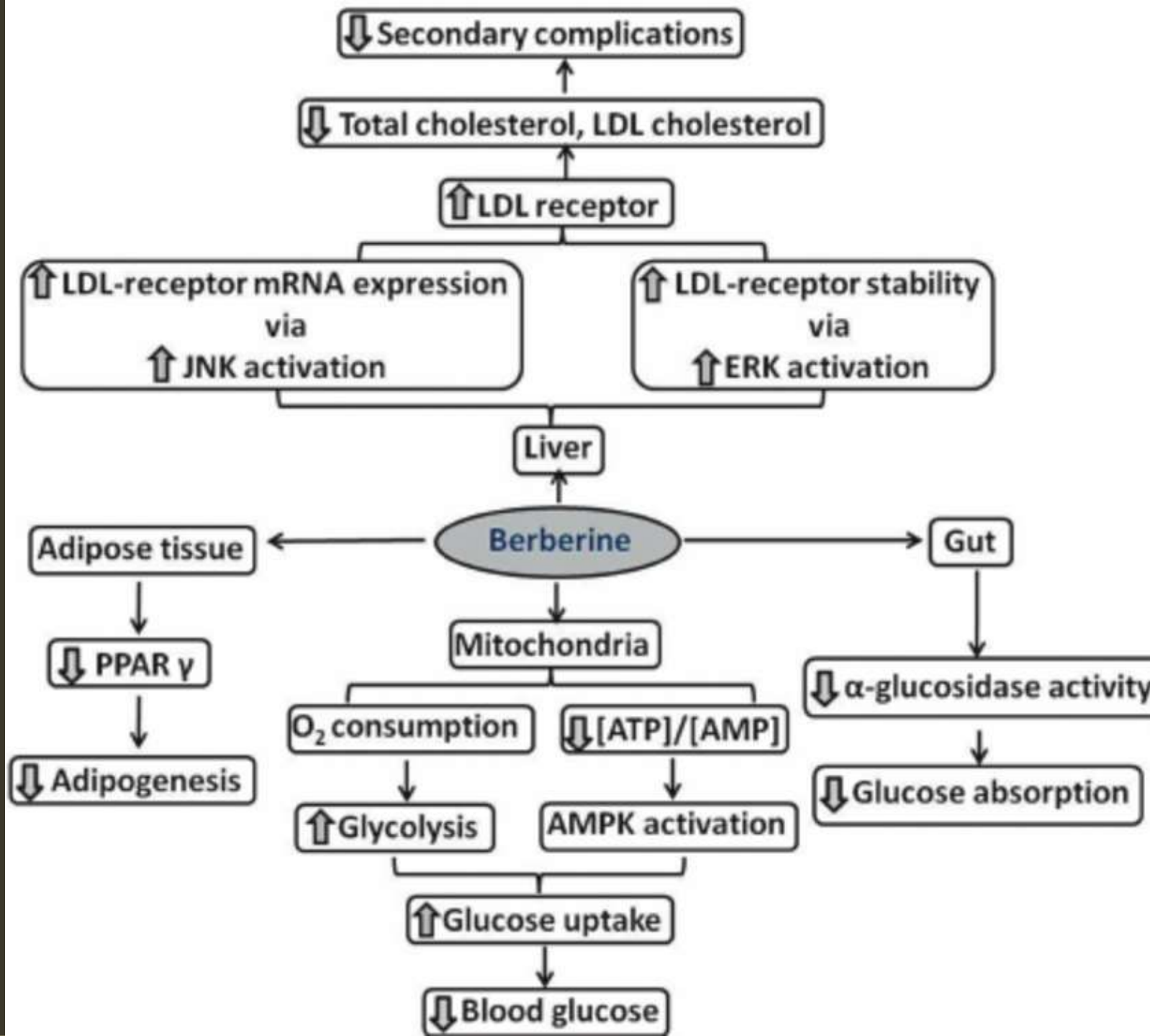
BERBERINE HAS BROAD ANTI-INFLAMMATORY AND IMMUNE MODULATING ACTIVITIES

BERBERINE IMPROVES HEPATIC LIPID METABOLISM



BERBERINE AGAINST DIABETES AND METABOLIC SYNDROME

- Berberine offers broad metabolic support, improving lipid and carbohydrate metabolism.



PLOS | ONE

RESEARCH ARTICLE

Identification and Verification of Potential Therapeutic Target Genes in Berberine-Treated Zucker Diabetic Fatty Rats through Bioinformatics Analysis

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Data Availability Statement: All microarray data files are available from ArrayExpress database (accession number: E-MTAB-5178).

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Abstract

Background

Berberine is used to treat diabetes and dyslipidemia. However, the effect of berberine on specific diabetes treatment targets is unknown. In the current study, we investigated the effect of berberine on the random plasma glucose, glycated hemoglobin (HbA1C), AST, ALT, BUN and CREA levels of Zucker diabetic fatty (ZDF) rats, and we identified and verified the importance of potential therapeutic target genes to provide molecular information f further investigation of the mechanisms underlying the anti-diabetic effects of berberine.

Methods

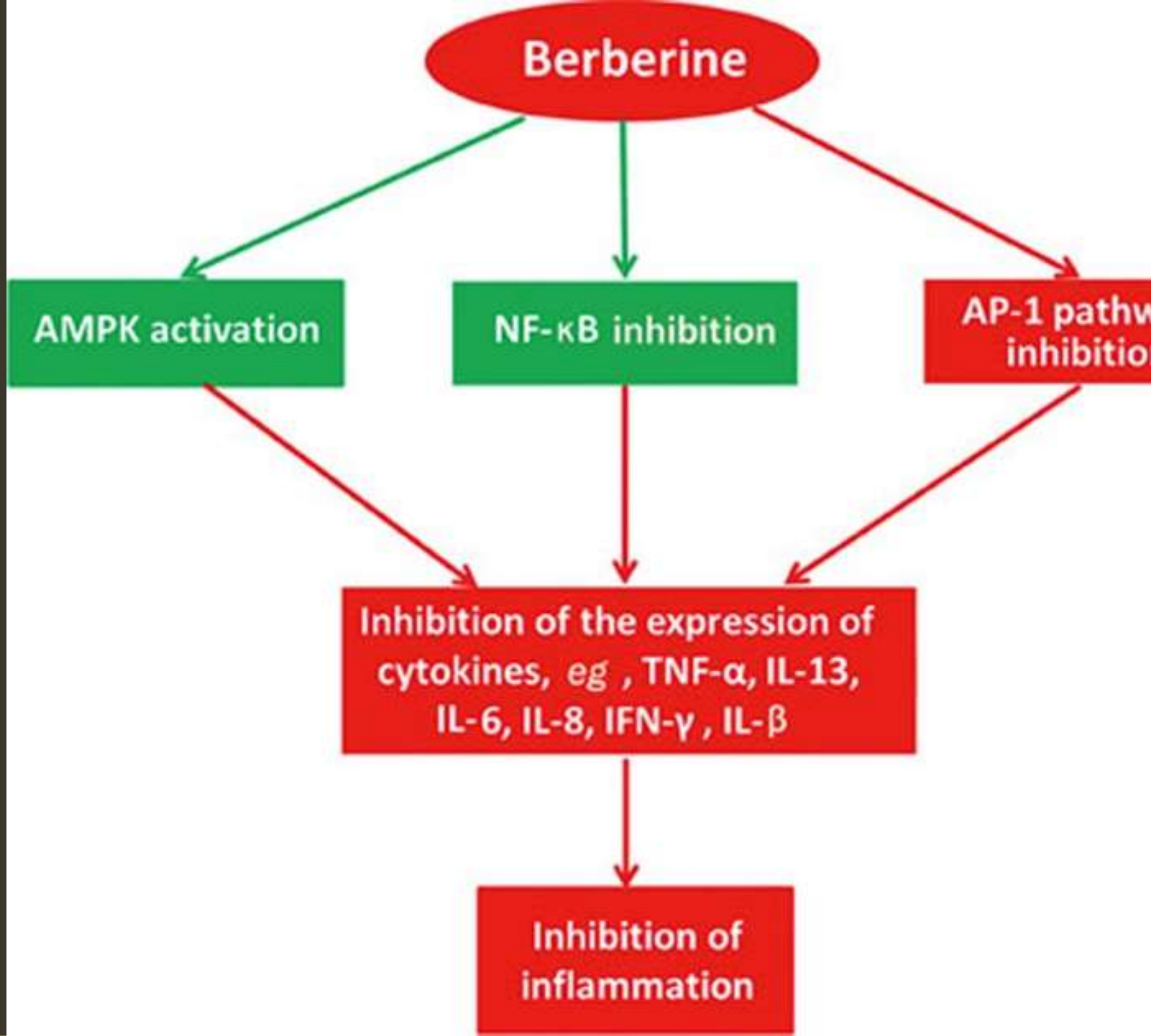
ZDF rats were randomly divided into control (Con), diabetic (DM) and berberine-treated (300 mg·kg^{-1}, BBR) groups. After the ZDF rats were treated with BBR for 12 weeks, its effect on the random plasma glucose and HbA1C levels was evaluated. Aspartate amino-transferase (AST), alanine aminotransferase (ALT), blood urea nitrogen (BUN), CREA an OGTT were measured from blood, respectively. The levels of gene expression in liver sam ples were analyzed using an Agilent rat gene expression 4x44K microarray. The differen-tially expressed genes (DEGs) were screened as those with log2 (Con vs DM) $\geq$ 1 and log (BBR vs DM) $\geq$ 1 expression levels, which were the genes with up-regulated expression, and those with log2 (Con vs DM) $\leq$ -1 and log2 (BBR vs DM) $\leq$ -1 expression levels, which were the genes with down-regulated expression; the changes in gene expression were co sidered significant at $P<0.05$. The functions of the DEGs were determined using gene onto ogy (GO) and pathway analysis. Furthermore, a protein-protein interaction (PPI) network was constructed using STRING and Cytoscape software. The expression levels of the key node genes in the livers of the ZDF rats were also analyzed using qRT-PCR.

BERBERINE HAS ANTI-DIABETIC 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.

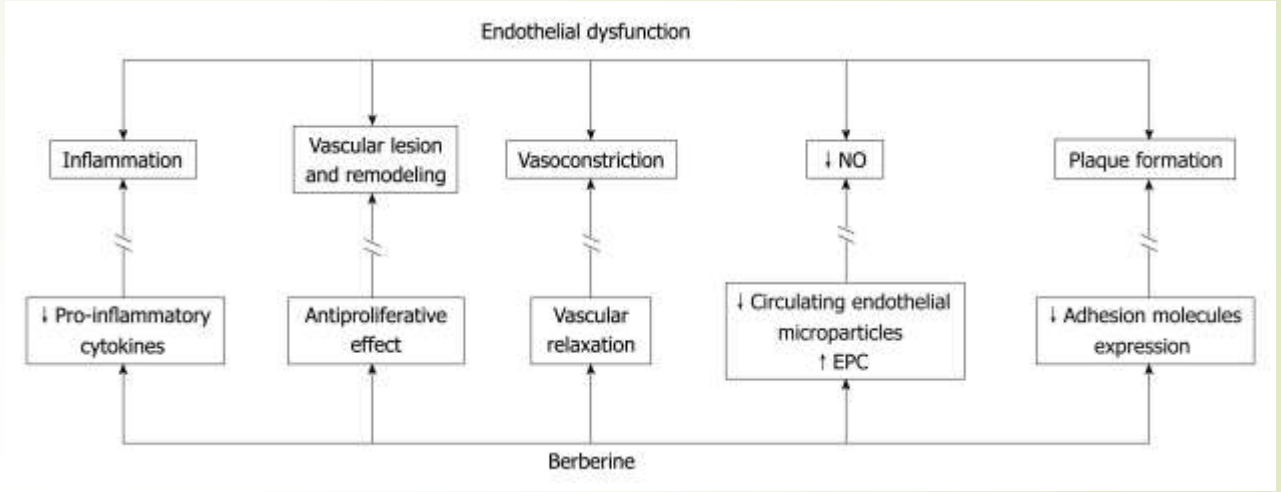
BERBERINE HAS NUMEROUS ANTI-INFLAMMATORY EFFECTS

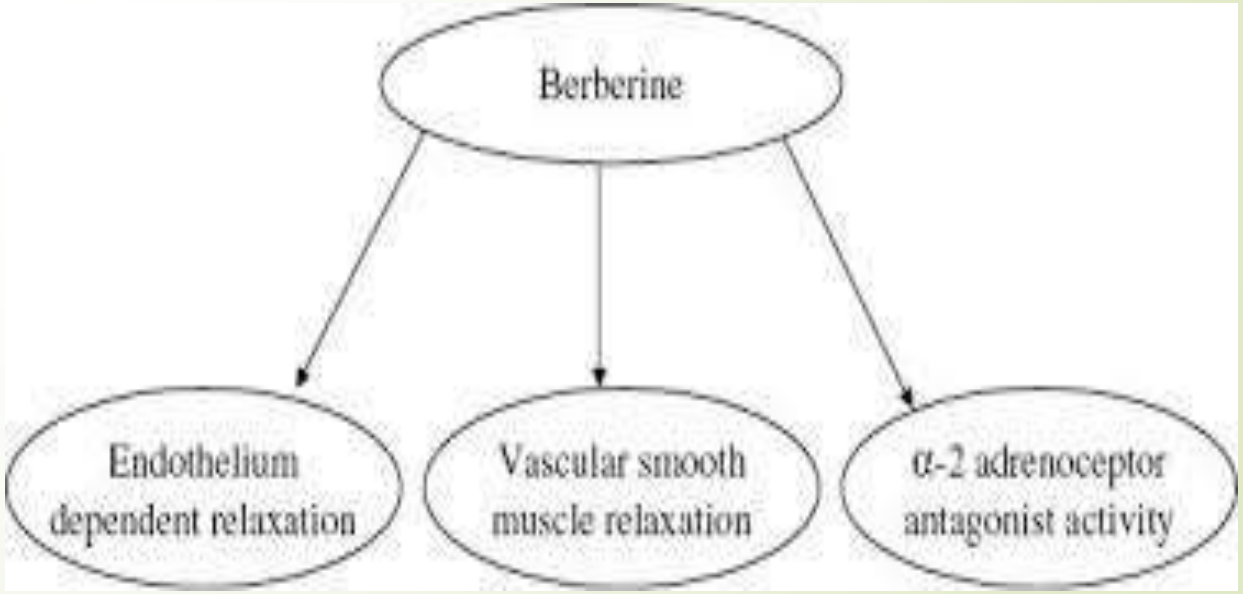
- Berberine affects AMP kinases, NF-kB, TNF, Interleukins and other cytokines to inhibit inflammatory pathways.
- Berberine helps to protects against inflammatory damage in the vasculature and many tissues.



