Therapeutic potential of curcumin in digestive diseases

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Abstract

Curcumin is a low-molecular-weight hydrophobic polyphenol that is extracted from turmeric, which possesses a wide range of biological properties including anti-inflammatory, anti-oxidant, anti-proliferative and anti-microbial activities. Despite its diverse targets and substantial safety, clinical applications of this molecule for digestive disorders have been largely limited to case series or small clinical trials. The poor bioavailability of curcumin is likely the major hurdle for its more widespread use in humans. However, complexation of curcumin into phytosomes has recently helped to bypass this problem, as it has been demonstrated that this new lecithin formulation enables increased absorption to a level 29-fold higher than that of traditional curcuminoid products. This allows us to achieve much greater tissue substance delivery using significantly lower doses of curcumin than have been used in past clinical studies. As curcumin has already been shown to provide good therapeutic results in some small studies of both inflammatory and neoplastic bowel disorders, it is reasonable to anticipate an even greater efficacy with the advent of this new technology, which remarkably improves its bioavailability. These features are very promising and may represent a novel and effective therapeutic approach to both functional and organic digestive diseases.

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Key words: Curcumin; Curcumin-phytosome; Curcumin bioavailability; Digestive disorders

Core tip: Curcumin is a well-established molecule with multiple pharmacological activities, mainly anti-inflammatory and anti-proliferative. The major hurdle for a widespread clinical use has been represented by its poor bioavailability, which has been recently overcome by the development of a new formulation combining curcumin with phospholipids (curcumin-phytosome). This compound permits to improve markedly intestinal absorption of curcumin and guarantees a greater tissue delivery than the traditional curcuminoid mixtures. So, curcumin-phytosome has the potential to be exploited in many gastrointestinal diseases, both functional and organic.


INTRODUCTION

In recent years, we have witnessed a shortage of certain types of drugs synthesized from chemical laboratories and a growing interest in therapeutic substances derived from natural plants. Curcumin represents one of these compounds, and this nutraceutical has already undergone many experimental and clinical studies to assess its use in the treatment of various human diseases.

This polyphenol has been shown to possess anti-inflammatory, anti-oxidant, immuno-modulatory, wound-healing, anti-proliferative and antimicrobial activities. These diverse properties, together with the fact that curcumin is innocuous, inexpensive and easily available,
have sparked interest in its therapeutic application for several digestive disorders. Moreover, recent progress in the formulation of curcumin complexes with other substances, in particular with phospholipids, has remarkably increased the bioavailability of this compound, leading to greater absorption and a higher concentration in human tissues. This allows us to use lower dosages of curcumin than have been used in the past, which greatly reduces the number of tablets taken during the day while maintaining no adverse side effects.

Finally, distribution studies of curcumin in human tissues have shown that it preferentially accumulates in the intestine, colon and liver. This finding might be one major reason for the anticipation and observation of its most promising in vivo effects in gastrointestinal diseases when compared with other organ systems.

This review presents current knowledge of the physical and molecular properties of curcumin, its pharmacokinetics and metabolism, its mechanism of action and results of the few published clinical trials, as well as the potential therapeutic perspectives in patients with various digestive disorders.

Literature searches were performed in PubMed, Ovid, EMBASE and the Cochrane Library databases in accordance with published recommendations. We critically analyzed all full-text papers and reviews written in the English language and searched them using the terms curcumin, turmeric, colorectal cancer (CRC), inflammatory bowel diseases (IBD), functional digestive disorders, irritable bowel syndrome and liver diseases. Both animal and human studies were reviewed.

PHYSICAL AND MOLECULAR PROPERTIES OF CURCUMIN

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[3].

The primary active constituent of turmeric, which is responsible for its vibrant yellow color, is curcumin, which was first identified in 1910 by Lampe and Milobe[2]. Curcumin exists as a bright yellow powder that provides the pigmentation of turmeric, which is used in the dye industry. Turmeric is composed of volatile oils (tumerone, atlantone, and zingiberone), sugars, proteins, resins and a group of the following three curcuminoids: about 75% curcumin (diferuloylmethane), about 16% demethoxycurcumin (DMC), about 8% bisdemethoxycurcumin (bDMC). DMC and bDMC possess similar molecular and biological properties. It is proposed that within natural pathways (Figure 1), bDMC is converted to DMC, which is then converted to curcumin[3].

Curcumin (or diferuloylmethane) is a poly-phenolic molecule that exhibits keto-enol tautomerism and has a predominant keto form in acidic and neutral solutions and a stable enol form in alkaline medium[4]. The molecule is lipophilic and consists of two aromatic rings connected by two unsaturated carbonyl groups; therefore, it has poor solubility in water. The molecule is stabilized by hydrogen-bonding associated with the central OH group. This may be one of the important functional sites that is responsible for the array of molecular biological activities[5]. Curcumin is photosensitive, and precautions should be taken to avoid exposure and subsequent degradation.

PHARMACOKINETICS AND METABOLISM OF CURCUMIN

Absorption and systemic bioavailability

Over the past three decades, animal studies have shown that curcumin is hydrolytically unstable at intestinal pH, rapidly metabolized, conjugated in the liver, and excreted in the feces. Therefore, it has limited systemic bioavailability. The effects of reduced bioavailability of any agent within the body are low intrinsic activity, poor absorption, high rate of metabolism, inactivity of metabolic products and/or rapid elimination and clearance from the body. In this section, problems of limited curcumin bioavailability such as low serum levels, limited tissue distribution, apparent rapid metabolism and short half-life are described in detail.

Serum concentration

One of the major observations from curcumin studies is very low serum levels. The first reported study to examine the uptake, distribution, and excretion of curcumin was by Wahlstrom and Blennow[6] in 1978 using Sprague-Dawley rats. Negligible amounts of curcumin in the blood plasma of rats after oral administration of 1 g/kg of curcumin showed that this molecule was poorly absorbed from the gut.

