Review

Anticancer and carcinogenic properties of curcumin: Considerations for its clinical development as a cancer chemopreventive and chemotherapeutic agent

Miguel López-Lázaro

Department of Pharmacology, Faculty of Pharmacy, University of Seville, Sevilla, Spain

A growing body of research suggests that curcumin, the major active constituent of the dietary spice turmeric, has potential for the prevention and therapy of cancer. Preclinical data have shown that curcumin can both inhibit the formation of tumors in animal models of carcinogenesis and act on a variety of molecular targets involved in cancer development. In vitro studies have demonstrated that curcumin is an efficient inducer of apoptosis and some degree of selectivity for cancer cells has been observed. Clinical trials have revealed that curcumin is well tolerated and may produce antitumor effects in people with precancerous lesions or who are at a high risk for developing cancer. This seems to indicate that curcumin is a pharmacologically safe agent that may be used in cancer chemoprevention and therapy. Both in vitro and in vivo studies have shown, however, that curcumin may produce toxic and carcinogenic effects under specific conditions. Curcumin may also alter the effectiveness of radiotherapy and chemotherapy. This review article analyzes the in vitro and in vivo cancer-related activities of curcumin and discusses that they are linked to its known antioxidant and pro-oxidant properties. Several considerations that may help develop curcumin as an anticancer agent are also discussed.

Keywords: Clinical trials / Oxidative stress / Reactive oxygen species / Safety / Toxicity

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1 Introduction

Curcumin (diferuloylmethane) is a yellow pigment derived from the rhizome of the plant Curcuma longa L. The powdered rhizome of this plant, called turmeric, is commonly used in the preparation of curries. In addition to its preservative, flavoring, or coloring properties in the diet, turmeric has been used in Asian medicine for generations for the treatment of many disorders including inflammation, skin wounds, hepatic and biliary disorders, cough, as well as certain tumors. Curcumin, a polyphenol with a diarylheptanoid structure that contains two α,β-unsaturated ketones, is considered to be the major active constituent of turmeric. The chemical properties and the historical background of curcumin have been reviewed elsewhere [1, 2].

Although curcumin has shown a wide range of pharmacological activities, its anticancer properties have attracted a great interest. The anticancer activity of curcumin has been the subject of hundreds of papers and has been reviewed in several recent articles [1–15]. These review articles have summarized preclinical data showing that curcumin can inhibit the formation of tumors in animal models of carcinogenesis, can induce apoptosis in cancer cells from different origin, and can act on a variety of signal transduction pathways and molecular targets involved in the development of cancer. Based on preclinical and clinical studies in which curcumin was administered orally to animals and humans, most of these articles consider that curcumin is a nontoxic or low-toxic agent. This seems to indicate that the putative anticancer activity of curcumin may be accompanied by a low toxicity. These articles also show that the systemic bioavailability of curcumin following oral dosing is
low and that this agent is rapidly cleared from the body, therefore suggesting that the anticancer activity of oral curcumin may be limited to the gastrointestinal tract [1–15].

The present article compiles and analyzes the in vitro and in vivo cancer-related properties of curcumin. Since cancer chemopreventive and chemotherapeutic strategies are usually aimed at preventing or treating a specific type of cancer, the first aim of this work is to compile the most relevant cancer-related effects of curcumin on several common types of cancer. The limited bioavailability and extensive metabolism of curcumin suggest that many of its anticancer effects observed in vitro may not be attainable in vivo. This article analyzes which of these reported anticancer effects may be relevant in vivo. It is also discussed that, although relatively high concentrations of curcumin have not shown significant toxicity in short-term studies, these concentrations may lead to toxic and carcinogenic effects in the long term. In addition, this article provides evidence that suggests that the cancer-related activities of curcumin may be linked to its known antioxidant and pro-oxidant properties. After a critical analysis of the cancer-related properties of curcumin, several considerations that may help develop curcumin as a cancer chemopreventive and chemotherapeutic agent are discussed.

2 Anticancer activity of curcumin

The most relevant cancer chemopreventive and chemotherapeutic effects of curcumin on several common types of cancer are compiled in Table 1. This table gathers reports in which curcumin has shown cancer chemopreventive activity in animal models of carcinogenesis, as well as selected in vitro and in vivo studies that may have relevance to cancer chemoprevention. This table also compiles the most relevant reports in which curcumin has shown chemotherapeutic effects; it mainly includes selected studies in which this dietary agent induced apoptosis in cancer cells from different cancer types, as well as several works that studied the chemotherapeutic effects of curcumin in vivo. The chemopreventive and chemotherapeutic properties of curcumin are discussed in the following sections.

2.1 Cancer chemopreventive activity of curcumin. Possible in vivo mechanisms

The limited progress achieved by cancer therapy in the last three decades [16, 17] has increased the interest of researchers in cancer chemoprevention. It is becoming accepted that cancer chemoprevention (the use of chemicals to prevent, stop, or reverse the process of carcinogenesis) is an essential approach to controlling cancer. In addition, since the process of carcinogenesis can take several decades to complete, it makes more sense to prevent cancer at its earliest stages by using low-toxic chemicals (chemoprevention) than to wait until the disease has reached its final stages, where it becomes necessary to use more toxic chemicals (chemotherapy). Cancer chemoprevention can be aimed at healthy populations or at those with cancer predisposition (people with precancerous lesions or those who are at high risk for developing cancer). In the first case, chemopreventive interventions must be completely devoid of toxicity and chemicals should be supplemented orally. In the second case, some degree of toxicity is acceptable and the oral route is preferable [18–20].