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.





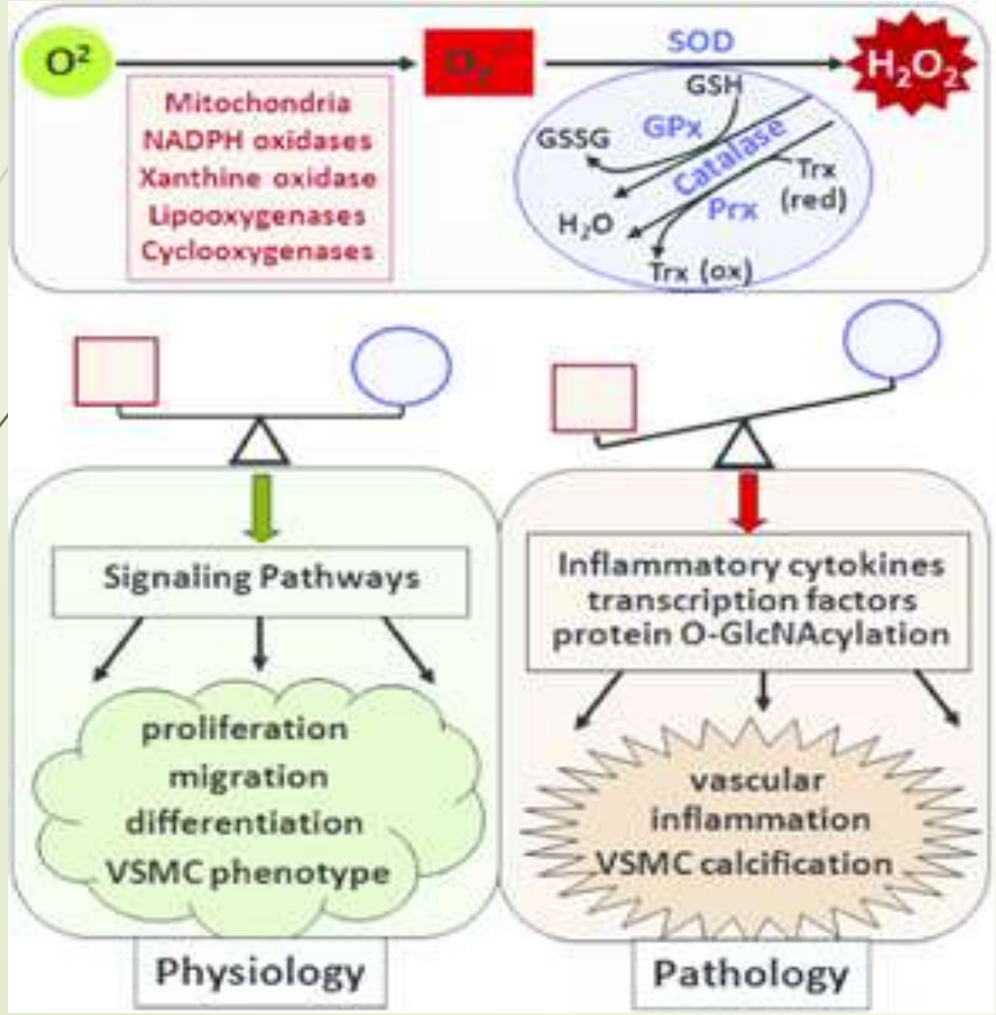
Cardiovasc Diabetol. 2016; 15: 63. PMCID: PMC4828787
PMID: 27067643 *Berberine alleviates the cerebrovascular contractility in streptozotocin-induced diabetic rats through modulation of intracellular Ca2+ handling in smooth muscle cells* Yu-Guang Ma, et al

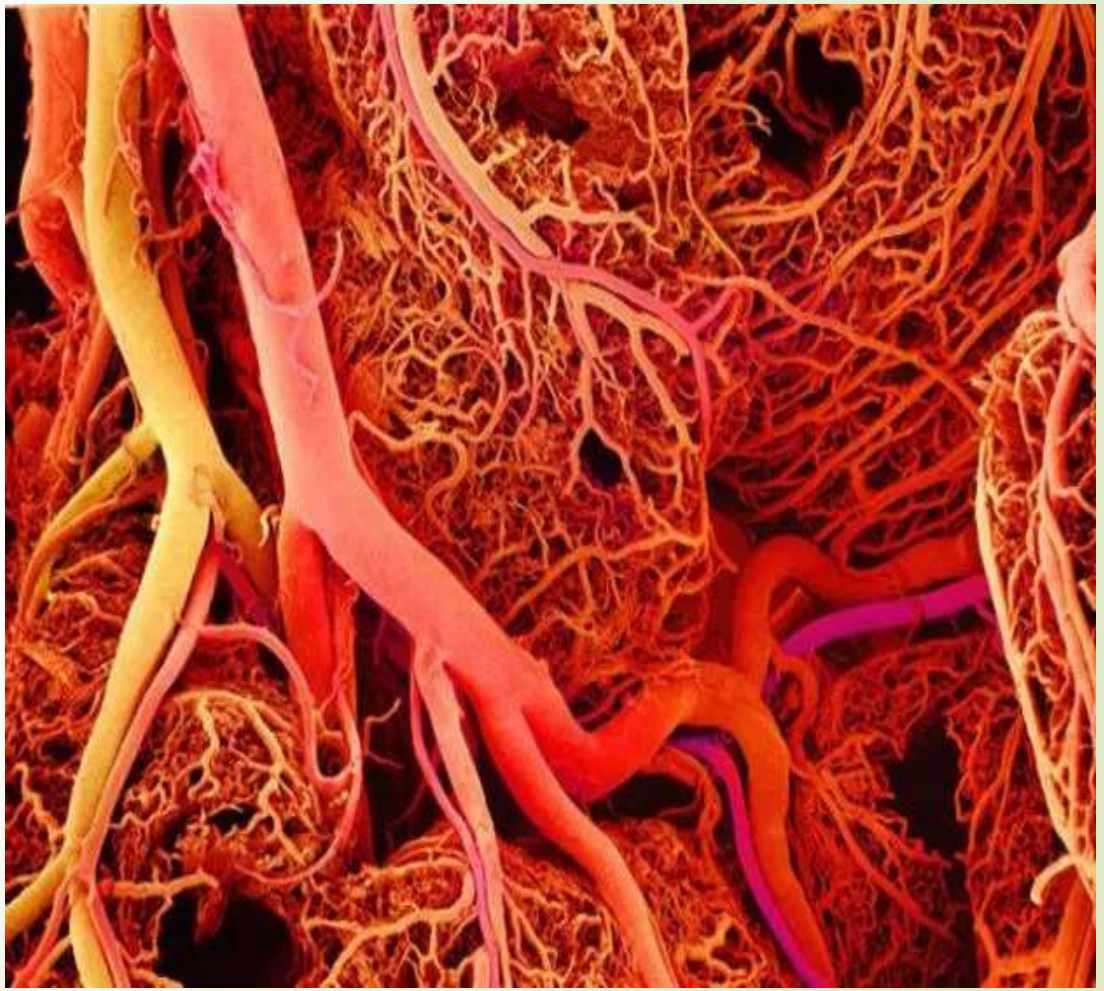
STRONG CORRELATION BETWEEN CHRONIC INFLAMMATION AND CANCER

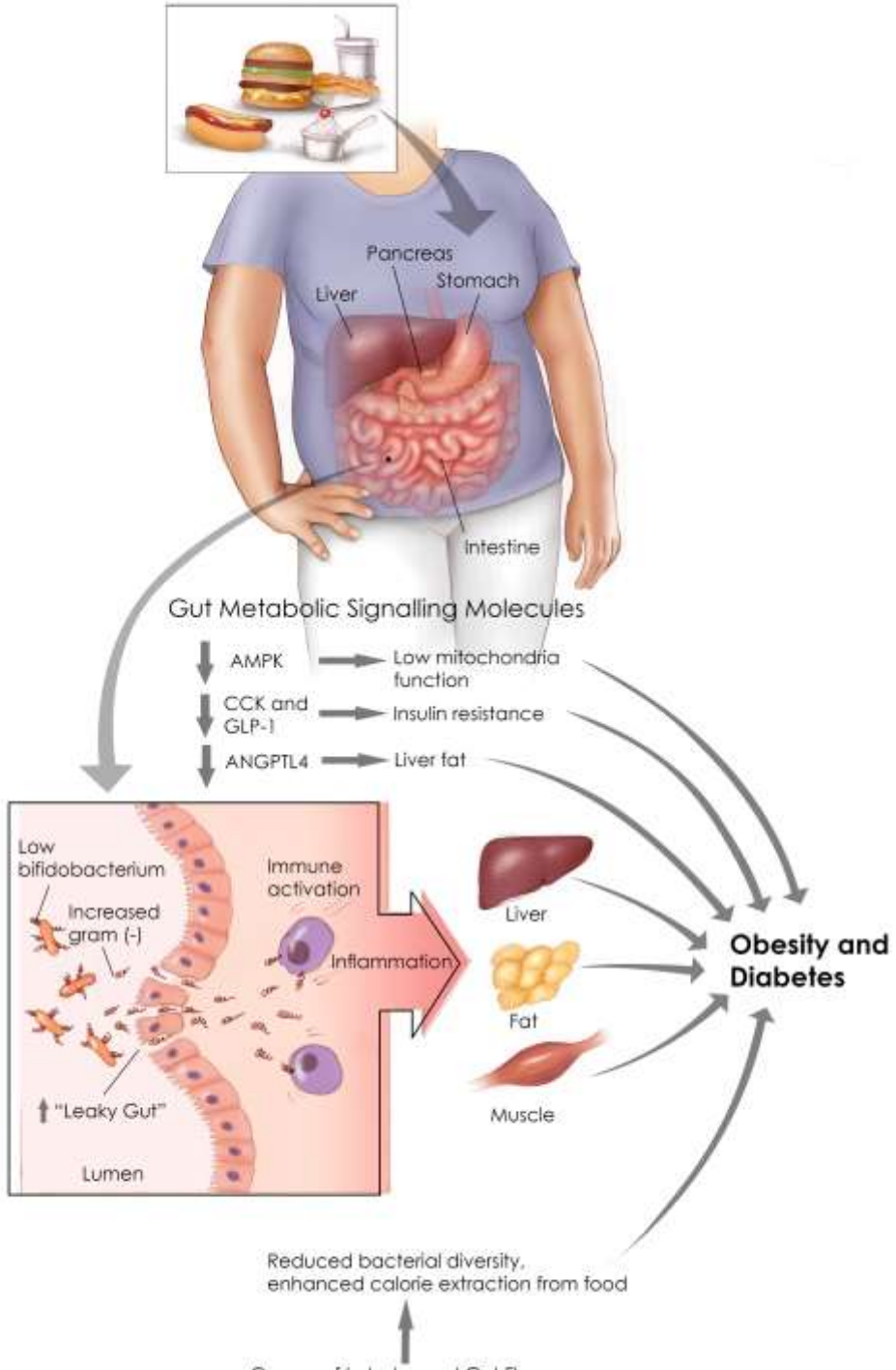
- Chronic inflammation increases the risk of cancer.
- Berberine has numerous anti-inflammatory effects that contribute to its anti-cancer effects.
- Berberine inhibits mitogen-activated protein kinase signaling and cellular reactive oxygen species production.
- Berberine forms strong complexes with 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.

Acta Pharmacol Sin. 2017 Feb; 38(2): 157–167. PMCID: PMC5309756 PMID: 27917872 *Advances in the study of berberine and its derivatives: a focus on anti-inflammatory and anti-tumor effects in the digestive system* Kun Zou et al.