In 1980, Ravindranath et al[7] showed that after oral administration of 400 mg of curcumin in rats, no curcumin
was found in the heart blood, whereas a trace amount (less than 5 μg/mL) was found in the portal blood from 15 min to 24 h after curcumin administration. When curcumin was given orally at a dose of 2 g/kg in rats, a maximum serum concentration of 1.35 ± 0.23 μg/mL was observed after 0.83 h, whereas in humans, the same dose of curcumin resulted in either undetectable or extremely low (0.006 ± 0.005 μg/mL at 1 h) serum levels.

A phase 1 clinical trial conducted among 25 patients with various precancerous lesions demonstrated that oral doses of 4, 6 and 8 g of curcumin administered daily for three months yielded serum curcumin concentrations of only 0.51 ± 0.11, 0.63 ± 0.06, and 1.77 ± 1.87 μg/mL, respectively. This finding indicates that curcumin is poorly absorbed and may have limited systemic bioavailability. Serum levels peaked between one and two hours after administration and declined rapidly thereafter. This study did not identify curcumin metabolites, and urinary excretion of curcumin was undetectable.

Another phase 1 trial involving 15 patients with advanced colorectal cancer administered curcumin at doses between 0.45 and 3.6 g daily for four months. In three of six patients who were given the 3.6 g dose, the mean plasma curcumin measured after one hour on day 1 was 11.1 ± 0.6 nmol/L. This measurement remained relatively consistent at all-time points measured during the first month of curcumin therapy. The molecule was not detected in the plasma of patients taking lower doses.

A very recent study by Yang et al showed that 10 mg/kg of curcumin given intraperitoneally in rats yielded a maximum serum curcumin level of 0.36 ± 0.05 μg/mL, whereas a 50-fold higher curcumin dose administered orally yielded a maximum serum level of only 0.06 ± 0.01 μg/mL.

These studies clearly suggest that the route of administration affects achievable serum levels of curcumin, and they further indicate that the serum levels of this compound in rats and in humans are not directly comparable.

### Tissue distribution

The uptake and distribution of curcumin in body tissues are obviously important factors determining its biological activity, yet a limited number of studies have addressed this issue.

Ravindranath et al showed that after oral administration of 400 mg of curcumin in rats, only traces of the unchanged molecule were found in the liver and kidney. At 30 min, 90% of the curcumin was found in the stomach and small intestine, but only 1% was present at 24 h.

Another study of the same group evaluated the tissue distribution of curcumin using a tritium-labeled molecule. They found that radioactivity was detectable in the bile, liver, and kidney following doses of 4000 mg/kg, or 10 mg of 3H curcumin. With 400 mg, considerable amounts of the radio-labeled products were present in tissues 12 d after dosing. The percentage of curcumin absorbed (60%-66% of the given dose) remained constant regardless of the dose, indicating that increased administration of the drug does not result in greater absorption.

Similarly, the concentrations of curcumin in normal and malignant colorectal tissue of patients receiving 3600 mg of the compound were 12.7 ± 5.7 and 7.7 ± 1.8 nmol/g, respectively, and these doses had pharmacological activity in the colorectum as measured by their effects on levels of M1G and cyclooxygenase-2 (COX-2) protein. Another study by the same authors showed no curcumin in the liver tissue of patients with hepatic metastases from colorectal cancer who received 450-3600 mg of curcumin daily for 1 wk prior to surgery.

### Metabolites

Various studies have evaluated the metabolism of curcumin in rodents and in humans. Once absorbed, curcumin is subjected to conjugations such as sulfation and glucuronidation at various tissue sites. The very first biodistribution study reported the metabolism of the major part of curcumin orally administered in rats. The liver was indicated as the major organ responsible for metabolism of this drug.

Holder et al reported that the major biliary metabolites of curcumin in rats are glucuronides of tetrahydrcocurcumin (THC) and hexahydrocurcumin. A minor biliary metabolite was dihydroferulic acid together with traces of ferulic acid. In addition to glucuronides, sulfate conjugates were found in the urine of curcumin-treated mice.

Asai et al evaluated the absorption and metabolism of orally administered curcumin in rats. The enzymatic hydrolysis of plasma samples showed that the predominant metabolites in plasma following oral administration were glucuronides/sulfates of curcumin. The plasma concentrations of conjugated curcuminoids reached a maximum at 1 h after administration. The presence of conjugative enzyme activities for glucuronidation and sulfation of curcumin in the liver, kidney and intestinal mucosa suggests that orally administered curcumin is absorbed from the alimentary tract and is present in the general blood circulation after largely being metabolized to form glucuronide/sulfate conjugates.

Whether curcumin metabolites are as active as curcumin itself is not clear. While most studies indicate that curcumin glucuronides and THC are less active than curcumin itself, other studies suggest that they may actually be more active than curcumin.

### Half-life

Systemic elimination or clearance of curcumin from the body is another important factor that determines its relative biological activity. Wahlstrom and Blennow reported that when 1 g/kg curcumin was given orally to rats, 75% of it was excreted in the feces, and negligible amounts were found in the urine. Intravenous (ip) and intraperitoneal (ip) administration of curcumin resulted in biliary excretion of the molecule from cannulated rats.

A clinical study of 15 patients receiving oral curcumin in doses between 36 and 180 mg daily for up to 4 mo found neither curcumin nor its metabolites in urine, but the drug was recovered from feces. The absorption and
elimination half-lives of orally administered curcumin (2 g/kg) in rats were reported to be 0.31 ± 0.07 and 1.7 ± 0.5 h, respectively. However, in humans, the same dose of curcumin did not allow the calculation of these half-life values because the serum curcumin levels were below the detection limit at the majority of time points in most of the experimental subjects.

The existing evidence in the literature is not sufficient to make conclusions about the factors controlling the in vivo elimination half-life of curcumin, and future studies are warranted to address this issue.

METHODS TO OVERCOME THE TRADITIONAL LOW BIOAVAILABILITY OF CURCUMIN

Because of the above-mentioned poor bioavailability, which limits the therapeutic usefulness of curcumin, many attempts have been made to improve oral absorption of the compound\(^\text{[23]}\). Among them, the complexation of curcumin with phospholipids using so-called phytosome technology has emerged as one of the most documented approaches from a preclinical and clinical standpoint.