Several lines of evidence suggest that curcumin may be used in cancer chemoprevention. Firstly, epidemiological data suggest that the incidence of several common cancers (i.e., colon, breast, prostate, and lung cancer) is higher in Western countries than in countries such as India, where curcumin is highly consumed [1, 16]. Secondly, an elevated number of studies in rodents has shown that curcumin can prevent several types of cancer (e.g., colon, lung, breast, liver, stomach, esophagus, skin, lymphomas, and leukemia).
Table 2. Recent selected reports showing possible molecular targets of curcumin

<table>
<thead>
<tr>
<th>Molecular targets</th>
<th>References</th>
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<tbody>
<tr>
<td>Inhibition of NF-kappaB in cancer cells by curcumin. These recent reports, which</td>
<td>[176, 182, 335]</td>
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<tr>
<td>are in agreement with previous results, suggest that this effect of curcumin might</td>
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<td>be exploited therapeutically.</td>
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<tr>
<td>Inhibition of MDM2 oncogen through the transcription factor ETS2 by modulation</td>
<td>[173]</td>
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<td>of the PI3K/mTOR signaling pathway. This report also shows that curcumin</td>
<td></td>
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<td>sensitizes human cancer cells to chemotherapy and radiation through down-regulation</td>
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<tr>
<td>of this oncogen.</td>
<td></td>
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<tr>
<td>Induction of proteasome-mediated down-regulation of cyclin E and up-regulation</td>
<td>[337]</td>
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<tr>
<td>of the CDK inhibitors p21 and p27 in several cancer cell lines; these effects</td>
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<tr>
<td>may contribute to the antiproliferative effects of curcumin against various</td>
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<tr>
<td>tumors.</td>
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<tr>
<td>Inhibition of the Akt/mammalian target of rapamycin (mTOR)/p70S6K and the</td>
<td>[322]</td>
</tr>
<tr>
<td>extracellular signal-regulated kinases 1/2 (ERK1/2) pathways. These effects</td>
<td></td>
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<tr>
<td>resulted in the induction of autophagy (a response of cancer cells to various</td>
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<tr>
<td>anticancer therapies, also designated as programmed cell death type II) and</td>
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<td>suppression of the growth of malignant gliomas.</td>
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<tr>
<td>Inhibition of Akt and its key target Bad in B lymphoma via inhibition of spleen</td>
<td>[299]</td>
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<tr>
<td>tyrosine kinase (Syk). This report shows that c-Abl, a nonreceptor tyrosine</td>
<td></td>
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<tr>
<td>kinase that regulates stress responses induced by oxidative agents such as</td>
<td>[338]</td>
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<tr>
<td>ionizing radiation and H2O2, regulates curcumin-induced cell death through</td>
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<tr>
<td>activation of c-Jun N-terminal kinase.</td>
<td></td>
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<tr>
<td>Induction of an increase in the protein levels of the proapoptotic Bcl-2 family</td>
<td>[339]</td>
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<tr>
<td>members Bax and Bak, which was essential for maximum apoptotic activity</td>
<td></td>
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<tr>
<td>Regulation of signal transducer and activator of transcription (STAT)</td>
<td>[297, 340, 341]</td>
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<tr>
<td>Inhibition of human colon cancer cell growth by suppressing gene expression of</td>
<td></td>
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<tr>
<td>epidermal growth factor receptor (EGFR) through reduction of the activity of the</td>
<td></td>
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<tr>
<td>transcription factor Egr-1.</td>
<td></td>
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<tr>
<td>Inhibition of constitutively activated targets of PI3-kinase (AKT, FOXO and GSK3</td>
<td>[296]</td>
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<tr>
<td>in T-cell acute lymphoblastic leukemia cells, leading to the inhibition of</td>
<td></td>
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<tr>
<td>proliferation and induction of caspase-dependent apoptosis.</td>
<td></td>
</tr>
<tr>
<td>Down-regulation of the Notch-1 signaling pathway</td>
<td>[289]</td>
</tr>
</tbody>
</table>

Table 3. Concentrations of curcumin in human plasma or tissues following oral administration

<table>
<thead>
<tr>
<th>Oral dose</th>
<th>Plasma/tissue concentrations (μmol/L or μmol/kg)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 g</td>
<td>&lt;0.03 in plasma</td>
<td>[342]</td>
</tr>
<tr>
<td>4, 6, and 8 g</td>
<td>0.51 ± 0.11, 0.63 ± 0.06, and 1.77 ± 1.87 in plasma</td>
<td>[21]</td>
</tr>
<tr>
<td>0.18 g/day/4 months</td>
<td>Not detectable in plasma or urine</td>
<td>[343]</td>
</tr>
<tr>
<td>3.6 g/day/4 months</td>
<td>0.01 in plasma, 0.1–1.3 in urine</td>
<td>[84]</td>
</tr>
<tr>
<td>3.6 g/day/7 days</td>
<td>Traces in peripheral circulation, 12.7 ± 5.7 in normal colorectal tissue,</td>
<td>[81]</td>
</tr>
<tr>
<td>3.6 g/day/7 days</td>
<td>7.7 ± 1.8 in malignant colorectal tissue</td>
<td></td>
</tr>
<tr>
<td>3.6 g/day/7 days</td>
<td>Low nM levels in the peripheral or portal circulation, not found in liver tissue</td>
<td>[71]</td>
</tr>
</tbody>
</table>