BERBERINE HELPS TO OPTIMIZE CELL RECOVERY AND SIGNALING VIA REDUCING OXIDATIVE AND TOXIC STRESS TO CELL ORGANELLES

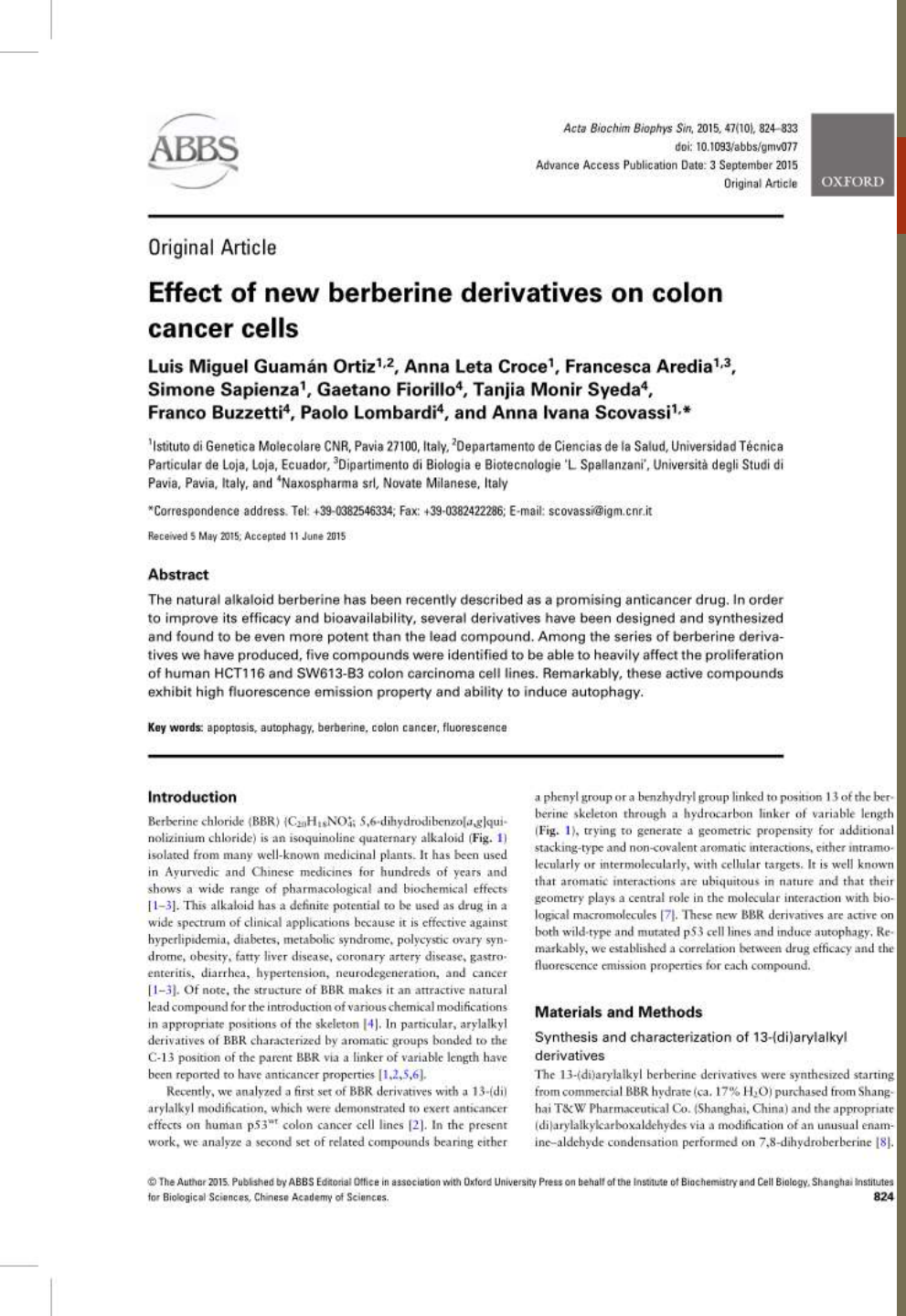






AMP-ACTIVATED PROTEIN KINASE

- The AMPK pathway can regulate tumor growth and proliferation.
- Berberine activates AMPK and can suppress colon tumor growth in animals.



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Original Article

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Original Article

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 SW613-B3 colon carcinoma cell lines. Remarkably, these active compounds exhibit high fluorescence emission property and ability to induce autophagy.

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

Introduction

Berberine chloride (BBR) ($C_{20}H_{18}NO_4^+$; 5,6-dihydrodibenzo[*a*,*g*]quinolizinium chloride) is an isoquinoline quaternary alkaloid (**Fig. 1**) isolated from many well-known medicinal plants. It has been used in Ayurvedic and Chinese medicines 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 drug in a wide spectrum of clinical applications because it is effective against hyperlipidemia, diabetes, metabolic syndrome, polycystic ovary syndrome, obesity, fatty liver disease, coronary artery disease, gastroenteritis, diarrhea, hypertension, neurodegeneration, and cancer [1–3]. Of note, the structure of BBR makes it an attractive natural lead compound for the introduction of various chemical modifications in appropriate positions of the skeleton [4]. In particular, arylalkyl derivatives of BBR characterized by aromatic groups bonded to the C-13 position of the parent BBR via a linker of variable length have been reported to have anticancer properties [1,2,5,6].

Recently, we analyzed a first set of BBR derivatives with a 13-(di)arylalkyl modification, which were demonstrated to exert anticancer effects on human $p53^{wt}$ colon cancer cell lines [2]. In the present work, we analyze a second set of related compounds bearing either a phenyl group or a benzhydryl group linked to position 13 of the berberine skeleton through a hydrocarbon linker of variable length (**Fig. 1**), trying to generate a geometric propensity for additional stacking-type and non-covalent aromatic interactions, either intramolecularly or intermolecularly, with cellular targets. It is well known that aromatic interactions are ubiquitous in nature and that their geometry plays a central role in the molecular interaction with biological macromolecules [7]. These new BBR derivatives are active on both wild-type and mutated p53 cell lines and induce autophagy. Remarkably, we established a correlation between drug efficacy and the fluorescence emission properties for each compound.

Materials and Methods

Synthesis and characterization of 13-(di)arylalkyl derivatives

The 13-(di)arylalkyl berberine derivatives were synthesized starting from commercial BBR hydrate (ca. 17% H_2O) purchased from Shanghai T&W Pharmaceutical Co. (Shanghai, China) and the appropriate (di)arylalkylcarboxaldehydes via a modification of an unusual enamine–aldehyde condensation performed on 7,8-dihydroberberine [8].

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.

Mol Carcinog. 2015 Oct; 54(10): 1096–1109. PMCID: PMC4504840
PMID: 24838344 *Berberine regulates AMP-activated protein kinase signaling pathways and inhibits colon tumorigenesis in mice* Weidong Li ET AL

Available online at www.sciencedirect.com
ScienceDirect
Chinese Journal of Natural Medicines 2017, 15(3): 0178–0191
Chinese Journal of Natural Medicines

Mechanism underlying berberine's effects on HSP70/TNFα under heat stress: Correlation with the TATA boxes

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Available online 20 Mar., 2017

[ABSTRACT] Heat stress can stimulate an increase in body temperature, which is correlated with increased expression of heat shock protein 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 conditions, using *in vivo* and *in vitro* models. The expression levels of HSP70 and TNFα were determined using RT-PCR 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 homeostasis 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
CLC Number] R965 [Document code] A [Article ID] 2095-6975(2017)03-0178-14

Introduction

Berberine (BBR) is an effective small molecule with a variety of biological activities. It was first applied as an antibacterial agent [1-2] for the treatment of intestinal infection associated fever [3]. It has been also used a classical anti-inflammatory drug [4-6]. Moreover, BBR has been shown to have therapeutic effects on major diseases, such as hypolipidemia [7-10], hypoglycemia [11], and cancer [12-14]. BBR is also useful for prevention and treatment of cerebral ischemia [15-17], Alzheimer's disease [18-20]. 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 stress [21]. TNFα is an endogenous pyrogen that increases temperature [22]. In the thermo-response process, HSP70 plays a key role in the physiological response of biological systems to high temperature [23-24]. Our previous work has comprehensively evaluated the antagonistic effects of BBR on environment-induced body temperature changes, which provides a novel candidate for the development of body temperature-regulating agents [25]. 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.

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These authors have no conflict of interest to declare.

BERBERINE HAS BROAD ANTI-INFLAMMATORY AND IMMUNE MODULATING EFFECTS

- Berberine affects on Heat Shock proteins and TNF alpha reducing inflammatory damage and offering possible anti-mutagenic affects.

BERBERINE'S ANTICANCER EFFECTS

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Role of Berberine on molecular markers involved in migration of esophageal cancer cells

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Abstract

Berberine is an isoquinoline alkaloid found in several plant species like famous chinese herb, *Rhizoma coptidis* which has been used locally as a strong gastrointestinal remedy for thousands of years. The inhibitory effects of berberine on tumor progression properties have been reported before. In this study, we investigated the effect of berberine on an esophageal cancer cell line, KYSE-30 with emphasis on its effects on the expression of certain chemokine receptors. The cytotoxic effect of berberine on KYSE-30 cells was analyzed by MTT assay. *In vitro* cell migration assay was also applied to the treated cells and the expression levels of the selected chemokine receptors (CXCR4 and CCR7) was measured at mRNA level. A retarded growth, associated with increasing concentrations of berberine, was obvious. On the other hand, the migration rate of the cells was decreased when they were treated with different concentrations of berberine and the expression levels of the two chemokine receptors, involved in the migration and metastasis of esophageal cancer cells, were decreased following the same treatments. With these results, we tend to conclude that berberine might be a proper candidate for further investigations, by targeting the chemokine receptors, and possible applications as anti-metastatic agent in cancer studies.

Key words: Esophageal cancer, metastasis, chemokine receptor, berberine, cell migration.

Introduction

Cancer is the second cause of death in the world and esophageal cancer is among the eight most common malignancies and the sixth most common cause of cancer related death (1). The two main subtypes of esophageal cancer are squamous cell carcinoma (ESCC) that arise from the epithelial cells of esophagus, and esophageal adenocarcinoma (EAC) that derived from glandular cells. Higher incidences of ESCC have been reported from Iran and other parts of Asia, and Africa, while in the United States of America, EAC is more common (2).

The most common cause of death from cancer is related to a process called metastasis (3). This is process by which malignant cells leave the primary tumor and enter bloodstream or lymphatic system and migrate to other organs. It is a non-random and sequential process which is linked to specific organs. While metastasis is a complex process involving multiple factors and regulatory molecules, recent studies have suggested that chemokines and their receptors play a key role in this process (4).

In a study on T-cell leukemia patients, it was revealed that there is a correlation between the expression of CCR7 and the metastasis of cancer. In these patients, leukemia cells in lymphoid organs had high expression of CCR7, compared with normal T cells (5). In another study, the critical role of CXCR4, beside CCR7, in the metastasis of breast cancer was identified (6). Their respective ligands CXCL12 and CCL21 exhibit increased levels of expression in lymph nodes which representing the first destinations of breast cancer metastasis (6).

CCR7 up-regulation have been reported in many cancers including Melanoma (7), B-cell Chronic Lymphocytic Leukemia (9), T cell Leukemia (13), none-Hodgkin's Lymphoma (12), Esophageal Squamous Cell Carcinoma (20), none-small Cell Lung cancer (11), Breast (6), Head and Neck (8), Prostate (10) Gastric (14), Colorectal (15), Bladder(16), Ovarian (17), Pancreatic (18) and Thyroid (19).