Phytosome technology was developed in 1989 (Figure 2). Water-soluble phytosomes can be converted into a lipid-compatible molecular complex. Phytosomes are more available than uncomplexed products due to their enhanced capacity to cross the lipid biomembranes and to reach the systemic circulation\(^\text{[24]}\).

It is inferred that, at the intestinal level, the water-miscible phosphatidylcholine (PC) molecules enhance the dispersion of the poorly water-soluble polyphenol molecules into the water-soluble environment of the gastrointestinal lumen. PC further enhances transfer from the lumen into the lipid-soluble environment of the outer cell membrane of the epithelial absorptive cells (enterocytes). The enterocyte outer membrane has a lipid molecular bilayer that consists largely of PC. It is feasible that the PC in the phytosome merges into this PC domain of the enterocyte membrane, and by carrying the polyphenol with it, the PC “ushers” the polyphenol into the cell.

The bioavailability of the curcumin phytosome (CP) preparation (Meriva\(^\text{®},\) Indena Spa, Milan, Italy) has been tested against an equivalent non-phytosome curcumin extract by Marczylo et al\(^\text{[25]}\). These authors administered equivalent dosages (340 mg of curcumin) of curcumin or curcumin phytosome preparation to rats and reported a dramatic increase in the bioavailability among the animals that received the curcumin phytosome preparation (Figure 3). Peak plasma levels of curcumin were approximately
Table 1  Pharmacokinetics parameters in healthy volunteers after administration of curcuminphytosomes or unformulated curcumin

<table>
<thead>
<tr>
<th>Curcuminoid</th>
<th>Formulation</th>
<th>AUC (ng/mL)</th>
<th>Cmax (ng/mL)</th>
<th>tmax (h)</th>
<th>Relative absorption</th>
</tr>
</thead>
<tbody>
<tr>
<td>Curcumin (1a)</td>
<td>Curcuminphytosome high</td>
<td>538.0 ± 130.7</td>
<td>50.3 ± 12.7</td>
<td>3.8 ± 0.6</td>
<td>19.2²</td>
</tr>
<tr>
<td></td>
<td>Curcuminphytosome low</td>
<td>272.6 ± 68.52</td>
<td>24.2 ± 5.9</td>
<td>4.2 ± 0.8</td>
<td>17.5³</td>
</tr>
<tr>
<td></td>
<td>Reference</td>
<td>122.5 ± 29.3</td>
<td>9.0 ± 2.8</td>
<td>6.9 ± 2.2</td>
<td>1</td>
</tr>
<tr>
<td>Demethoxycurcumin (1b)</td>
<td>Curcuminphytosome high</td>
<td>655.0 ± 195.7</td>
<td>134.6 ± 40.6</td>
<td>2.4 ± 0.3</td>
<td>68.3⁴</td>
</tr>
<tr>
<td></td>
<td>Curcuminphytosome low</td>
<td>297.4 ± 107.3</td>
<td>39.1 ± 11.4</td>
<td>3.1 ± 0.4</td>
<td>55.5⁵</td>
</tr>
<tr>
<td></td>
<td>Reference</td>
<td>55.8 ± 15.5</td>
<td>4.2 ± 1.1</td>
<td>4.4 ± 1.0</td>
<td>1</td>
</tr>
<tr>
<td>Bisdemethoxycurcumin (1c)</td>
<td>Curcuminphytosome high</td>
<td>142.2 ± 58.2</td>
<td>24.9 ± 8.1</td>
<td>2.2 ± 0.4</td>
<td>56.8⁶</td>
</tr>
<tr>
<td></td>
<td>Curcuminphytosome low</td>
<td>70.1 ± 34.3</td>
<td>8.8 ± 3.1</td>
<td>2.4 ± 0.6</td>
<td>53.1⁷</td>
</tr>
<tr>
<td></td>
<td>Reference</td>
<td>24.6 ± 10.3</td>
<td>2.1 ± 0.8</td>
<td>3.4 ± 1.2</td>
<td>1</td>
</tr>
<tr>
<td>Total curcuminoids</td>
<td>Curcuminphytosome high</td>
<td>1336.0 ± 357.1</td>
<td>206.9 ± 54.9</td>
<td>2.7 ± 0.3</td>
<td>31.5⁸</td>
</tr>
<tr>
<td></td>
<td>Curcuminphytosome low</td>
<td>640.2 ± 197.7</td>
<td>68.9 ± 16.9</td>
<td>3.3 ± 0.3</td>
<td>27.2⁹</td>
</tr>
<tr>
<td></td>
<td>Reference</td>
<td>202.8 ± 53.8</td>
<td>14.4 ± 4.2</td>
<td>6.9 ± 2.2</td>
<td>1</td>
</tr>
</tbody>
</table>

1Actual results not baseline subtracted, and errors are standard error of the mean ± SE; ²Area under the curve (AUC) normalized; ³Average: 18.3; ⁴Average: 61.9; ⁵Average: 54.1; ⁶Average: 29.4.

Figure 4  Image of Norflo® tablet in water after few seconds.

5-fold higher for CP than for traditional curcumin. Plasma levels of curcumin sulfate and curcumin glucuronide observed after the administration of CP were 3- to 20-fold higher, respectively, than those observed after the administration of uncomplexed curcumin. In the same study, significant amounts of curcumin were also measured at the tissue level and were found to have particular relevance for the liver and intestine.

More recently, Cuomo et al.[34] reported the results of a comparative pharmacokinetic study of healthy volunteers. In this randomized, double-blind, cross-over study, subjects received curcumin and the CP formulation at 2 dosage levels (209 and 376 total curcuminoids). The average dose-related absorption of curcumin following the 2 doses of CP was approximately 18-fold higher than the absorption of the reference curcumin. Moreover, the absorption of total curcuminoids was approximately 29-fold higher for CP in comparison with the unformulated reference, as the plasma concentration of demethoxycurcumin and bis-demethoxycurcumin from the former compound was approximately 50- to 60-fold higher than the concentration from the unformulated curcumin (Table 1).