induced by different carcinogens (see Table 1). Thirdly, a Phase I clinical trial in participants with cancer predisposition taking curcumin orally for 3 months showed little toxicity and revealed histological improvement of precancerous lesions in 7 out of 25 patients [21]. Finally, hundreds of preclinical studies have reported that curcumin can act on a variety of pathways and molecular targets involved in cancer development (see ref. [5, 13, 15, 22] for reviews and Table 2 for recent selected reports). Most of these studies, however, have been conducted using high concentrations of curcumin, which cannot be achieved through the oral route. Several human studies have revealed that, after oral administration, the levels of curcumin in plasma are very low (generally in the nanomolar range); while they are higher in colorectal tissue (low micromolar) (see Table 3). This suggests that, outside of the gastrointestinal tract, most of the reported cancer-related effects of curcumin may not be achieved in vivo. In order to understand the possible mechanisms involved in the putative cancer preventive activity of curcumin, it is essential to analyze which of these numerous targets are really implicated in vivo. After reviewing the literature, the most relevant effects of curcumin in vivo have been compiled in Table 4.

Despite being challenged by some researchers [23–26], the most accepted theory of cancer (“somatic mutation theory of cancer”) considers that this disease is caused by DNA alterations [27]. As shown in Table 4, several in vivo studies have revealed that curcumin can protect DNA from damage induced by different carcinogens. It is widely accepted, even by those who challenge the somatic mutation theory of cancer, that the formation of a malignant tumor requires that tumor cells acquire several capabilities (the so-called hallmarks of cancer), such as apoptosis resistance, increased angiogenesis, or capacity of invasion and metastasis [28]. The formation of a cancer requires that tumor cells develop apoptosis resistance, and it has been observed that curcumin can produce a mild but yet significant activation of apoptosis in vivo (see references in Table 4). Angiogenesis,
the generation of new blood vessels, is necessary for the formation of solid tumors; without vascular growth, the tumor mass is restricted to a tissue-diffusion distance of approximately 0.2 mm. Malignant tumors are known to activate angiogenesis, and several reports have shown that curcumin can inhibit angiogenesis in vivo. It is recognized that the metastatic spread of primary tumors accounts for approximately 90% of all cancer deaths. The process by which cells from a localized tumor invade adjacent tissues and metastasize to distant organs can therefore be considered the most clinically relevant process involved in carcinogenesis [29, 30]. Experimental data support that curcumin can inhibit invasion and metastasis in vivo (Table 4).

Accumulating evidence suggests that reactive oxygen species (ROS) play a key role in carcinogenesis [31–33]. It has been demonstrated that the malignant phenotype of cancer cells can be reversed simply by reducing the cellular levels of ROS [34–38]. Antioxidant agents prevent or reduce excessive cellular levels of ROS and, therefore, play a protective role in cancer development. For instance, experimental data revealed that the expression of the antioxidant enzyme catalase in malignant cells decreased their cellular levels of hydrogen peroxide (H₂O₂); these cells reverted to a normal appearance, their growth rate normalized, and they were no longer capable of producing tumors in athymic mice [34]. These data suggest that the extensively reported antioxidant activity of curcumin may be a key mechanism by which this dietary phytochemical prevents cancer in vivo. As shown in Table 4, numerous studies have reported that curcumin exerts antioxidant effects in vivo. Interestingly, the antioxidant effects of curcumin following oral administration are not restricted to the gastrointestinal tract, as they have also been observed, for instance, in the liver [39–44], kidneys [40, 41, 45], or the brain [41, 46–49].

Inhibition of Phase I enzymes, such as cytochromes P450 (CYP), and activation of Phase II enzymes, such as glutathione S-transferases (GST), may participate in the cancer preventive activity of curcumin, as these enzymes play an important function in the activation and detoxification of carcinogens. As shown in Table 4, some studies indicate that curcumin can inhibit cytochromes P450 and activate GST in vivo.

Based on hundreds of preclinical reports, curcumin is regarded in the scientific literature as an anti-inflammatory agent. Several studies have reported beneficial effects when oral curcumin has been given to patients suffering from inflammatory disorders [50–52]. Recent research has established that the activation of the nuclear factor kappa B (NF-κB) is a crucial event both in inflammation and cancer [53]. Many recent reports have shown that curcumin is an efficient NF-κB inhibitor. For instance, Bharti et al. [54] observed that curcumin induced down-regulation of NF-κB in multiple myeloma cells in a time and dose-dependent manner. The efficient down-regulation of NF-κB in these cell lines required concentrations of curcumin in the 5–50 μM range and exposure times of approximately 2–4 h. As shown in Table 3 and observed in some animal studies, most data suggest that the plasma concentration of curcumin following oral dosing is low, and that this agent is rapidly cleared from the plasma and tissues [55–57]. This suggests that NF-κB inhibition by curcumin may not be relevant in vivo. Experimental data have demonstrated, however, that curcumin can