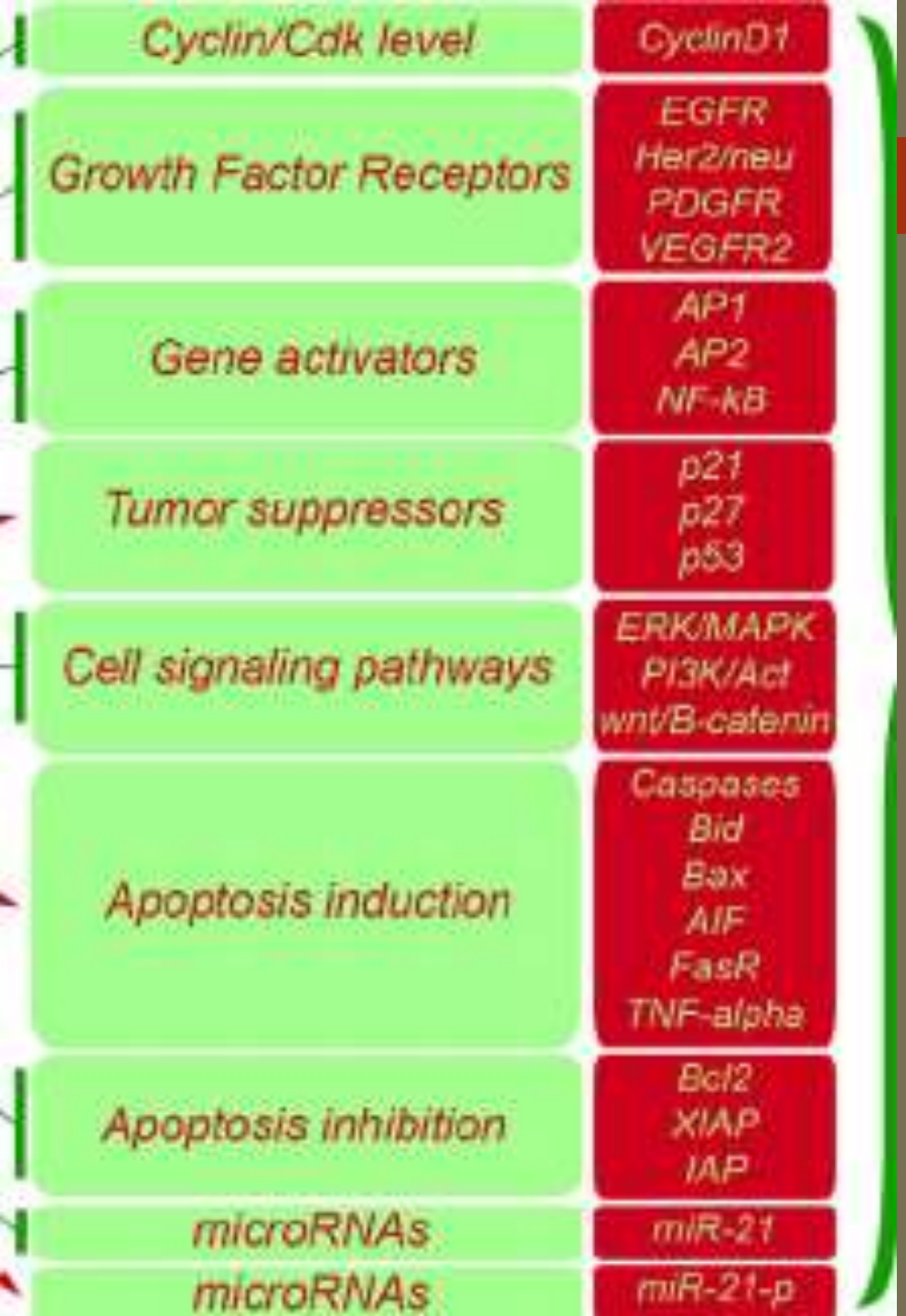
Chemokine receptor CXCR4 is involved in proliferation and progression of various cancers including Melanoma(21), B-cell Chronic Lymphocytic Leukemia (28), none-Hodgkin's lymphoma (25), Esophageal Squamous Cell Carcinoma(20), non-small Cell Lung cancer (24), Breast (6), Head and Neck (8), Prostate (23), Gastric (32), Ovarian (22), Pancreatic (26), Glioma(27), Acute Lymphoblastic Leukemia(29), Renal Cell Carcinoma (30), Bladder (31), Colorectal (15), Osteosarcoma (33), Neuroblastoma (34) and thyroid (35).

These studies have revealed the prominent role of CCR7 and CXCR4 chemokine receptors in cancer and the-state-of-the-art studies have been conducted with focus on the chemokine receptors as major targets for remedy of cancer (36).

Berberine (2,3-methylenedioxy-9,10-dimethoxy-protoberberine chloride) is an isoquinoline alkaloid, that has been found in many plants such as *Hydrastis canadensis* (goldenseal), *Berberis aquifolium* (Oregon grape), *Berberis vulgaris* (barberry), and *Berberis aristata* (tree turmeric) and *Rhizoma coptidis* (Huang Lian) and has a wide range of pharmacological and biochemical effects (37). It has been used as a drug in gastrointestinal disorders for thousands of years in china. Recent

GROWING ANTICANCER RESEARCH ON BERBERINE

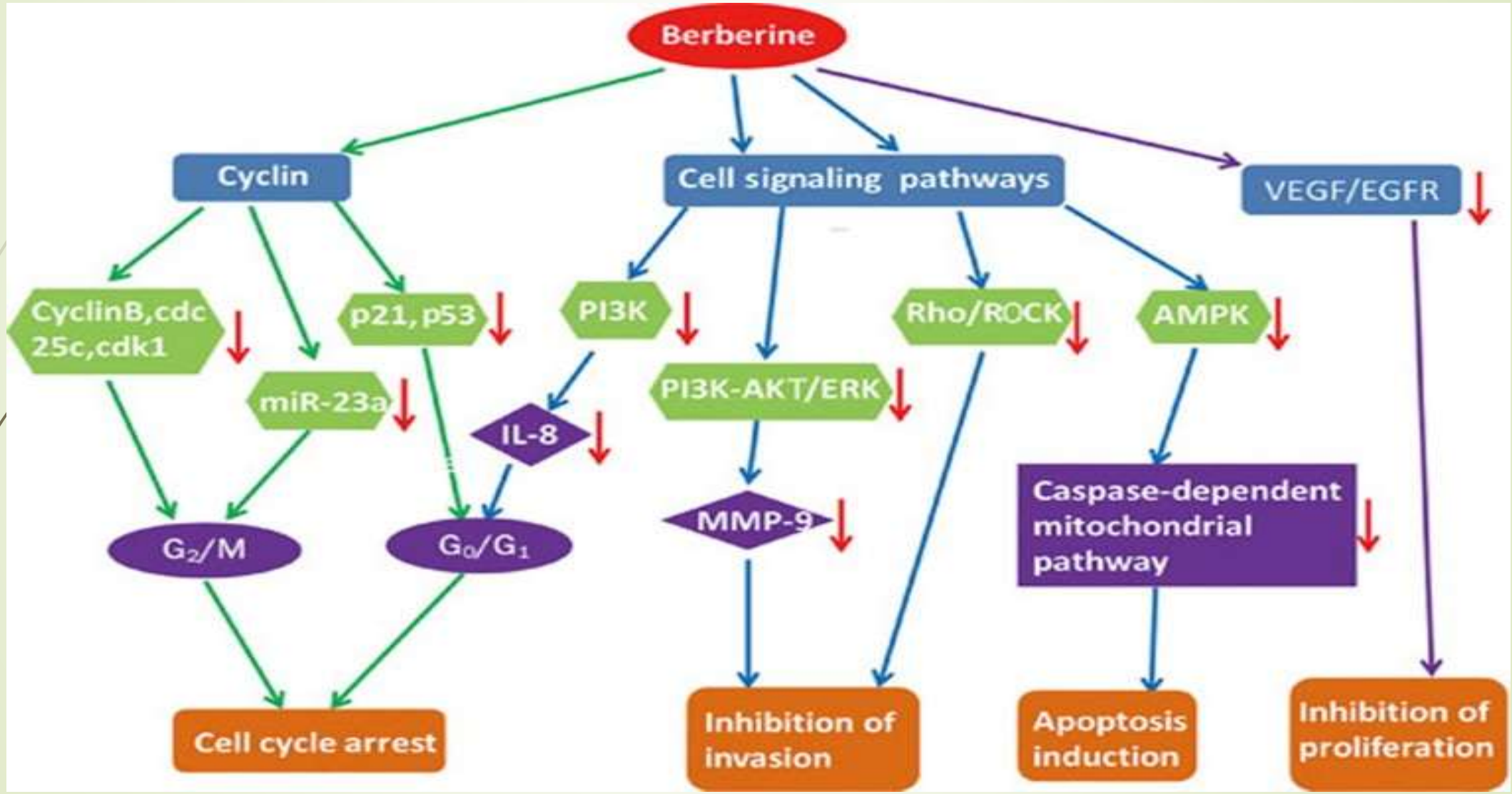
- There are over 1,000 papers published on berberine's anticancer, anti-tumor, apoptotic, and anti-mutagenic effects.



BERBERINE'S ANTI-CANCER 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



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http://dx.doi.org/10.4236/jbnb.2015.61006

Gold Nanoparticle and Berberine Entrapped into Hydrogel Matrix as Drug Delivery System

Camila Rufino Souza[1], Henrique R. Oliveira[1], Wagner M. Pinheiro[2], Lubhandwa S. Biswaro[2], Ricardo B. Azevedo[2], Anderson J. Gomes[1*], Claure N. Lunardi[1*]

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Abstract

In this study the novel hydrogel loaded with gold nanoparticle (AuNP) enhanced the berberine (BS) release when compared with other formulations of hydrogel. Hydrogels are hydrophilic polymer networks having the capacity to absorb water, ranging from about twenty to thousand times their dry weight. BS is a natural product, a quaternary ammonium salt from the group of isoquinoline alkaloids found in medicinal plants as Berberis Vulgaris. BS has some activity against dysentery, hypertension, inflammation, and liver disease in China and Japan. In this work, BS was used as a model drug to study its association with different types of hydrogel composites of polyvinyl alcohol (BS-PVA 10%); gellan gum (BS-GG 2%), gellan gum-PVA crosslinked with cysteine (cys) (BSGG2%PVA2%cys) and gellan gum-PVA cosslinked with cysteine associated with gold nanoparticles (AuNP-BSGG2%PVA2%cys). Several parameters such as fraction of retained water (Wf), hydration percentage (%H), Swelling (DSw) and time course profile (t = 100%) (TC) were evaluated for all preparations. The results showed that the AuNP-BS-GG2%PVA2%cys was able to retain more water and swelling than the other preparations. The time course of release of the BS to the medium was greater for AuNP-BS-GG2%PVA2%cys making it a candidate to drug delivery studies in biological assays. Also Scanning Electron Microscopy (SEM) images of the surface of these hydrogel were performed. Furthermore, crosslink of the resulting hydrogels were investigated by Fourier Transform Infrared Spectroscopy (FTIR) and differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA). Thus, briefly, the aim of this work was to study three composition of hydrogel loaded with BS and its composition in relation to addition to AuNP and evaluate its profile for further drug delivery application using the Surface Plasmonic Resonance (SPR) as a tool improving the drug release in the new hydrogel.

*Corresponding authors.

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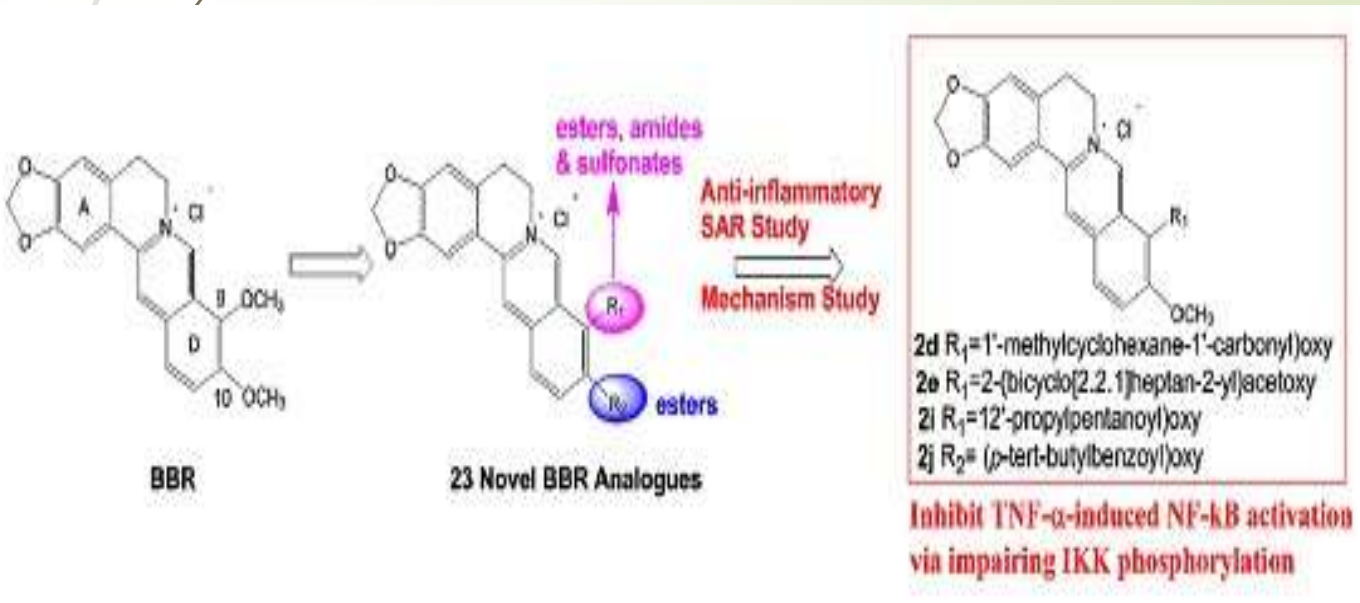
NOVEL MOLECULES ARE BEING EXPLORED

- Novel molecular forms of berberine are being explored to boost the absorption bioavailability and pharmacodynamics of berberine in various types of cancer.



International Journal of *Molecular Sciences*

MDPI

Article

Regulation of Akt/FoxO3a/Skp2 Axis Is Critically Involved in Berberine-Induced Cell Cycle Arrest in Hepatocellular Carcinoma Cells

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Abstract: The maintenance of ordinal cell cycle phases is a critical biological process in cancer genesis, which is a crucial target for anti-cancer drugs. As an important natural isoquinoline alkaloid from Chinese herbal medicine, Berberine (BBR) has been reported to possess anti-cancer potentiality to induce cell cycle arrest in hepatocellular carcinoma cells (HCC). However, the underlying mechanism remains to be elucidated. In our present study, G0/G1 phase cell cycle arrest was observed in berberine-treated Huh-7 and HepG2 cells. Mechanically, we observed that BBR could deactivate the Akt pathway, which consequently suppressed the S-phase kinase-associated protein 2 (Skp2) expression and enhanced the expression and translocation of Forkhead box O3a (FoxO3a) into nucleus. The translocated FoxO3a on one hand could directly promote the transcription of cyclin-dependent kinase inhibitors (CDKIs) $p21^{Cip1}$ and $p27^{Kip1}$, on the other hand, it could repress Skp2 expression, both of which lead to up-regulation of $p21^{Cip1}$ and $p27^{Kip1}$, causing G0/G1 phase cell cycle arrest in HCC. In conclusion, BBR promotes the expression of CDKIs $p21^{Cip1}$ and $p27^{Kip1}$ via regulating the Akt/FoxO3a/Skp2 axis and further induces HCC G0/G1 phase cell cycle arrest. This research uncovered a new mechanism of an anti-cancer effect of BBR.