CP is a powder that contains 20% curcumin, 40% microcrystalline cellulose and 40% phospholipids. It is utilized as an active ingredient in several food supplements in different markets. The product is available in various formulations including hard gel capsules and tablets. In Italy, for example, the product has been developed as 500-mg tablets that combine CP with some dissolving substances (Curcusol) under the name Norflo® (Eyepharma, Genoa, Italy). These tablets dissolve very rapidly in the first part of the intestine, favoring the formation of an emulsion with bile acids (Figure 4), which permits almost complete absorption of phospholipids (unpublished data). The use of this formulation overcomes the risk that undissolved tablets may pass through the entire intestine and be eliminated in the feces either intact or partially dissolved.

CP has been widely documented in several health settings, but few studies have focused on gastrointestinal disorders, which, nevertheless, seem to be a very promising therapeutic area. From this perspective, a colon-targeted delivery preparation could further optimize the clinical effects.

TOXICITY AND TOLERABILITY OF CURCUMIN

Curcumin has been reported to be safe in many human studies, and only minimal toxicity has been associated with this polyphenol[27]. In a dose escalation study among 34 healthy volunteers, in whom the doses of curcumin ranged from 500 to 12000 mg, safety was assessed after 72 h. Only 7 subjects complained of disturbances, which were mild and included headache, skin rash, diarrhea and yellow stool[28]. In another investigation lasting for 1-4 mo, escalating doses of curcumin from 0.45 to 3.6 g/d found rare instances of nausea and diarrhea, as well as an increase in alkaline phosphatase and LDH[29]. Some patients treated with doses as high as 8 g/d for 2 wk reported abdominal pain and complained about the bulky volume of the tablets[30]. As curcumin is particularly concentrated in the human liver, the risk of hepatotoxicity has been closely evaluated, but liver function tests have been shown to be unaffected with doses as high as 2-4 g/d[29]. As one of the most documented bioavailable curcumin formulations, the CP formulation has been widely employed in the clinical setting with a daily dosage rang-
Curcumin therapeutic potential for digestive disorders

ing between 1 and 2 g, and this preparation has shown good tolerability and compliance, even in medium-term trials. However, we must stress that studies of more than 6 mo of treatment are lacking, and it is not possible to draw any firm conclusions regarding the long-term safety profile of this compound.

MECHANISMS OF ACTION AGAINST INFLAMMATORY AND NEOPLASTIC CONDITIONS

Anti-inflammatory mechanisms
Curcumin is a highly pleiotropic molecule capable of interacting with numerous molecular targets involved in inflammation. It has been proposed that this compound modulates the inflammatory response by the following mechanisms[30,31]. (1) Down-regulation of COX-2, lipoxigenase, and inducible nitric oxide (iNOS) enzymes; (2) Inhibition of the inflammatory cytokines, tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1, -2, -6, -8, and -12, monocyte chemoattractant protein, and migration inhibitory protein; and (3) Down-regulation of mitogen-activated and Janus kinases.

COX-2 inhibition and iNOS inhibition are likely achieved via curcumin suppression of nuclear factor kappa B (NF-κB) activation. NF-κB is a ubiquitous eukaryotic transcription factor involved in the regulation of inflammation, cellular proliferation, transformation, and tumorigenesis[32]. NF-κB is not a single gene but rather a family of interrelated transcription factors that include the following five genes: NF-κB1 (p50/p105), NF-κB2 (p52/p100), RelA (p65), c-Rel, and RelB[33]. The member proteins form homo- or heterodimers, of which the p50/p65 heterodimer is the most abundant and is responsible for the majority of NF-κB canonical transcriptional activity. Generally, NF-κB dimers associate with an inhibitory-κB (IκB-α) protein that keeps the dimer in the cytoplasm in an inactive state.

NF-κB activation begins with the activation of an IκB kinase (IKK) complex that consists of catalytic subunits IKK-α and IKK-β and the scaffolding subunit IKK-γ (the NF-κB essential modifier)[34]. Several mitogen-activated protein (MAP) kinases that also include NF-κB-inducing kinase (NIK) activate IKK through the phosphorylation of IKK-α and IKK-β. IKK-β has higher activity than IKK-α for IκB-α and is considered important in the canonical pathway.

In the canonical pathway, as shown in Figure 4, phosphorylation of I-kappa B kinase (IκB) kinase α/β by mitogen-activated protein kinase (MAPK) is followed by phosphorylation of IκB-α, which occurs in an inactive complex with p50/p65. Phosphorylated IκB-α is released and degraded in the cytoplasm. The active heterodimer of p50/p65 enters the nucleus to regulate expression of multiple genes[35].

Curcumin is thought to suppress NF-κB activation and proinflammatory gene expression by blocking phosphorylation of inhibitory factor IκB. Suppression of NF-κB activation subsequently down-regulates COX-2 and iNOS expression, thus inhibiting the inflammatory process and tumorigenesis[36]. In an animal model of inflammation, curcumin also inhibited arachidonic acid metabolism and inflammation in mouse skin epidermis via down-regulation of the cyclooxygenase and lipoxygenase pathways[37].

In vitro studies indicate that curcumin inhibition of inflammatory cytokines is achieved through suppression of cytokine gene expression and down-regulation of intracellular signaling proteins, such as protein kinase C[38].

Curcumin anticancer effects
There has been some promising research concerning curcumin as a safe therapeutic agent for many cancers, including colorectal cancer. This has been shown through various studies in cell cultures, animal models, and humans[39,40].