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**Table 4. Possible mechanisms involved in the cancer chemopreventive activity of curcumin in vivo**

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhibition/protection from DNA damage/alterations</td>
<td>[81, 183, 191, 240, 275, 313, 344–348]</td>
</tr>
<tr>
<td>Inhibition of angiogenesis</td>
<td>[208, 209, 259, 349–352]</td>
</tr>
<tr>
<td>Inhibition of invasion/metastasis</td>
<td>[215, 250, 353, 354]</td>
</tr>
<tr>
<td>Induction of apoptosis</td>
<td>[82, 83, 259]</td>
</tr>
<tr>
<td>Inhibition of cytochromes P450</td>
<td>[210, 321, 376, 377]</td>
</tr>
<tr>
<td>Induction of GST</td>
<td>[40, 220, 240, 377–379]</td>
</tr>
<tr>
<td>Inhibition of NF-κB</td>
<td>[190, 271, 273, 276, 281, 310, 353, 371, 380–387]</td>
</tr>
<tr>
<td>Inhibition of AP-1</td>
<td>[381, 384, 387]</td>
</tr>
<tr>
<td>Inhibition of MMPs</td>
<td>[250, 266, 353, 384, 388]</td>
</tr>
<tr>
<td>Inhibition of COX-2</td>
<td>[273, 276, 310, 348, 353, 389–391]</td>
</tr>
<tr>
<td>Inhibition of TNF-α</td>
<td>[187, 206, 381, 392–394]</td>
</tr>
<tr>
<td>Inhibition of IL-6</td>
<td>[381, 392]</td>
</tr>
<tr>
<td>Inhibition of iNOS</td>
<td>[276, 389, 395]</td>
</tr>
<tr>
<td>Inhibition of IL-1β</td>
<td>[47, 381, 384]</td>
</tr>
<tr>
<td>Inhibition of oncogens ras/jos/jun/myc</td>
<td>[272, 306, 308, 396]</td>
</tr>
<tr>
<td>Inhibition of MAPK</td>
<td>[385, 389]</td>
</tr>
<tr>
<td>Activation of Nrf2</td>
<td>[130]</td>
</tr>
<tr>
<td>Induction of HO-1</td>
<td>[131]</td>
</tr>
<tr>
<td>Inhibition of ornithine decarboxylase</td>
<td>[45, 223, 239, 304, 305, 314, 315, 397]</td>
</tr>
<tr>
<td>Activation of PPAR-γ</td>
<td>[206, 375, 391]</td>
</tr>
<tr>
<td>Immunostimulant/immunorestorer</td>
<td>[59, 398–401]</td>
</tr>
</tbody>
</table>
inhibit NF-κB activity in vivo (Table 4). It is well accepted that an increase in the cellular levels of ROS such as H₂O₂ results in the activation of NF-κB [58] and many reports have shown that curcumin can reduce the cellular levels of ROS in vivo (Table 4, antioxidant activity). This suggests that curcumin may prevent the activation of NF-κB in vivo by reducing the cellular levels of ROS.

Table 4 compiles references showing that, in vivo, curcumin can also modulate several other targets involved in carcinogenesis, including inhibition of activator protein 1 (AP-1), matrix metalloproteinases (MMPs), cyclooxygenase-2 (COX-2), tumor necrosis factor alpha (TNF-α), IL-6, IL-1β, inducible nitric oxide synthase (iNOS), oncogenes ras/ fos/jun/myc, mitogen-activated protein kinases (MAPK), and ornithine decarboxylase; or induction/activation of nuclear factor E2-related factor 2 (Nrf2), heme oxygenase 1 (HO-1), and peroxisome proliferator-activated receptor-gamma (PPAR-γ). Curcumin has also been shown as an immunomodulator and immunorestorer in vivo; this mechanism may also participate in the cancer preventive activity of curcumin [59].

Recent data suggest that the hypoxia-inducible factor 1 (HIF-1) may be a key target for cancer chemoprevention [20]. In fact, the most important cancer gene pathways seem to culminate in the activation of this transcription factor [27]. HIF-1 activation is observed in most human cancers and has been associated with increased patient mortality. For instance, Zhong et al. [60] identified increased HIF-1 expression (relative to adjacent normal tissue) in 13 tumor types, including lung, prostate, breast, and colon carcinoma, which are the most common cancers in developed countries. In addition, HIF-1 activation seems to explain all the hallmarks of cancer [20, 61, 62]. These data suggest that HIF-1 activation is a key event in carcinogenesis and may therefore represent a key target for cancer chemoprevention. Recent in vitro studies have shown that curcumin can inhibit HIF-1 [63, 64]. Evidence suggests that curcumin might also inhibit HIF-1 activity in vivo. Indeed, it is now well established that HIF-1 can be activated by an increase in the cellular levels of ROS (e.g., H₂O₂) [65–68], and curcumin can reduce the cellular levels of ROS in vivo (see references in Table 4, antioxidant activity, e.g., [69, 70]).

Since curcumin is extensively metabolized in the body [55–57, 71–73], it is important to note that the in vivo anticancer properties of curcumin (Table 4) may be mediated, at least in part, by its metabolites. The evaluation of the anticancer properties of curcumin metabolites at relevant doses will probably help understand how curcumin works in vivo.