Keywords: hepatocellular carcinoma; berberine; Akt; FoxO3a; Skp2

1. Introduction

Hepatocellular carcinoma (HCC) is one of the most prevalent malignancies throughout the world, with a particularly high incidence in the Asian population. Despite the substantial advances in drug discovery and development, the treatment options for HCC are still limited [1,2]. Although chemotherapy and radiotherapy for HCC have significantly increased the survival rate, HCC treatment is still struggling due to considerable limitations and deleterious clinical side effects [3,4]. Herein, to develop safer effective agents in HCC therapy is urgently needed. Among all the therapeutic strategies, traditional Chinese medicine (TCM) and its phytochemicals have been reported to be effective in the treatment and improvement of quality of life (QOL) for HCC patients [5].Therefore, research to uncover the underlying mechanisms of the anti-tumor effect of TCM in HCC seems rather imperative.

Accumulated evidence has emerged, illuminating anti-cancer effects of phytochemical-berberine (BBR) [6], which is an isoquinoline type of botanical alkaloid present in many traditional Chinese medicines as the major bioactive compound. BBR has several potent pharmacological functions and has been used for its antidiabetic, antimicrobial, antidiabetic, antidiarrheal and anti-inflammatory activities [7–9]. Additionally, BBR has been reported to possess anti-tumor activity in multiple types of cancers including HCC [10,11]. According to previous studies, BBR could not only induce HCC

BERBERINE CAN SUPPRESS COLON AND LIVER CANCER VIA A VARIETY OF MECHANIISMS

- 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

Jiwei Wang[1], Qichao Qi[1], Zichao Feng[1], Xin Zhang[1], Bin Huang[1], Anjing Chen[1], Lars Prestegarden[2,3], Xingang Li[1], Jian Wang[1,2]

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

Received: *March 15, 2016* ***Accepted:*** *August 09, 2016* ***Published:*** *August 19, 2016*

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

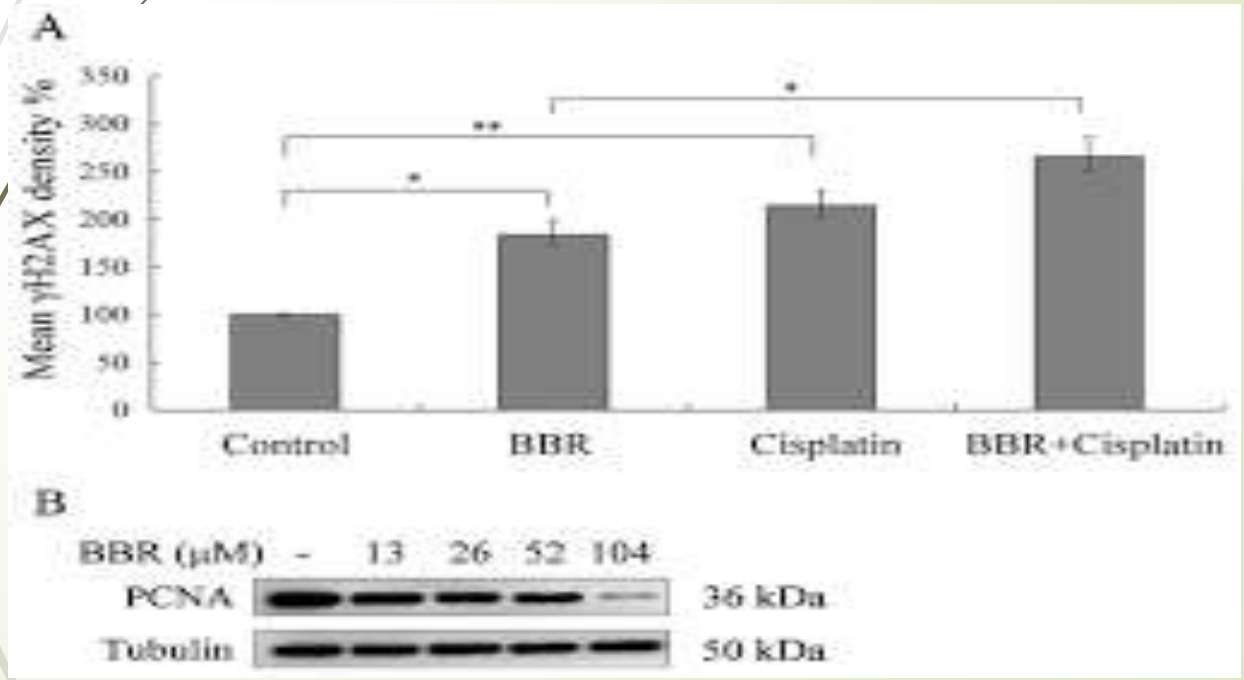
Glioblastoma multiforme (GBM) is the most aggressive primary brain tumor characterized by a highly infiltrative growth pattern and resistance to chemotherapy [1]. Despite multimodal treatment with surgery followed by radio- and chemotherapy with Temozolomide (TMZ), the 5-year survival rate of WHO grade IV glioblastoma is still less than 5% [2, 3]. As such, there is a critical need to identify new efficacious therapeutic strategies.

Berberine (BBR), 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 impairs the glycolytic capacity. Importantly, these changes reduce the invasive potential of GBM cells and induce cell death.

BERBERINE'S ANTICANCER EFFECTS

- Berberine may both enhance cell recovery and autophagy cycles, as well as promote apoptosis in cancer cells.



Original Article

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

Yun S. Lee,[1,2] Woo S. Kim,[1,2] Kang H. Kim,[1,2] Myung J. Yoon,[1] Hye J. Cho,[1] Yun Shen,[3,4] Ji-Ming Ye,[3] Chul H. Lee,[5] Won K. Oh,[5] Chul T. Kim,[5] Cordula Hohnen-Behrens,[3] Alison Gosby,[3] Edward W. Kraegen,[3] David E. James,[3] and Jae B. Kim[1,2]

Berberine has been shown to have antidiabetic properties, although its mode of action 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 *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 reduced lipid accumulation 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. *Diabetes* 55:2256–2264, 2006

Obesity poses a serious health risk contributing to the increased prevalence 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-to-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 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 an ill-defined 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 antidiabetic effects (10), 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 myotubes and adipocytes in vitro, contributing to enhanced GLUT4 translocation in myotubes 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.

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Received for publication 4 January 2006 and accepted in revised form 22 May 2006.

Y.S.L. and W.S.K. contributed equally to this study.

Additional information on this article can be found in an online appendix at http://diabetes.diabetesjournals.org.

AICAR, 5-aminoimidazole-4-carboxamide riboside; AMPK, AMP-activated protein kinase; DMEM, Dulbecco's modified Eagle's medium; FAS, fatty acid synthase; MAPK, mitogen-activated protein kinase; PI, phosphatidylinositol; PPAR, peroxisome proliferator–activated receptor; TZD, thiazolidinedione; UCP, uncoupling protein; WAT, white adipose tissue.

DOI: 10.2337/db06-0006

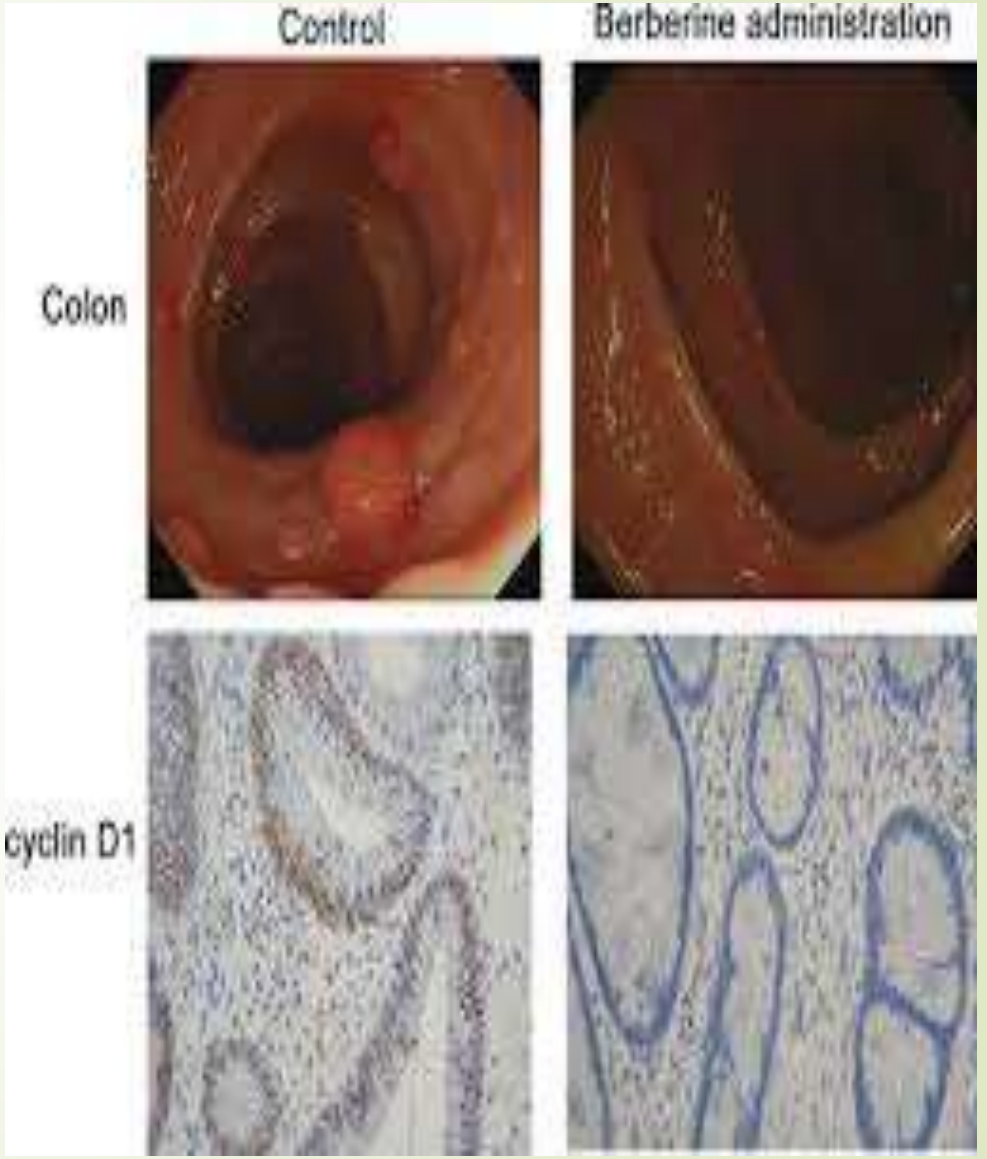
BERBERINE EFFECTS ON AMP-ACTIVATED PROTEIN KINASE

- 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.