Carcinogenesis is a complex process mainly consisting of the following three phases: initiation, promotion, and progression[41]. There is suggestive evidence that inflammation may play a role in the three phases of carcinogenesis[42]. Cancer initiation is produced by oxidative stress and chronic inflammation[43]. Inflammation acts as a key regulator in the promotion of these initiated cells, possibly by providing them with proliferating signals and by preventing apoptosis[44]. The role of inflammation in tumor induction and subsequent malignant progression has also been investigated[45]. An inflammatory response produces cytokines, which act as growth and/or angiogenic factors, leading transformed cells to proliferate and undergo promotion. Leukocytes produce cytokines and angiogenic factors as well as matrix-degrading proteases that allow the tumor cells to proliferate, invade, and metastasize. Tumor-infiltrating lymphocytes secrete matrix-degrading proteases such as matrix metallo-peptidase 9 (MMP-9) and thus promote neoplastic proliferation, angiogenesis, and invasion[46].

These details demonstrate the role of inflammation in all three stages of carcinogenesis. Substantial evidence for the role of inflammation in cancer is provided by the frequent up-regulation of inflammatory mediators such as NF-κB. The pathways activated by NF-κB up-regulators are implicated not only in tumor growth and progression but also in the development of cancer cell resistance to anti-cancer drugs, radiation and death cytokines. NF-κB is an excellent target for anti-cancer therapy[47].

Effects on tumor initiation by curcumin
Curcumin has demonstrated a significant reduction in the levels of iNOS, which produces oxidative stress, which is itself one of the main causes of tumor initiation. Curcumin inhibits the induction of nitric oxide synthase and is a potent scavenger of free radicals such as nitric oxide[48].

NF-κB has been implicated in the induction of iNOS. Curcumin prevents phosphorylation and degradation
of inhibitor \( \kappa B \)-\( \alpha \) and thereby blocks NF-\( \kappa B \) activation, which down-regulates iNOS gene transcription\(^{48}\). Curcumin was found to inhibit cell proliferation and cytokine production by inhibiting NF-\( \kappa B \) target genes involved in this mitogen induction of T-cell proliferation, interleukin IL-2 production and nitric oxide generation. The over-expression of cytokines, such as IL-10, IL-6, and IL-18, is accompanied by NF-\( \kappa B \) induction that is controlled and inhibited by curcumin\(^{46}\). Curcumin has been shown to increase expression of conjugation enzymes (phase II), which suppress ROS-mediated NF-\( \kappa B \), activator protein I (AP-1) and MAPK activation\(^{47}\).

**Tumor proliferation and progression suppression by curcumin**

We have already mentioned that NF-\( \kappa B \) has an important role in cancer initiation, promotion and progression. In addition to suppressing various cell survival and cell proliferative genes, including Bcl-2, cyclin D1, IL-6, COX-2, and MMP-9, curcumin induces apoptosis, as shown by caspase activation and poly (ADP-ribose) polymerase-cleavage\(^{48-50}\).

Curcumin is also able to block NF-\( \kappa B \) signaling and inhibit IKK activation. The suppression of cell survival and cell proliferation genes, including Bcl-2, cyclin D1, IL-6, COX-2 and MMP, has also been noted\(^{48,50}\). It has been suggested that COX-2 induction is mediated by the NF-\( \kappa B \) intracellular signaling pathway, and over-expression of COX-2 leads to malignant cell proliferation and invasion\(^{34,53}\). Curcumin inhibits COX-2 expression by repressing degradation of the inhibitory unit inhibitor \( \kappa B \)-\( \alpha \) and hindering the nuclear translocation of the functionally active subunit of NF-\( \kappa B \), thereby blocking improper NF-\( \kappa B \) activation\(^{50}\).

Curcumin has been found to reduce the invasion and subsequent metastasis of cancer cells. It suppresses MMP expression, which is believed to play a major role in mediating neovascularization and is increased during tumor progression\(^{53}\).

Curcumin down-regulates MMP-9 expression by inhibiting NF-\( \kappa B \) and AP-1 binding to the DNA promoter region. MMP-9 is one of the two determinants of neovascularization that help to form new capillaries from preexisting blood vessels\(^{53}\).

Curcumin has been noted to cause significant inhibition of tumor necrosis factor \( \alpha \)-induced VCAM-1 expression, which is related to the activation of the MAPK NF-\( \kappa B \) pathway\(^{53,54}\). Curcumin has been shown to reduce cell migration and invasion induced by osteopontin, an extracellular matrix protein, through the NF-\( \kappa B \) pathway\(^{57}\).

Curcumin may inhibit cancer cell growth through down-regulation of IL-1- and IL-8-induced receptor internalization. It controls cancer progression by either blocking tumor growth or inhibiting its invasive and aggressive potential. In both cases, most of the effects are exerted by curcumin-induced NF-\( \kappa B \) inhibition\(^{57}\).

However, curcumin has been found to arrest the cell cycle and to induce apoptotic cell death through inhibition of the Janus family of kinase-signal transducer and activator of transcription (JAK-STAT) signaling pathway\(^{58}\).

The JAK and STAT comprise an important signaling pathway involved in dysregulation of cell growth, invasion, angiogenesis, metastasis and resistance to apoptosis\(^{59,60}\). The JAK-STAT system consists of the following three main components: (1) A receptor, (2) JAK; and (3) STAT.

The receptor is activated by a signal from interferon, IL-6, growth factors, or other chemical messengers\(^{61}\). This activates the kinase function of the JAKs (JAK1, JAK2, and JAK3), which autophosphorylation (phosphate groups act as “on” and “off” switches on proteins). The STAT protein then binds to the phosphorylated receptor, where STAT is phosphorylated by JAK. The phosphorylated STAT protein binds to another phosphorylated STAT protein (dimerizes) and translocates into the cell nucleus. In the nucleus, it binds to DNA and promotes transcription of genes responsive to STAT\(^{62,63}\).

Studies have evaluated the regulators of cytokine signaling including protein tyrosine phosphatases (PTPases) such as Src homology 2 (SH2) domain-containing PTPases (SHIP)-1 and SHIP-2. Potential roles for SHP-1 and SHP-2 have been investigated for their use in the control of cytokine signaling through the dephosphorylation of JAKs and their receptors\(^{64}\).