2.2 Cancer chemotherapeutic properties of curcumin

Therapeutic selectivity, or preferential killing of cancer cells without significant toxicity to normal cells, is one of the most desirable properties of a cancer chemotherapeutic agent. It is worth mentioning that several reports have shown that curcumin can kill cancer cells selectively [74–78]. For instance, the percentage of apoptosis induced by curcumin (40 μM, 24 h) in three cancer cell lines (including HepG2 hepatocellular carcinoma cells) was approximately 90%, while it was lower than 3% in five different types of normal cells (including normal hepatocytes) [76]. Likewise, curcumin (48 h exposure) induced apoptosis in chronic lymphocytic leukemia (B-CLL) cells from 14 patients at lower concentrations (EC₅₀ = 5.5 μM) than in whole mononuclear cells from healthy donors (EC₅₀ = 21.8 μM) [77]. The percentage of apoptotic cells induced by curcumin (40 μM, 24 h) was also higher in the multi-drug-resistant breast carcinoma cell line MCF-7/TH (46.65%) than in the human mammary epithelial cell line MCF-10A (1.80%) [74]. Gautam et al. [79] observed, however, that curcumin-induced inhibition of cell proliferation was not selective for cancer cells, although they also found that inhibition of cell proliferation by curcumin was not always associated with apoptosis.

Table 1 (chemotherapeutic effects) compiles experimental studies that have demonstrated that curcumin induces apoptosis in cancer cells from different origins. These reports show that curcumin induces apoptosis in a dose-dependent and time-dependent manner (see, for instance, ref. [76, 80]). Although the exposure times and doses required to induce apoptosis in cancer cells vary depending on the studied cell lines, most reports show that cancer cells exposed to curcumin 5–50 μM for 24 h or longer undergo apoptosis. At short exposure times, however, these concentrations of curcumin are not high enough to induce apoptosis efficiently. For instance, the percentage of apoptosis observed in MCF-7, MDAMB, and HepG2 cancer cells exposed to curcumin 50 μM for 2 h was 10% or lower [76]. As mentioned before, curcumin has low oral bioavailability (Table 3) and is rapidly cleared from the plasma and tissues [55–57]. This suggests that the oral administration of curcumin may not result in efficient induction of apoptosis in vivo.

The concentrations of curcumin observed in colon tissue following oral administration (approximately 10 μmol/kg) [81] suggest that oral curcumin can induce apoptosis in the gastrointestinal tract efficiently. This is supported by experimental data that have shown that curcumin can induce apoptosis in colon cells in vivo [82, 83]. On the other hand, it has been shown that curcumin undergoes extensive metabolic conjugation and reduction in the gastrointestinal tract [57]; this suggests that the high concentrations of curcumin achieved in the colon may not be held enough time to allow this agent to induce apoptosis efficiently. For instance, the apoptotic index in azoxymethane-induced colonic tumors in rats was 8.3% in the control group and 17.7% in a group that received 0.2% of curcumin in the diet [82]. Although this mild activation of apoptosis may be useful in cancer chemoprevention, it does not seem to be enough to be use-
ful in cancer chemotherapy. Accordingly, when 15 patients with advanced colorectal cancer refractory to standard chemotherapies were treated with curcumin at doses up to 3.6 g daily for up to 4 months, no partial responses to treatment or decreases in tumor markers were observed [84]. These data suggest that the therapeutic potential of oral curcumin is low and that alternative routes of administration or delivery systems should be explored. A different approach to overcome the “unfavorable” pharmacokinetics of curcumin would be the development of curcumin analogs with a better pharmacokinetic profile that retained curcumin anticancer properties. Several curcumin analogs have been synthesized and their anticancer activity has been evaluated [85–90].

3 Toxic and carcinogenic properties of curcumin

The toxic and carcinogenic properties of an extract of turmeric that is commonly added to food items and contains a high percentage of curcumin (79–85%) were evaluated in rats and mice by the National Toxicology Program, USA [91]. The percentage of curcumin of this extract is similar to that of commercial grade curcumin [2]. Animals were fed diets containing the turmeric extract at different concentrations for periods of 3 months (0.1, 0.5, 1, 2.5, and 5%) and 2 years (0.2, 1, and 5%). Hyperplasia of the mucosal epithelium was observed in the colon of rats that received 5% of turmeric extract for 3 months in the diet. Despite this unfavorable effect and a significant increase in liver weights in rats and mice fed with concentrations of 0.5% or higher, no signs of carcinogenic lesions were observed in these 3-month studies. However, toxic and carcinogenic effects were observed when animals were fed with the turmeric extract for a period of 2 years. Thus, male or female rats that received turmeric extract had ulcers, chronic active inflammation, hyperplasia of the cecum or forestomach, or increased incidences of clitoral gland adenomas; these effects were mainly observed in the group fed with a 5% of turmeric extract. Likewise, mice fed with different concentrations of the turmeric extract had increased incidence of hepatocellular adenoma (1% group) or carcinomas of the small intestine (0.2 and 1% groups). In the 2-year study of mice, a 0.2% of turmeric extract in the diet was estimated to deliver average daily doses of curcumin of approximately 200 mg/kg body weight [91].