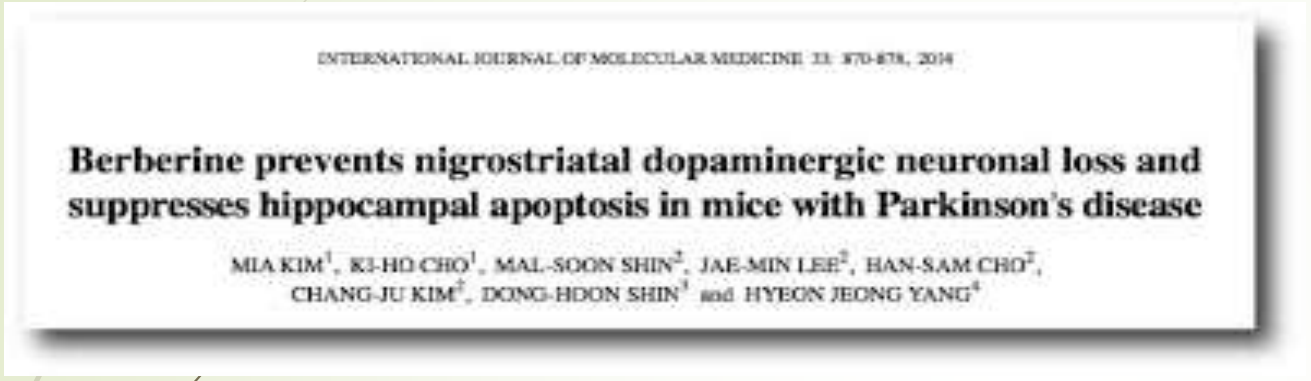


J Cell Mol Med. 2013 Nov;17(11):1484-93. doi: 10.1111/jcmm.12119. *Berberine potently attenuates intestinal polyps growth in ApcMin mice and familial adenomatous polyposis patients through inhibition of Wnt signalling.*

Oncogene. 2017 Dec 14; 36(50): 6906–6918. PMCID: PMC5735301 PMID: 28846104 *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

MIA KIM[1], KI-HO CHO[1], MAL-SOON SHIN[2], JAE-MIN LEE[2], HAN-SAM CHO[2], CHANG-JU KIM[2], DONG-HOON SHIN[3] and HYEON JEONG YANG[4]

RESEARCH ARTICLE

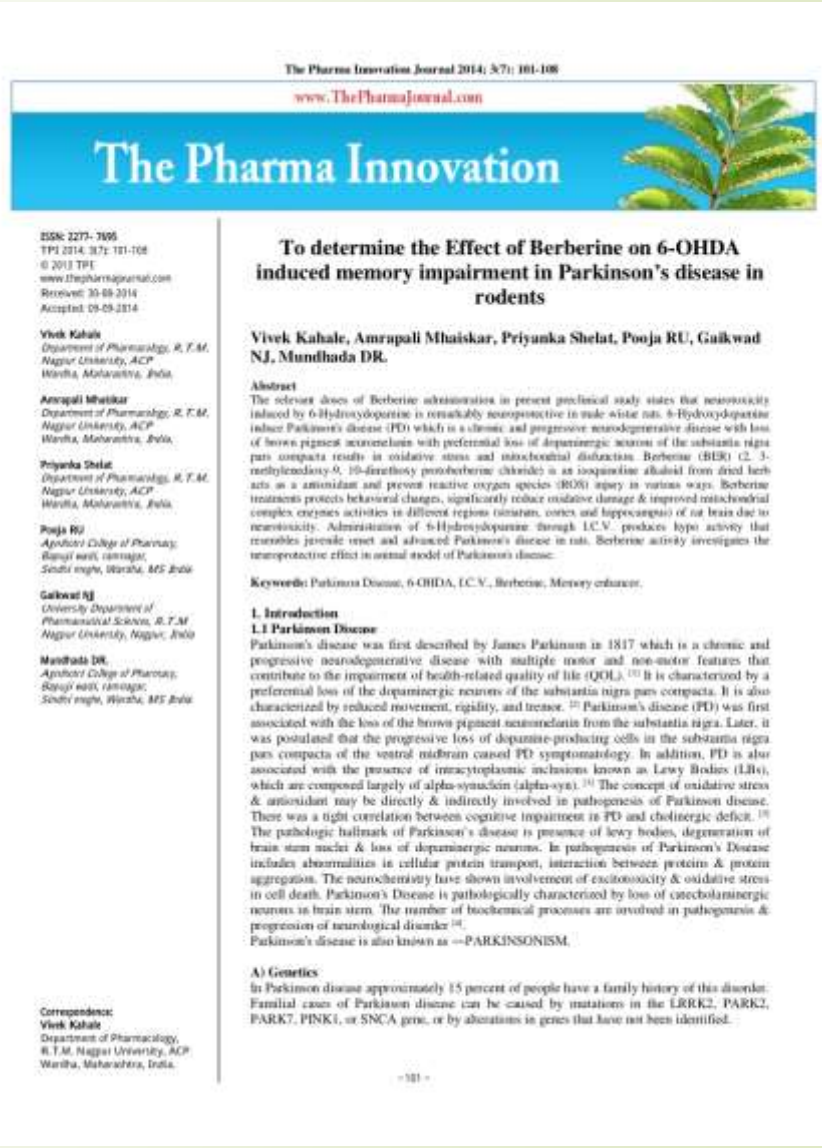
Neurotoxic effects of berberine on long-term L-DOPA administration in 6-hydroxydopamine-lesioned rat model of Parkinson's disease

Keon Sung Shin · Hyun Sook Choi · Ting Ting Zhao · Kwang Hoon Suh · Ik Hyun Kwon · Soon Ok Choi · Myung Koo Lee

Neuroscience Letters

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

Ik Hyun Kwon[a], Hyun Sook Choi[a], Kun Seong Shin[a], Byung Koo Lee[b], Chong Kil Lee[a], Bang Yeon Hwang[a], Sung Cil Lim[a], Myung Koo Lee[a,*]



The Pharma Innovation Journal 2014; 3(7): 101-108

www.ThePharmaJournal.com

The Pharma Innovation

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

Vivek Kahale, Amrapali Mhaiskar, Priyanka Shelat, Pooja RU, Gaikwad NJ, Mundhada DR.

Abstract

Keywords: Parkinson Disease, 6-OHDA, I.C.V., Berberine, Memory enhancer.

1. Introduction

1.1 Parkinson Disease

A) Genetics

BERBERINE FOR TRAUMATIC BRAIN INJURY (TBI)

- 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.

PLoS One. 2014; 9(12): e115694. PMCID: PMC4278716 PMID: 25546475*Berberine Protects against Neuronal Damage via Suppression of Glia-Mediated Inflammation in Traumatic Brain Injury* Chien-Cheng Chen et al

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

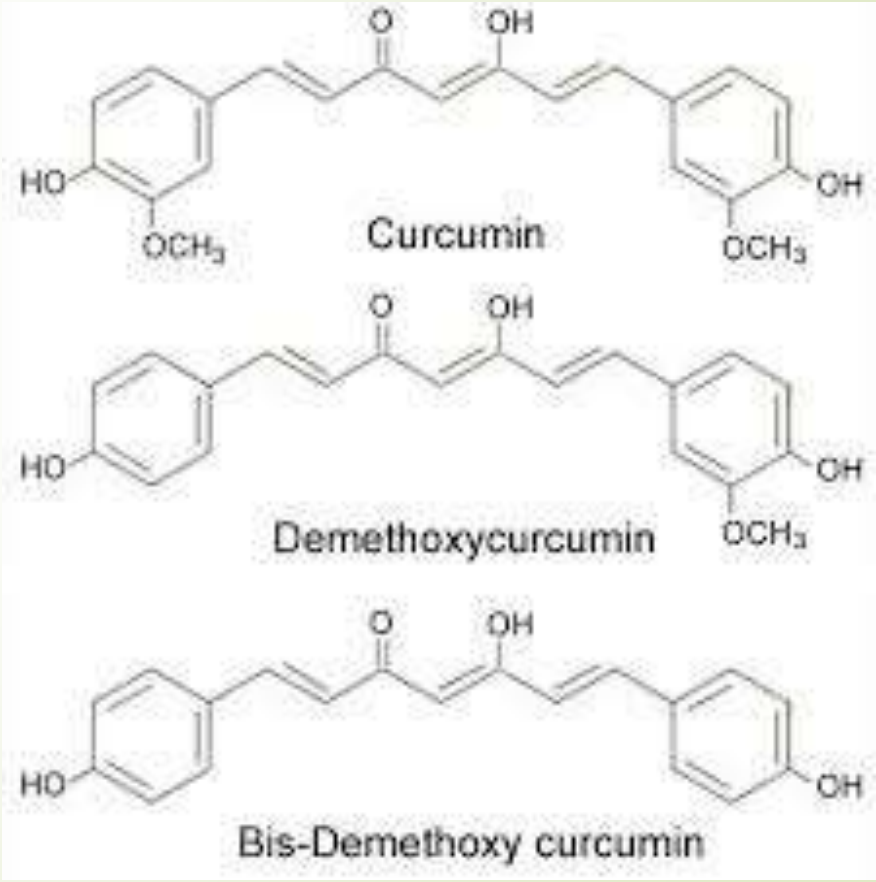
BERBERINE DOSAGE AND SAFETY

- 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.

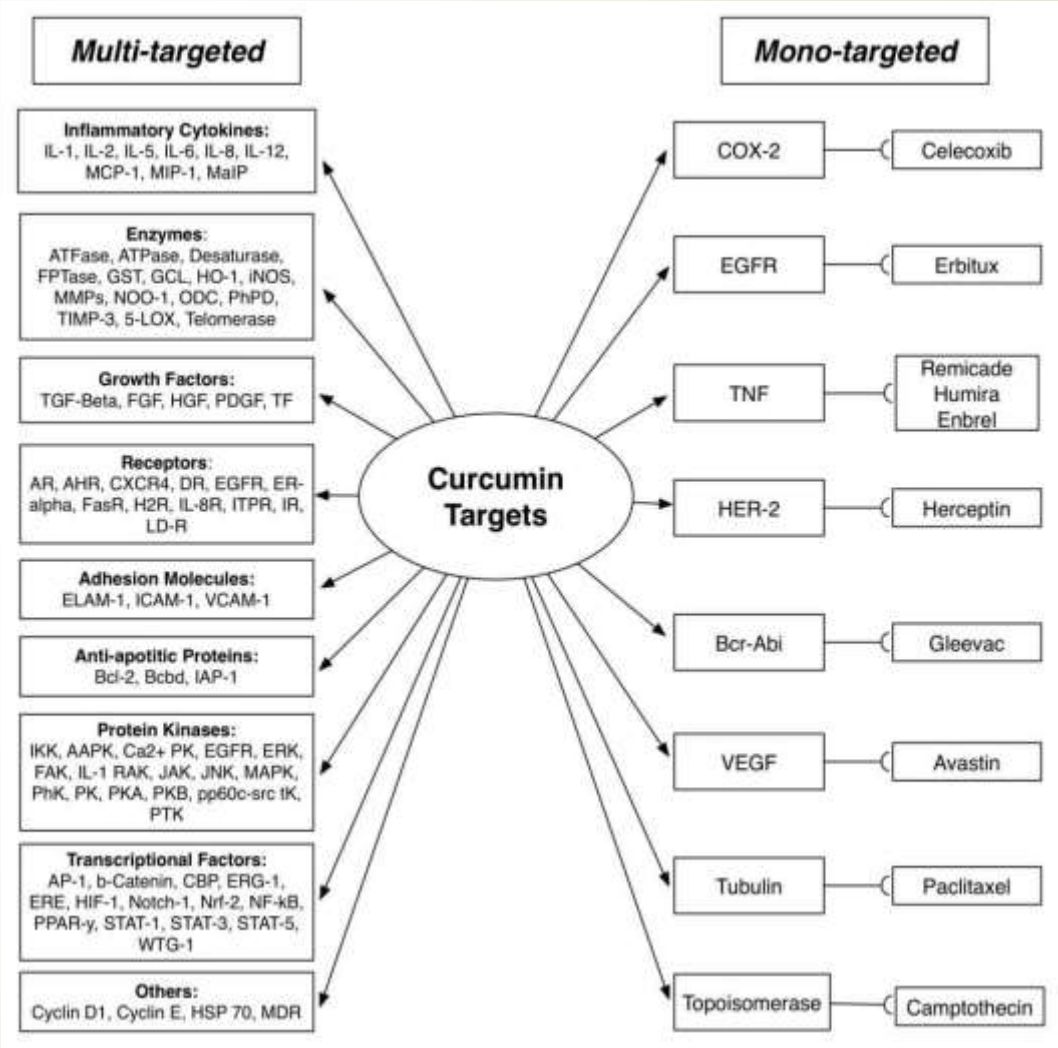


CURCUMA LONGA - TURMERIC

- *Curcuma longa* rhizomes are traditional medicines for arthritis, diarrhea and cancer
- Many of medicinal effects are credited to the curcumnoids, 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.

CURCUMIN THE SUBJECT OF ROBUST RESEARCH

- There are over 21,000 papers on curcumin listed on pubmed.



TURMERIC IS POPULAR IN THE PRESS

- 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.

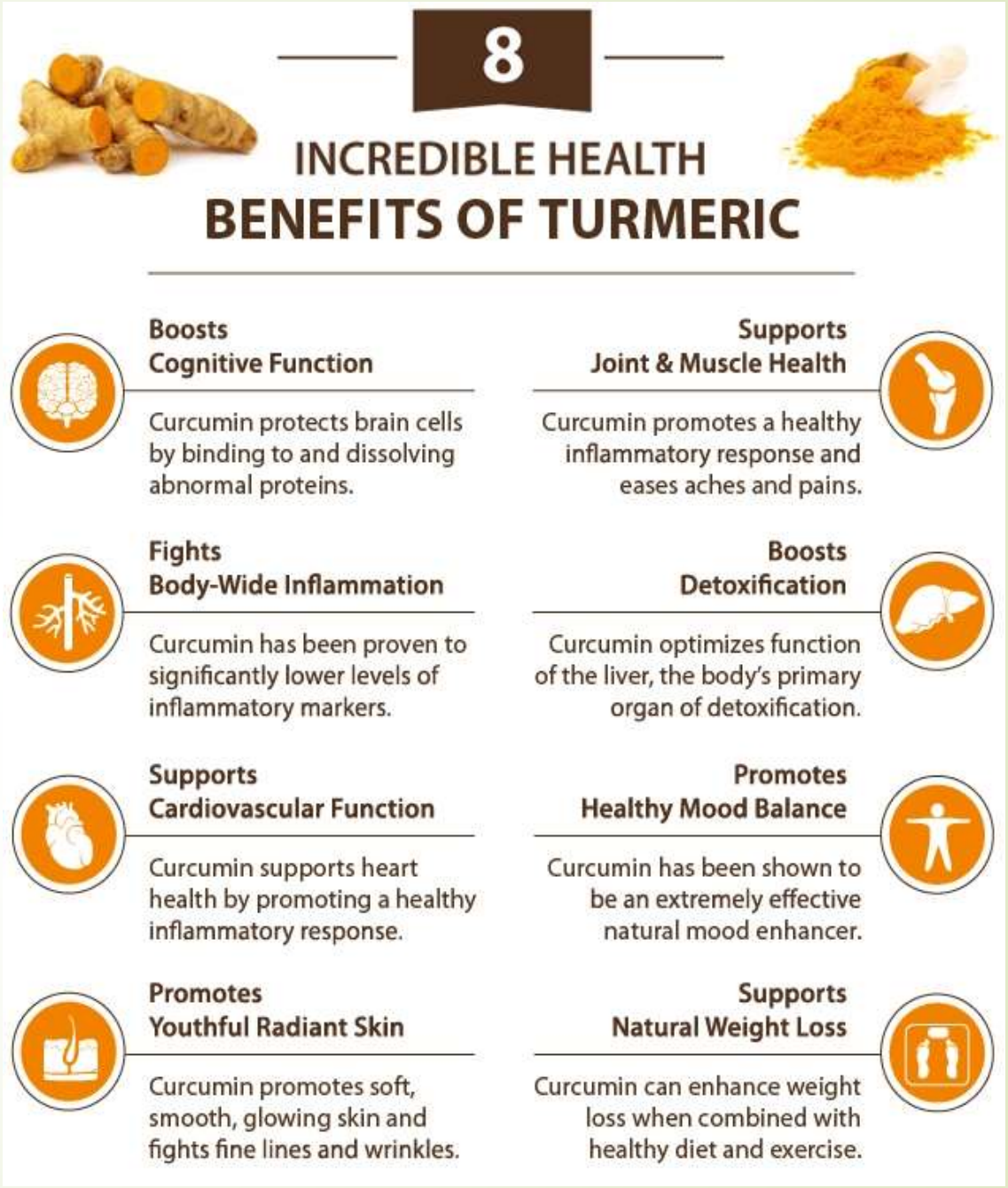


Image from rntl.net

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

Planta Med. 1998 May;64(4):353-6.