Of the seven STAT proteins identified thus far, only activated STAT3 and STAT5 have been implicated in multiple myeloma, lymphomas, leukemias and several solid tumors\(^{65}\). Aberrant STAT3 signaling is an important process in the development and progression of cancer, thus, agents that block its activation have therapeutic potential. Rajasingh et al\(^{64}\) have demonstrated that in vitro, treatment with curcumin induced a dose-dependent decrease in JAK and STAT phosphorylation, resulting in the induction of growth-arrest and apoptosis in T cell leukemia. Curcumin reversibly inhibits STAT3 activation in human multiple myeloma cells and, by this mechanism, suppresses IL-6-induced cell proliferation\(^{67,68}\). It also inhibits STAT3 activation in five different human Hodgkin and Reed-Sternberg lymphoma cell lines\(^{69}\).

It has been shown that curcumin inhibits lysophosphatidic acid-induced IL-6 and IL-8 secretion and STAT3 phosphorylation in ovarian cancer cells\(^{70}\), and curcumin has also been shown to have a significant effect upon CRC by blocking STAT3-driven cancer cell growth\(^{70}\). In summary, the anti-inflammatory and anticancer effects of curcumin are listed in Table 2.

**CLINICAL TRIALS EXPLORING THE THERAPEUTIC POTENTIAL OF CURCUMIN IN GASTROINTESTINAL DISEASES**

Because of its higher bioavailability in the gastrointestinal
Table 2 Curcumin’s anti-inflammatory and anticancer effects

<table>
<thead>
<tr>
<th>Anti-inflammatory effects</th>
<th>Anticancer effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Downregulation of NF-κB, inhibition, via NF-κB, of COX-2, lipooxygenase, and iNOS enzymes</td>
<td>Inhibition of carcinogen activation</td>
</tr>
<tr>
<td>Inhibition of the inflammatory cytokines, such as TNF-α, interleukin (IL)-1, -2, -6, -8, and -12, MCP, and migration inhibitory protein</td>
<td>Stimulation of carcinogen detoxification</td>
</tr>
<tr>
<td>Inhibition of PPAR-γ</td>
<td>Suppression of pro-inflammatory signaling</td>
</tr>
</tbody>
</table>

TNF-α: Tumor necrosis factor-α; MCP: Monocyte chemoattractant protein; PPAR-γ: Peroxisome proliferator-activated receptor-γ; iNOS: Inducible nitric oxide synthase; STAT: Signal transducer and activator of transcription; NF-κB: Nuclear factor kappa B; COX-2: Cyclooxygenase-2.

Inflammatory bowel disease
Idiopathic IBD comprises the following two types of chronic intestinal disorders: Crohn’s disease (CD) and ulcerative colitis (UC)[71-73]. Accumulating evidence suggests that IBD results from an inappropriate inflammatory response to intestinal microbes in a genetically susceptible host[74]. Pathogen recognition by innate immune cells is coupled to the secretion of cytokines that inform the adaptive immune system about the nature of the pathogen and instruct naïve T cells to differentiate into the appropriate T cell subtypes required to clear the infection[80]. Thus, naïve T cells are induced to differentiate into Th1, Th2, Th17 and/or regulatory T cells (Treg) depending on the pathogen eliciting the response[77]. Recent studies reveal that IL-6/IL-12 family cytokines (IL-6, IL-12, IL-23, IL-27 and IL-35) play pivotal roles in these lymphocyte cell-fate decisions, and their influence on the T cell developmental program is mediated primarily through activation of an evolutionarily conserved family of latent cytoplasmic transcription factors called STATs[77,78].

The progressive damage to the gut is characterized by an aberrant inflammatory response to components of the bacterial microflora, and Th17 cells are thought to contribute to the destruction of gut tissues by inducing secretion of the extracellular matrix-degrading enzymes MMP-3 and II-21. Autocrine secretion of II-21, which perpetuates a cycle of elevated II-21 secretion, and sustained STAT3 activation in the gut play important roles in exacerbating the disease[79]. In addition, pSTAT3 enhances survival of the pathogenic Th17 cells by up-regulating Bcl-2, Bcl-xL, and Mcl-1 genes[80] and may thereby contribute to maintaining the chronic inflammatory process.

Very recently, the role of NF-κB in IBD has been elucidated[81]. Colon biopsies in IBD patients with active disease showed increased levels of NF-κB p65 protein, a member of the NF-κB family of proteins. The amount of NF-κB p65 in the tissue samples correlated with the severity of intestinal inflammation. This increased expression of NF-κB results in an increased ability to secrete inflammatory cytokines, such as TNF-α, IL-1, IL-6, IL-12, and IL-23, the latter of which are directly responsible for mucosal damage in IBD. TNF-α is also able to up-regulate the production of NF-κB, which results in a cyclical feedback loop of inflammation[81]. Additionally, the findings that the degree of gut tissue inflammation correlates with the level of pSTAT3 in histological sections of IBD patients support a role of STAT3 and Th17 cells in IBD[82].

Anti-inflammatory drugs, immunosuppressants, and TNF blockers are used to manage IBD. However, the high cost and adverse effects associated with these drugs encourage the use of alternative management options[83].

Because curcumin plays a key role in the inhibition of both the activation of NF-κB pro-inflammatory cytokines and the IL-6/STAT3 signaling pathway, it could be proposed as a novel therapeutic agent in several inflammatory diseases, such as IBD[84]. However, to date, there have been only two human studies of curcumin in patients with IBD that have achieved encouraging results. Holt et al[85] conducted a small, open-label, pilot study of curcumin in five patients with ulcerative colitis/ proctitis and five patients with Crohn’s disease. Patients with ulcerative proctitis, who were currently using 5-aminosalicylic acid (5-ASA) compounds and corticosteroids (four of five patients were on corticosteroids + 5-ASA compounds), were given 550 mg curcumin twice daily for one month and then 550 mg three times daily for the second month. Patients with CD were treated with 360 mg curcumin three times daily for 1 mo followed by 360 mg four times daily for another 2 mo. All patients were assessed at baseline and after two months of curcumin administration via hematological, biochemical, and inflammatory analysis (C-reactive protein and erythrocyte sedimentation rate) and by sigmoidoscopy and biopsy. Subjective analysis was performed via a self-reported symptom diary. In the ulcerative proctitis group, all five patients had significant improvement with reductions in concomitant medications in 4 patients. Although only four of five CD patients completed the study, they also improved, as evidenced by a lowered Crohn’s Disease Activity Index. There was a mean reduction of 55 points and a mean reduction in the sedimentation rate of 10 mm/h. Based on the symptom diary (P < 0.02), all patients improved from baseline after two months of ther-
therapy, and the inflammatory markers decreased to normal limits.