Several mechanisms may account for the toxic and carcinogenic properties of curcumin. Although many studies have shown that curcumin can prevent DNA damage (see references in Table 4), it has also been demonstrated that curcumin can induce DNA damage/alterations in vitro [92–103] and in vivo [104, 105]. These studies revealed that copper facilitates curcumin-induced DNA damage and that ROS play an important role in this activity. DNA topoisomerase II (topo II) may also play a role in curcumin-induced DNA damage, as curcumin has been described in vitro as a topo II poison and as topo II poisons induce topo II-mediated DNA damage [106]. We have recently observed that curcumin induces high levels of topoisomerase I and II–DNA complexes in human leukemia cells; although the induction of cytotoxic levels of topo–DNA complexes may be exploited therapeutically, the induction of nonlethal levels of these complexes may lead to carcinogenic effects [107]. Other dietary agents such as flavonoids (e.g., genistein) are known to induce topo II-mediated DNA damage, and a high consumption of these agents has already been associated with a higher risk of leukemia in humans [108, 109].

Curcumin possesses two electrophilic α,β-unsaturated ketones that can react with nucleophilic groups (e.g., SH groups of proteins) through a reaction called Michael addition; this may produce toxic and carcinogenic effects. Specific concentrations of curcumin can also produce toxic and carcinogenic effects by increasing the cellular levels of ROS.

Figure 1. Possible mechanisms involved in the toxic and carcinogenic properties of curcumin. Curcumin possesses two electrophilic α,β-unsaturated ketones that can react with nucleophilic groups (e.g., SH groups of proteins) through a reaction called Michael addition. These α,β-unsaturated ketones can react covalently with the thiol (SH) groups of cysteine residues of different proteins; this may produce toxic effects (Fig. 1). For instance, Wang et al. [110] showed that thiol-reactive drugs containing an α,β-unsaturated ketone induced topo II–DNA complexes through thiol alkylation of topo II, and that these topo II–
DNA complexes were completely abolished in mutant yeast topo II with all cysteine residues replaced with alanine. They also showed that the potency of these drugs to stimulate topo II cleavable complexes correlated with their ability to undergo Michael addition [110]. This suggests that the formation of topo II–DNA complexes induced by curcumin [106] may be mediated by this reaction. Likewise, since drugs containing an electrophilic \( \alpha,\beta \)-unsaturated ketone can produce inactivation of the tumor suppressor p53, Moos et al. evaluated the ability of curcumin to inactivate p53. They observed that curcumin disrupted the conformation of the p53 protein required for its serine phosphorylation, its binding to DNA, its transactivation of p53-responsive genes and p53-mediated cell cycle arrest [111]. These results are in agreement with another work that showed that curcumin can induce p53 degradation and inhibit p53-induced apoptosis [112]. Although these effects have not been observed in vivo, they support that curcumin may produce carcinogenic effects, as the inactivation of the tumor suppressor protein p53 is an important carcinogenic event.

Evidence indicates that an increase in the cellular levels of ROS (e.g., superoxide anion \( \text{O}_2^− \), \( \text{H}_2\text{O}_2 \)) plays a key role in carcinogenesis, and it is now well established that curcumin can increase the cellular levels of ROS (discussed in Section 4). Fang et al. [113] observed that curcumin increased the cellular levels of ROS by irreversibly modifying the antioxidant enzyme thioredoxin reductase (TrxR). In addition, the authors provided data supporting that this modification is caused by a reaction involving the \( \alpha,\beta \)-unsaturated ketones of curcumin and the -SH and -SeH groups of the cysteine and selenocysteine residues of the active site of the enzyme.

Based on short-term studies conducted in animals and humans, it is generally considered that curcumin is a safe agent when administered orally (see [1, 2, 14] and references therein). No treatment-related toxicity was reported in 25 patients taking curcumin at concentrations up to 8000 mg/day (~115 mg/kg/day) for a period of 3 months [21]. As discussed above, no carcinogenic effects were observed in mice fed with turmeric extract for 3 months [91]. After 2 years, however, carcinogenic effects were observed in mice fed with concentrations of turmeric that delivered average doses of curcumin of approximately 200 mg/kg/day [91]. This suggests that we cannot conclude that oral consumption of curcumin is safe without conducting long-term studies in humans, as dietary supplements containing high concentrations of curcumin may produce carcinogenic effects when ingested chronically.

### 4 ROS, cancer, and curcumin

This section of the article discusses that many cancer-related activities of curcumin may be mediated by its ability to both reduce and increase the cellular levels of ROS, *i.e.*, by its antioxidant and pro-oxidant properties.

#### 4.1 Key role of ROS in cancer development and cancer therapy

Most of the energy that aerobic cells need to live is obtained through oxidative phosphorylation. In this process, ATP generation is coupled with a reaction in which oxygen \( \text{O}_2 \) is reduced to water \( \text{H}_2\text{O} \) by a mitochondrial protein complex called cytochrome oxidase. In this reaction, four electrons and four protons are added to \( \text{O}_2 \) to form two molecules of \( \text{H}_2\text{O} \). However, when a molecule of \( \text{O}_2 \) gains only one electron to form \( \text{O}_2^− \), this highly reactive species tends to gain three more electrons and four protons to form two molecules of \( \text{H}_2\text{O} \); this process involves several reactions and generally results in the production of other ROS such as \( \text{H}_2\text{O}_2 \), hydroxyl radical \( \text{OH}^* \) and peroxynitrite \( \text{ONOO}− \).