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

Shoba G[1], **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

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Gianni Belcaro – Irvine3 Circulation-Vascular Laboratory, Department of Biomedical Sciences, Chieti-Pescara University, Italy

Maria Rosaria Cesarone – Irvine3 Circulation-Vascular Laboratory, Department of Biomedical Sciences, Chieti-Pescara University, Italy

Mark Dugall – Irvine3 Circulation-Vascular Laboratory, Department of Biomedical Sciences, Chieti-Pescara University, Italy

Luciano Pellegrini – Irvine3 Circulation-Vascular Laboratory, Department of Biomedical Sciences, Chieti-Pescara University, Italy

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 (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.
(*Altern Med Rev* 2010;15(4):337-344)

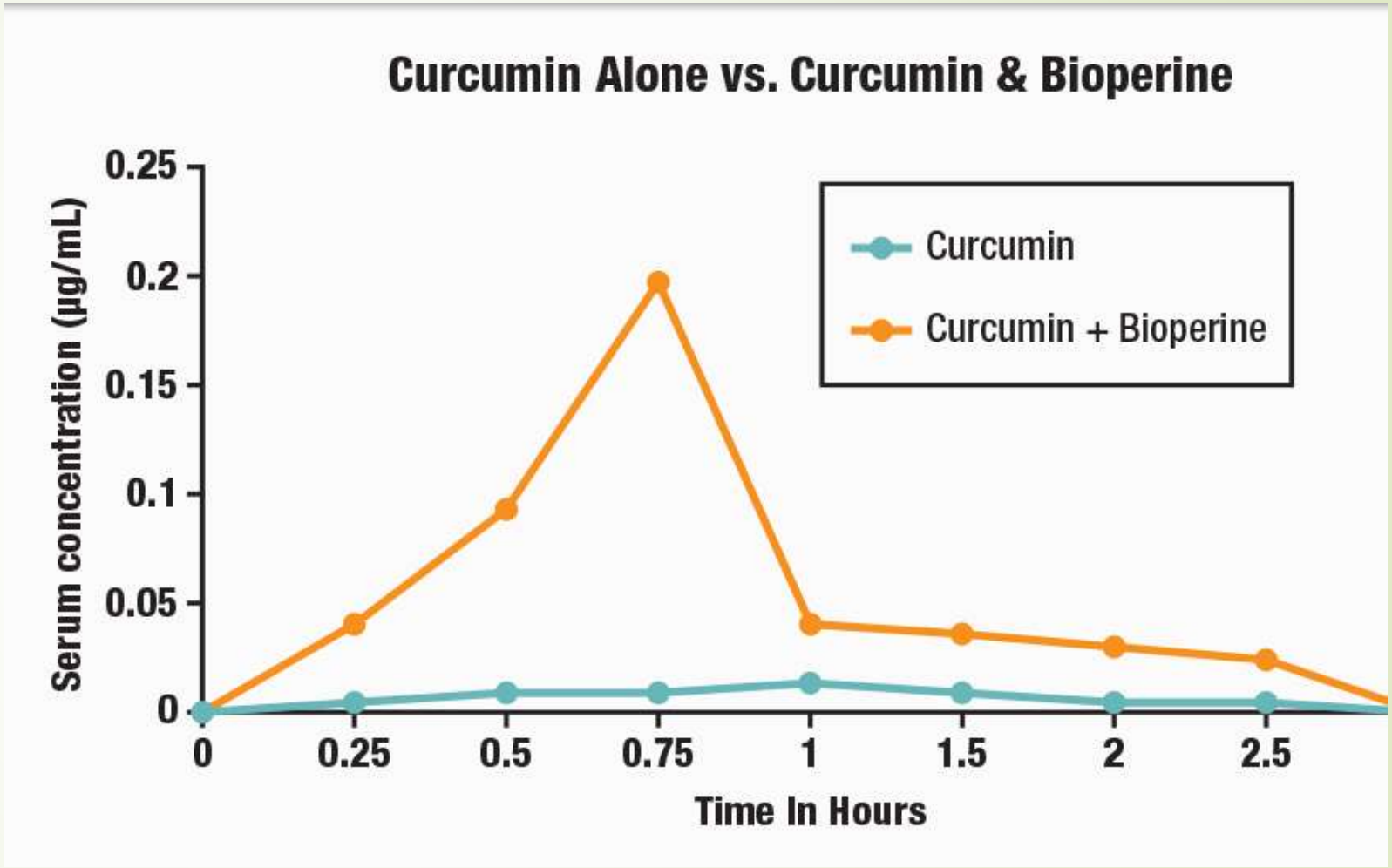
Introduction

demonstrated that curcumin acts as a master switch of inflammation by acting at the level of pro-inflammatory enzymes (cyclooxygenases [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.[3] 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.[2] 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),[4] 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.[4] Once in the plasma, however, curcumin enjoys a surprising stability and even permeability to tissues hard to reach like the brain.[4]

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 BIOAVAILABILTY

- Colloids Surf Biointerfaces. 2015 Sep 1;133:108-19. The mechanism of self-assembled mixed micelles inimproving curcumin oral absorptio n: In vitro and in vivo.
- Cancer Chemother Pharmacol. 2012 Mar;69(3):679-89. doi: 10.1007/s00280-011-1749 Enhancementof curcumin oral abso rption and pharmacokinetics of curcuminoids and curcumin metabolites in mice.
- J Nutr Sci Vitaminol (Tokyo). 2015;61(1):37-44.Colloidal submicron particle curcumin exhibits high absorption efficiency-a double-blind, 3-way crossover study.

- **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**

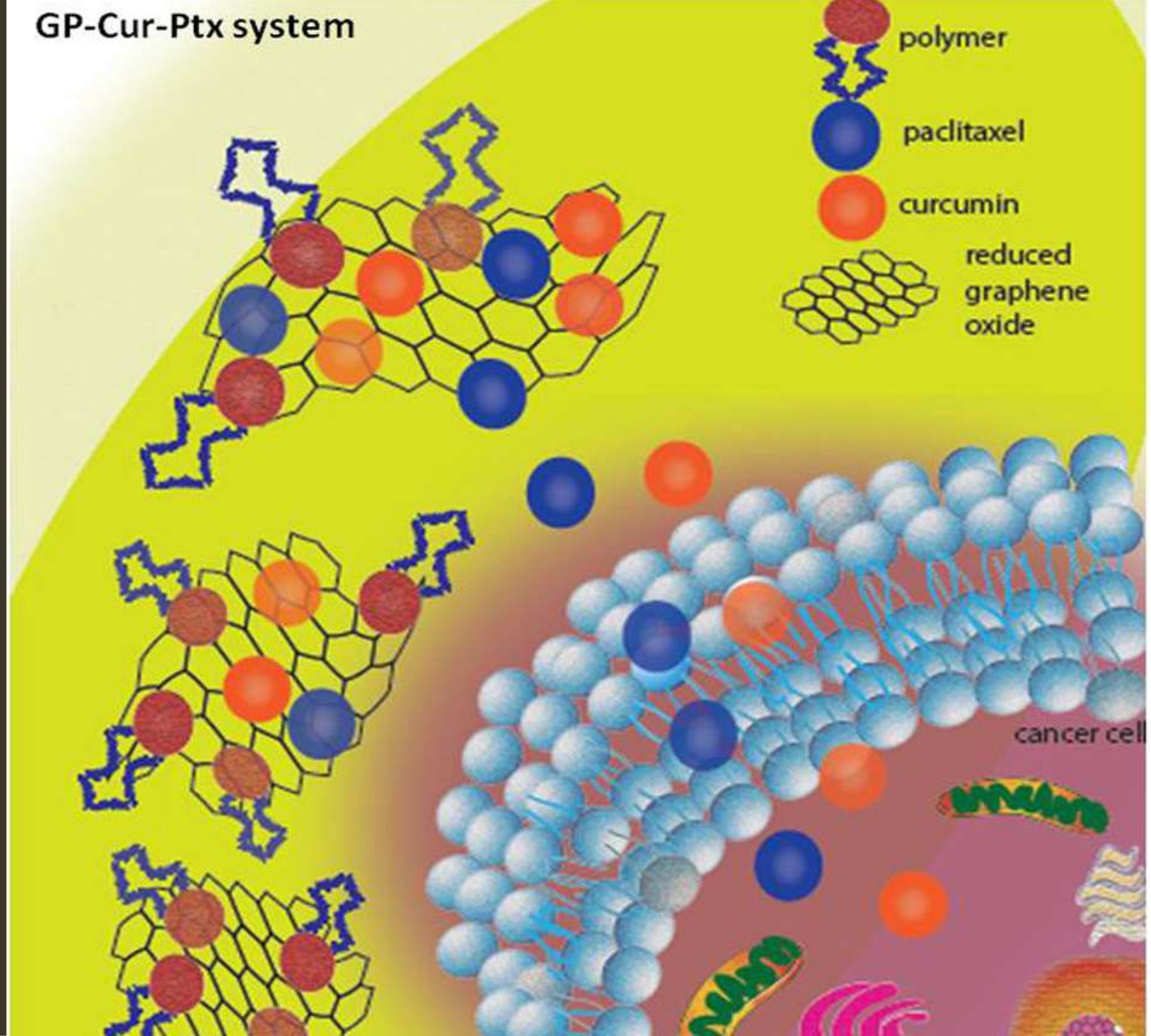
GOLDEN MILK

- 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 MANIPULATED INTO A VARIETY OF NOVEL MOLECULES

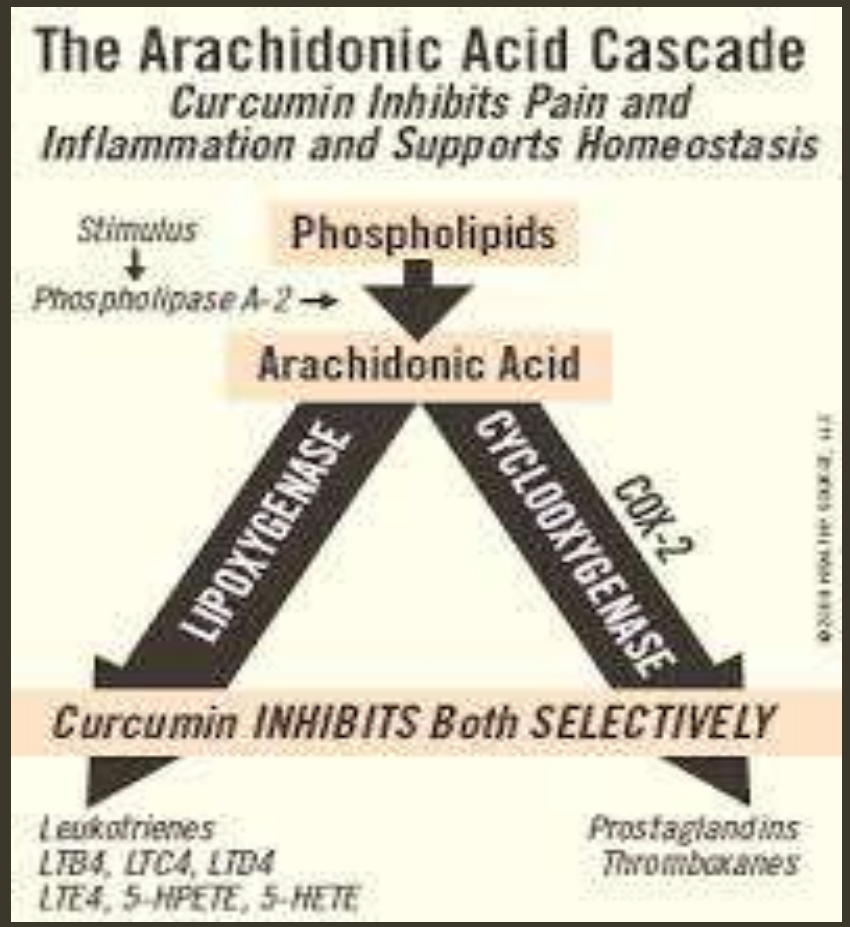
Curcumin may be micellized to enhance absorption as well as complexed with bioperine and even pharmaceutical drugs to create novel anti-cancer drugs.