Subsequently, Hanai et al.\textsuperscript{10} evaluated the use of curcumin in 89 patients with quiescent UC in a randomized, double-blind, multicenter trial. After a four-week washout period, subjects were randomly assigned to a six-month regimen of either placebo (\( n = 44 \)) or curcumin. The treatments consisted of 1000 mg after breakfast and 1000 mg after dinner (\( n = 45 \)) in combination with sulfasalazine (SZ) (1.3 g/d; median 2 g/d) or mesalamine (1.5-3 g/d; median 2.25 g/d).

Patients were followed during treatment and for six months after the treatment ended; they received only SZ or mesalamine during the six-month follow-up period. Of 43 patients (2 patients violated the protocol) who received curcumin, 2 relapsed during the 6 mo of therapy (4.65\%), compared to 8 of 39 patients (20.51\%) in the placebo group (\( P = 0.040 \)).

Recurrence rates evaluated on the basis of intention to treat showed a significant difference between curcumin and placebo (\( P = 0.049 \)). Furthermore, curcumin improved both the clinical activity index (CAI) (\( P = 0.038 \)) and the endoscopic index (EI) (\( P = 0.0001 \)), measures that are used to evaluate the morbidity associated with UC. The authors drew the following three major conclusions: (1) Curcumin had better clinical efficacy over placebo in the prevention of relapse; (2) Curcumin significantly improved the CAI and EI; and (3) Curcumin was well-tolerated.

Based on these two studies, curcumin seems to be a promising and safe therapy for maintaining remission in patients with quiescent UC as well as for improving symptoms in patients with proctitis and CD. It is evident that further rigorous randomized controlled trials in larger samples of IBD patients are needed to validate the results of the above clinical studies. Considering its effect on multiple inflammatory pathways, curcumin also has the potential to be used as a steroid-sparing induction agent in mild to moderate colitis or as an adjunct to maintain remission in patients who are losing response to immunomodulators.

### Colorectal cancer

Currently, it appears that the anti-carcinogenic properties of curcumin are most likely due to its effects on multiple molecular targets, such as NF-\( \kappa \)B and AP-1. These are both major transcription factors that regulate inflammation and thus affect cell proliferation, differentiation and even apoptosis.

We have already mentioned that curcumin has been shown to affect a variety of other key players involved in carcinogenesis, such as cyclooxygenase-2, matrix metalloproteinases 2 and 9 and tumor necrosis factor \( \alpha \)-induced vascular cell adhesion molecule.

Sharma et al.\textsuperscript{87} conducted two separate clinical trials exploring the effect of curcumin on malignancies and tumor marker levels. In the first pilot study, the pharmacokinetics and pharmacodynamics of a standardized Curcuma extract in capsule form (Phytopharm, United Kingdom) at doses ranging from 440 to 2200 mg/d, corresponding to 36-180 mg of curcumin, were evaluated. Fifteen patients with advanced CRC refractory to standard chemotherapies received Curcuma extract daily for up to 4 mo. In one patient, measurement of a serum tumor marker revealed a decrease in carcinoembryonic antigen levels from 310 ± 15 to 175 ± 9 \( \mu \)g/L after two months of treatment with 440 mg Curcuma extract. Stable disease \textit{via} computed tomography scan was observed in five of 15 patients. Oral Curcuma extract was well-tolerated, and dose-limiting toxicity was not observed.

In the second dose-escalation study\textsuperscript{88}, 15 patients with advanced CRC refractory to standard chemotherapies consumed capsules compatible with curcumin doses of between 0.45 and 3.6 g/d for up to 4 mo. Levels of curcumin and its metabolites in plasma, urine, and feces were analyzed. Blood and imaging tests were performed at baseline and at various points throughout the trial. A daily dose of 3.6 g of curcumin caused decreases of 62\% and 57\% in inducible prostaglandin E2 (PGE2) production in blood samples taken 1 h after the dose was administered on days 1 and 29, respectively. PGE2 is an end product of cyclooxygenase that has been shown to stimulate the growth of human colorectal cancer cells.

Garcea et al.\textsuperscript{89} studied curcumin levels in the colorectum and the pharmacodynamics of curcumin in 12 patients with confirmed CRC. The staging of patients was noted; 2 patients were Duke A, 3 patients were Duke B, and 7 patients were Duke C. Patients were assigned to 450, 1800 or 3600 mg of curcumin per day for 7 d prior to surgery. The recoveries of curcumin in normal and malignant colorectal tissues of patients receiving 3.6 g of curcumin were 12.7 ± 5.7 and 7.7 ± 1.8 nmol/g, respectively. Curcumin levels were highest in the normal tissue of the cecum and the ascending colon as opposed to the transverse colon, the splenic flexure and the descending colon, which suggests a local effect. The levels of M1G were also decreased by curcumin treatment in malignant colorectal tissue. COX-2 levels were undetectable in normal tissue but were detectable in malignant colorectal tissue. Curcumin was not found to modulate the expression of Cox-2 in malignant tissues. The study concluded that a daily dose of 3.6 g of curcumin is pharmacologically efficacious in CRC patients.