It is now recognized that the controlled generation of ROS has an important physiological role [114]. An unrestrained production of ROS, however, seems to play a fundamental role in cancer development [31–33]. Thus, it has been shown that ROS, such as \( \text{O}_2^− \) and \( \text{H}_2\text{O}_2 \), can cause and mediate cell malignant transformation [34, 115–118]. Overexpression of \( \text{O}_2^− \) and \( \text{H}_2\text{O}_2 \)-detoxifying enzymes (e.g., superoxide dismutases or catalase) can reverse the malignant properties of different types of cancer cells [34–38]. In addition, recent data suggest that an increase in the cellular levels of \( \text{O}_2^− \) and \( \text{H}_2\text{O}_2 \) may explain key aspects of the carcinogenesis process, including DNA alterations [119], increased cell proliferation [34], apoptosis resistance [120], angiogenesis [121], invasion/metastasis [122, 123], and HIF-1 activation [65, 66, 68].

Although an increase in the cellular levels of ROS seems crucial for cancer development, there is a threshold of ROS above which cells cannot survive. An adequate increase in the cellular levels of ROS can therefore induce cell death. It is recognized that \( \text{H}_2\text{O}_2 \) is an efficient inducer of apoptosis in cancer cells, and that the activity of several anticancer drugs commonly used in the clinic is mediated, at least in part, by \( \text{H}_2\text{O}_2 \). It has also been observed that specific concentrations of \( \text{H}_2\text{O}_2 \) can induce apoptosis in cancer cells without affecting nonmalignant cells. This suggests that any strategy capable of increasing the levels of this ROS adequately may produce selective killing of cancer cells and be useful in cancer therapy (see [33] and references therein).

#### 4.2 Curcumin can both decrease and increase the cellular levels of ROS

The ability of curcumin to decrease the cellular levels of ROS has long been recognized and has been discussed in numerous reports. Basically, the antioxidant activity of curcumin seems to be mediated by its ability to both scavenge...
ROS [70, 124–129] and activate endogenous antioxidant mechanisms that reduce the cellular levels of ROS [40, 42, 130–135]. Although it is well known that curcumin possesses antioxidant activity, numerous reports have demonstrated that curcumin is also a pro-oxidant agent able to increase the cellular levels of ROS [92, 100, 113, 134, 136–144]. For instance, Kang et al. observed a significant decrease in the levels of ROS in human hepatoma Hep3B cells treated for 8 h with curcumin at concentrations of 10 and 20 μM. At 25, 50, and 100 μM, however, curcumin induced a significant increase in the cellular levels of ROS, which was dose and time-dependent [138]. A time-dependent induction of ROS was also observed when the human breast cancer cell lines MDAMB and MCF-7 and the human hepatocellular carcinoma cell line HepG2 were treated with curcumin 50 μM; this increase in the levels of ROS was not observed in rat hepatocytes under the same experimental conditions. A dose-dependent induction of ROS was also observed in human primary gingival fibroblasts and cancerous human submandibular adenocarcinoma cells treated for 1 h with curcumin in the 3–30 μM range; ROS production was higher in the cancer cells [145]. The lack of activity shown by tetrahydrocurcumin in this study suggests that the double bond of the two α,β-unsaturated ketones is important for the pro-oxidant activity of curcumin [145]. As mentioned before, Fang et al. [113] proposed a possible mechanism involved in the pro-oxidant activity of curcumin. They observed that curcumin irreversibly modified TrxR in vitro (IC_{50} 3.6 μM) and in HeLa cells (IC_{50} 15 μM), and proposed that this modification resulted in an increased production of ROS by a double mechanism. Whilst the inhibition of TrxR would impair the antioxidant thioredoxin system against oxidative stress, they observed that the curcumin-modified TrxR showed a strongly induced NADPH oxidase activity that resulted in an increased generation of ROS. Since the levels of TrxR seem higher in cancer cells than in nonmalignant cells [113], this effect may contribute to explain why curcumin induces higher ROS levels in cancer cells than in nonmalignant cells [138, 145]. In short, experimental data strongly support that, while low concentrations of curcumin exert an antioxidant activity, higher concentrations of this dietary agent produce pro-oxidant effects.

4.3 Link between the antioxidant/pro-oxidant effects of curcumin and its cancer-related activities

Figure 2 illustrates that the antioxidant and pro-oxidant activity of curcumin play a key role in its chemopreventive, carcinogenic, and therapeutic properties. At low concentrations, the antioxidant activity of curcumin would reduce or keep the cellular levels of ROS within the physiological levels. This reduction in the levels of ROS may mediate the cancer chemopreventive properties of curcumin, as ROS are highly involved in carcinogenesis. At higher concentrations, the pro-oxidant activity of curcumin would increase the levels of ROS, which would produce carcinogenic effects. At concentrations that result in cytotoxic levels of ROS, curcumin would act as a chemotherapeutic agent.

In addition to the carcinogenic effects represented in Fig. 2, ROS are known to activate numerous cellular targets and pathways including, for instance, NF-κB [58], AP-1 [146], MMPs [122], TNF-α [65], Akt [147, 148], oncogenes, src, and myc [149–154], and the ERK/MAPK, PI3K/Akt pathways.
Akt, and JAK-signal transducer and activator of transcription (STAT) pathways [148, 155, 156]. Since curcumin can modulate the cellular levels of ROS, it is not surprising that it can interfere with these cellular targets and pathways (see [5, 13, 15, 22] and references in Tables 2 and 4).