CURCUMA LONGA'S MEDICINAL INDICATIONS

A SMALL SAMPLING

Curcumin can be Used in Arthritis and M/S Pain Protocols



Alternative Medicine Review Volume 14, Number 2 20

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

Julie S. Jurenka, MT(ASC

Abstract

Curcuma longa (turmeric) 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

Introduction

Turmeric (the common name for *Curcu*
longa) is an Indian spice derived from the rhizomes
the plant and has a long history of use in Ayurve
medicine as a treatment for inflammatory conditions
longa is a perennial member of the Zingiberaceae fam
and is cultivated in India and other parts of Southe
Asia.[1] The primary active constituent of turmeric
the one responsible for its vibrant yellow color is c
cumin, first identified in 1910 by Lampe and Milob
zka.[2] While curcumin has been attributed numer
pharmacological activities, including antioxidant[3]
antimicrobial properties,[4] this article focuses on one
the best-explored actions, the anti-inflammatory effe
of curcumin. Curcumin's effect on cancer (from an a
inflammatory perspective) is also discussed; however

CURCUMA PROTECTS CONNECTIVE TISSUE

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

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

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

K. Taty Anna[1], M.R. Elvy Suhana[1], S. Das[1], O. Faizah[1], A.H. Hamzaini[2]

Departments of [1]Anatomy, Faculty of Medicine, [2]Radiodiagnosis, Universiti Kebangsaan Malaysia Medical Centre

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 auto-immune 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 ankle 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 with arthritis score (AS) exceeding 1 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 erythrocyte 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 rhizomatous 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-arthritic 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

Pakistan J. Zool., vol. 49(5), pp 1665-1669, 2017. **DOI**: http://dx.doi.org/10.17582/journal.pjz/2017.49.5.1665.1669

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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Authors' Contribution
SI planned and supervised the research project. AA did all the practical work. AM prepared the Manuscript. AY helped in anticancer assays.

Key words
PC3 cells, Spice, Curcumin, Piperine, Lectin.

ABSTRACT

Plant extracts have been used as an active antimicrobial compound since long. The present study was intended to validate the antimicrobial, antidiarrheal 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 trail 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.

Thulasiraman *et al. BMC Cancer* 2014, **14**:724
http://www.biomedcentral.com/1471-2407/14/724

BMC Cancer

RESEARCH ARTICLE Open Access

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

Padmamalini Thulasiraman*, Daniel J McAndrews and Imran Q Mohiudddin

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 β/δ (PPARβ/δ) 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/ PPARβ/δ pathway. The objective of this research was to investigate the effect of curcumin, a polyphenol extract from the plant Curcuma longa, on the FABP5/ PPARβ/δ 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 MD-MB-468) treated with curcumin and/or retinoic 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 PPARβ/δ 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 PPARβ/δ target genes, PDK1and 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 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 PPARβ/δ. We provide evidence that curcumin suppresses p65, a transcription factor known to regulate FABP5. The combination of curcumin with retinoic acid suppressed PPARβ/δ target genes, VEGF-A and PDK1.

Conclusions: Curcumin suppresses the expression level of FABP5 and PPARβ/δ in triple negative mammary carcinoma cells. By targeting the FABP5/PPARβ/δ pathway, curcumin prevents the delivery of retinoic acid to PPARβ/δ and suppresses retinoic acid-induced PPARβ/δ target gene, VEGF-A. Our data demonstrates that suppression of the FABP5/ PPARβ/δ 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

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

Biochemical and Biophysical Research Communications 466 (2015) 247–253

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

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Keywords:
Curcumin
Weight loss
Thermogenesis
White adipose tissue browning
Plasma norepinephrine

ABSTRACT

Brown adipose tissue converts energy from food into heat via the mitochondrial uncoupling protein UCP1, 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 β3AR 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-β3AR pathway.

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 (UCP1), which is located in the mitochondrial inner membrane, and the unique thermogenic capacity of BAT results from mitochondrial energy uncoupling mediated by UCP1 [2]. When activated, UCP1 uncouples electron transport from ATP production, thus generating heat [6].

CURCUMA SUPPORTS METABOLISM AND IMROVES LIPID PROFILES

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

PLoS One. 2015; 10(8):*Metabolomic and Lipidomic Analysis of Serum Samples following Curcuma longa Extract Supplementation in High-Fructose and Saturated Fat Fed Rats*

Molecular and Cellular Biochemistry **166:** 169–175, 1997.

Hypolipidemic action of curcumin, the active principle of turmeric (*Curcuma longa*) in streptozotocin induced diabetic rats

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Department of Biochemistry and Nutrition, Central Food Technological Research Institute, Mysore-570 013, India

Received 26 January 1996, accepted 2 July 1996

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 hypocholesterolemic 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

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

CURCUMA AGAINST COLITIS

- Curcumin prevents the development of colitis through the inhibition of signal transduction pathways such as AP-1, protein kinase C, and NF-κB .

OPEN ACCESS Freely available online

PLOS ONE

Curcuma longa Extract Exerts a Myorelaxant Effect on the Ileum and Colon in a Mouse Experimental Colitis Model, Independent of the Anti-Inflammatory Effect

Rita Aldini[1*9], Roberta Budriesi[2*9], Giulia Roda[3¤], Matteo Micucci[2], Pierfranco Ioan[2], Antonia D'Errico-Grigioni[4], Alessandro Sartini[3], Elena Guidetti[3], Margherita Marocchi[3], Monica Cevenini[3], Francesca Rosini[4], Marco Montagnani[3], Alberto Chiarini[2], Giuseppe Mazzella[3]

1 Ospedale Policlinico S.Orsola and Dipartimento di Scienza dei Metalli, Elettrochimica e Tecniche Chimiche, Università degli Studi di Bologna, Bologna, Italy, **2** Dipartimento di Scienze Farmaceutiche, Università degli Studi di Bologna, Bologna, Italy, **3** Dipartimento di Medicina Clinica, Università degli Studi di Bologna, Ospedale Policlinico S. Orsola, Bologna, Italy, **4** Dipartimento di Medicina Interna, dell'Invecchiamento e Malattie Nefrologiche, Università degli Studi di Bologna; Ospedale Policlinico S. Orsola, Bologna, Italy

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 2.5% 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 spasmolytic agent.

Citation: Aldini R, Budriesi R, Roda G, Micucci M, Ioan P, et al. (2012) *Curcuma longa* Extract Exerts a Myorelaxant Effect on the Ileum and Colon in a Mouse Experimental Colitis Model, Independent of the Anti-Inflammatory Effect. PLoS ONE 7(9): e44650. doi:10.1371/journal.pone.0044650

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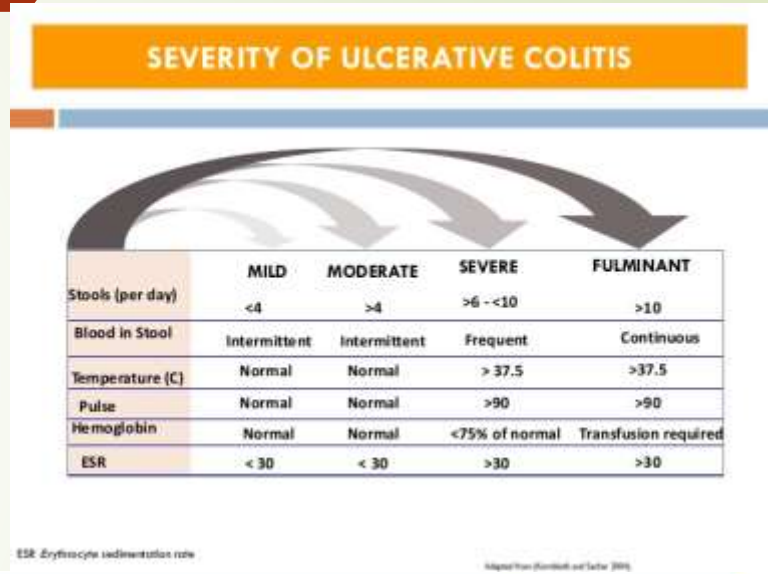
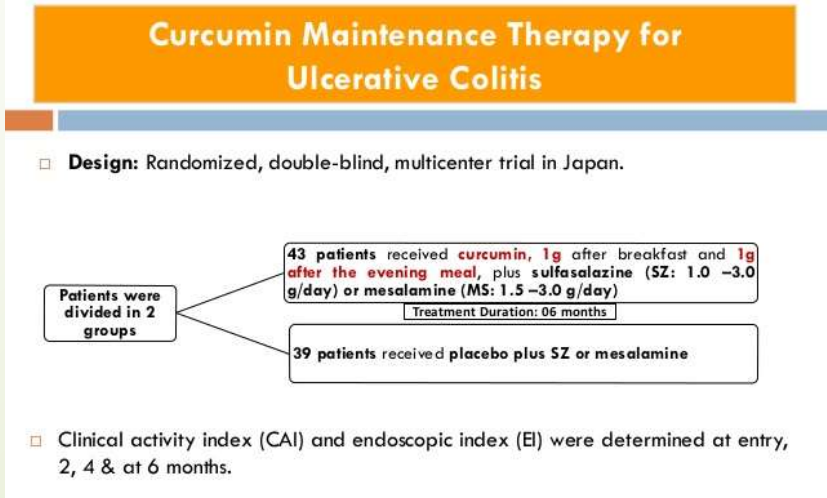
Competing Interests: The authors have declared that no competing interests exist.

CURCUMA FOR UC

- 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.

Hanai H, Iida T, Takeuchi K, Watanabe F, Maruyama Y, et al. (2006) Curcumin maintenance therapy for ulcerative colitis: randomized, multicenter, double-blind, placebo-controlled trial,. Clin Gastroenterol Hepatol 12: 1502–6.





CURCUMIN SAFETY AND DOSAGE

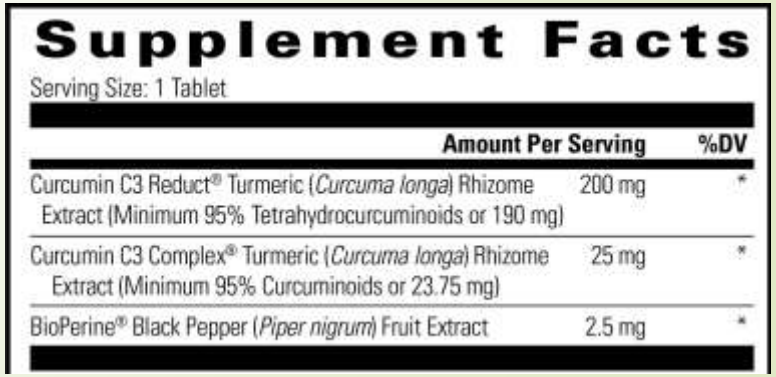
- *Curcuma* is considered very safe and without S/A, but should be avoided during pregnancy and in infants and young children
- Due to cholagogue activity, avoid *Curcuma* in biliary obstruction.
- Products standardized to 95 percent curcuminoids are of good quality.
- Concentrated products are best 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.

Supplement Facts

Serving Size 2 Capsules
Servings Per Container 30

Amount Per Serving	
Calories 10	
Turmeric root extract ✚ *(Curcuma longa)*	32 mg†
(Curcumins from total Turmeric root extracts 30mg†)	
Quercetin	60 mg†
Proprietary Extract Blend	618 mg†
Turmeric root ▲ *(Curcuma longa)*, Devil's Claw root ✚ *(Harpagophytum procumbens)*, Boswellia gum resin extract ✚	
Black Pepper fruit ✚ Supercritical extract *(Piper nigrum)*	10 mg†
Ginger root ▲ Supercritical extract *(Zingiber officinale)*	10 mg†

† Daily Value not established



Supplement Facts

Serving Size: 1 Tablet

	Amount Per Serving	%DV
Curcumin C3 Reduct® Turmeric (*Curcuma longa*) Rhizome Extract (Minimum 95% Tetrahydrocurcuminoids or 190 mg)	200 mg	*
Curcumin C3 Complex® Turmeric (*Curcuma longa*) Rhizome Extract (Minimum 95% Curcuminoids or 23.75 mg)	25 mg	*
BioPerine® Black Pepper (*Piper nigrum*) Fruit Extract	2.5 mg	*

CURCUMIN AND DRUG INTERACTIONS

- 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.

Eur Rev Med Pharmacol Sci. 2018 Aug;22(15):5042-5046. doi: 10.26355/eurrev_201808_15647. Interaction study between antiplatelet agents, anticoagulants, thyroid replacement therapy and a bioavailable formulation of curcumin (Meriva®).

Herbal Compendium Books

Sales and Book Signing at Restorative Formulations booth after presentation

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