Curcumin has also demonstrated potential for the prevention and treatment of CRC in combination with other agents. Familial adenomatous polyposis (FAP) is an autosomal-dominant disorder characterized by hundreds of colorectal adenomas that eventually develop into CRC. One study\textsuperscript{87} evaluated whether the combination of curcumin and quercetin could suppress adenomas in patients with FAP. Five patients with FAP received combinations of curcumin (480 mg) and quercetin (20 mg) orally three times a day, and the number and size of polyps were assessed at baseline and after therapy. Four patients had a retained rectum, and one had an ileoanal anastomosis. After 6 mo of combination treatment, all five patients had a
Curcumin therapeutic potential for digestive disorders

Dulbecco P et al. Curcumin therapeutic potential for digestive disorders

Curcumin is characterized by its high antioxidant activity, which is comparable to, if not higher than, that of vitamin C and is more than ten times higher than the activity of the scavenger vitamin E.

Liver disease
We are still remote from having available and effective drug therapies in hepatic diseases, with the exception of those with viral etiology. Especially in emerging liver diseases, such as non-alcoholic fatty liver disease (NAFLD), the only currently available therapies that have proven to be effective are those with nutritional agents such as vitamin E or those that are associated with antidiabetic drugs.

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We are still remote from having available and effective drug therapies in hepatic diseases, with the exception of those with viral etiology. Especially in emerging liver diseases, such as non-alcoholic fatty liver disease (NAFLD), the only currently available therapies that have proven to be effective are those with nutritional agents such as vitamin E or those that are associated with antidiabetic drugs. The only effective therapy for NAFLD/NASH remains non-pharmacological and involves a multidisciplinary treatment based not only on diet but also on frequent aerobic physical activity. In this scenario, curcumin appears to provide an opportunity to cure or improve liver pathologies. Curcumin has the following 4 basic effects on the hepatobiliary system: (1) Choleretic-cholagogue; (2) Antifibrotic; (3) Hepatoprotective; and (4) Antioxidant.
Overall, the antioxidant action, especially towards cells subjected to increased oxidative stress such as hepatocytes, results in an increase of cellular resistance to oxidative damage for at least 18 h\textsuperscript{[90]}. The antioxidant properties of curcumin reside in the same chemical structure. Numerous natural antioxidants can be classified into the following two types of compounds: phenolic (sesame extract) and β-diketonics (extracts of eucalyptus).

Curcumin is one of the few phenolic compounds that possess both a phenolic group and one diketonic in the same molecule. This explains why curcumin possesses the ability to interrupt the chain that transmits the oxidation of biological structures until the oxidant energy is sufficient\textsuperscript{[90]}. \textsuperscript{[99]}

In summary, the multiple positive effects of curcumin on both the biliary system and on liver structure and function encourage its clinical use, which needs to be validated in future controlled clinical trials.

**Functional digestive disorders**

The mechanisms of symptom generation in patients with functional digestive disorders are poorly understood due to the lack of a mucosal injury that enables us to explain their troublesome disturbances\textsuperscript{[100]}. Recent studies have shown that transient receptor potential vanilloid type 1 (TRPV1) receptors play a critical role in somatic and visceral nociceptive neural detection and transmission\textsuperscript{[101]}, and they have been implicated in the induction of symptoms in these diseases. TRPV1 is a polymodal sensory transducer that can be activated by multiple noxious stimuli such as heat, low pH, and endogenous lipid derivatives such as anandamide as well as by exogenous substances that possess a vanilloid moiety such as capsaicin\textsuperscript{[102]}. Of remarkable importance, the curcumin molecule has the same vanilloid ring moiety as capsaicin, making TRPV1 its likely target, and it has been shown in animals that curcumin blocks TRPV1 activation by capsaicin in a competitive manner\textsuperscript{[103]}. It has been suggested that up-regulation of TRPV1 signaling may contribute to visceral hypersensitivity in functional gastrointestinal diseases, including esophageal hypersensitivity\textsuperscript{[104]}. This condition can be found in more than 50% of patients with non-erosive reflux disease, which represents the most frequent form of gastro-esophageal reflux disease\textsuperscript{[105]}. Recent epidemiological studies have shown that the rate of reflux patients with negative endoscopy can be as high as 75%\textsuperscript{[106]}. This relevant population contains subgroups of patients with hypersensitive esophagus to both acid and non-acid reflux or patients with functional heartburn, who are difficult to treat with antisecretory therapies and who therefore may benefit from drugs that are able to act on TRPV1 receptors. In fact, curcumin has been shown to antagonize the vanilloid receptors even at low dosages and thus has the potential to modulate the response of TRPV1 to various stimulants and to prevent the generation of symptoms in patients with hypersensitive esophagus and functional heartburn\textsuperscript{[103]}

Moreover, the TRPV1 receptors are widely expressed in the entire gastrointestinal tract and enteric nervous system, and there is evidence that curcumin can inhibit GI nociception and reverse gut hypersensitivity by acting on peripheral terminals. Taking into account this mechanism of action, it cannot be excluded that this molecule may be beneficial in treating patients with functional dyspepsia and irritable bowel syndrome, which are disorders that remain clinically challenging in the setting of current drugs and whose patients may benefit from the pharmacological properties of curcumin on TRPV1 as a novel pain modulator.

Finally, as it has been shown that low-grade inflammation of the intestinal mucosa is responsible for symptoms of irritable bowel syndrome\textsuperscript{[107]}, we cannot exclude that the well-known anti-inflammatory effects of curcumin may also improve the quality of life of patients with this disease.

**CONCLUSION**

In summary, curcumin is a well-known molecule with multiple pharmacological activities that have the potential to be used to treat many gastrointestinal diseases, both functional and organic. It appears to be a very promising therapeutic compound on the basis of thousands of pre-clinical studies, but its poor bioavailability has greatly hampered more widespread clinical use. However, the new formulation of curcumin with phospholipids has allowed us to overcome this problem by markedly improving intestinal absorption compared with the traditional unformulated curcuminoid mixtures. If curcumin is truly beneficial, as has been suggested by prior clinical trials using curcumin with limited bioavailability, we can expect to see greater therapeutic effectiveness from phospholipid-complexed curcumin, which enables increased absorption
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