Although numerous mechanisms have been proposed to be involved in curcumin-induced cell death, evidence suggests that this process may be governed by an increase in the cellular levels of ROS. For instance, it is acknowledged that the inhibition of NF-κB plays an important role in curcumin-induced apoptosis [54, 157–161]. However, evidence supports that high cellular levels of ROS (e.g., H₂O₂) can inhibit this transcription factor [162–165]; this suggests that an increase in the cellular levels of ROS may precede curcumin-induced NF-κB inhibition and cell death. It is well known that curcumin can increase the cellular levels of ROS, and an increase in the levels of ROS has been observed in cells undergoing apoptosis during curcumin treatment. Numerous reports have demonstrated that curcumin-induced apoptosis is inhibited by antioxidants such as catalase or N-acetylcysteine [139, 140, 143–145, 166–168]. In addition, it is recognized that H₂O₂ is an efficient inducer of apoptosis in cancer cells and that several anticancer agents used in the clinic seem to exert their therapeutic effects by increasing the levels of this ROS [33, 169]. This suggests that the chemotherapeutic properties of curcumin may be mediated, at least in part, by an increase in the cellular levels of ROS.

The reported selectivity of curcumin for cancer cells [74–78] might also be explained by its ability to increase the cellular levels of ROS. It has been observed that the ROS H₂O₂ can produce selective killing of cancer cells [33, 170]. Experimental data indicate that cancer cells produce higher levels of H₂O₂ than nonmalignant cells [171], and it is recognized that there is a threshold of H₂O₂ above which cells cannot survive. This suggests that specific concentrations of H₂O₂ can increase the amounts of H₂O₂ to cytotoxic levels in cancer cells but not in normal cells [33]. As mentioned previously, it has been observed that specific concentrations of curcumin can increase the cellular levels of this ROS [92, 139, 140, 143–145, 166–168]. Overall, this suggests that concentrations of curcumin that result in an adequate increase in the cellular levels of H₂O₂ would produce selective killing of cancer cells.

Experimental data have shown that the therapeutic effects of radiotherapy and some anticancer drugs are increased by curcumin; this suggests that curcumin might be used in the clinic to sensitize cancer cells to radiotherapy and chemotherapy [159, 172–182]. Conversely, other reports have shown that curcumin can reduce the activity (and toxicity) of radiations and several chemotherapeutic agents [183–191]. The antioxidant/pro-oxidant activity of curcumin may explain these apparently controversial data. It is well known that, in addition to inducing apoptosis in cancer cells, ROS can sensitize these cells to drug-induced apoptosis [33, 192–195]. It is also known that the therapeutic effect of radiation and some anticancer agents is mediated, at least in part, by an increase in the cellular levels of ROS. Therefore, concentrations of curcumin that induce an elevation in the cellular levels of ROS would facilitate the anticancer effects of radiotherapy and chemotherapy. For example, evidence suggests that ROS play an important role in paclitaxel (taxol)-induced cell death [169] and that curcumin sensitizes cancer cells to paclitaxel-induced cell death [159]. Conversely, concentrations of curcumin that produce antioxidant effects would reduce the levels of ROS induced by radiation and chemotherapeutic agents, therefore reducing their activity and toxicity. Accordingly, Somasundaram et al. [189] observed that curcumin decreased the activity of several anticancer agents by reducing the cellular levels of ROS. Figure 3 illustrates that, while pro-oxidant concentrations of curcumin may increase the effects of cancer therapy, antioxidant concentrations of curcumin may reduce its activity/toxicity.

5 Considerations for the clinical development of curcumin as an anticancer agent

Accumulating experimental data have revealed that curcumin possesses both cancer chemopreventive and chemotherapeutic properties. This section of the article discusses several aspects that may help develop curcumin as a clinically useful agent for the prevention and treatment of cancer.
5.1 Development of curcumin as a cancer chemopreventive agent

Epidemiological evidence indicates that people taking higher concentrations of curcumin in their diet have lower incidence of several common cancer types. Hundreds of preclinical reports have shown that curcumin has cancer chemopreventive properties. The last step before using curcumin in cancer chemoprevention is the confirmation of such preventive efficacy by using randomized controlled clinical trials, which are commonly regarded as the definitive study design for proving casualty. Three key aspects should be considered carefully in the design of cancer chemoprevention clinical trials: (i) the doses at which curcumin should be supplemented, (ii) the selection of the participants for the trials, and (iii) the duration of the trials and follow-ups.

Several short-term (3–4 months) human trials revealed that curcumin induced low levels of toxicity at concentrations of 3600 mg/day; these doses of curcumin have been considered safe and are recommended for future cancer chemoprevention clinical trials [14, 84, 196]. These doses, however, are around 20-times higher than the doses of curcumin estimated in people consuming high amounts of turmeric in their diet, which are approximately 150 mg/day [2, 197]. Although the use of chemicals at the maximum tolerated dose is a valid approach in cancer chemotherapy, this strategy may not be appropriate for cancer chemoprevention, as it may produce toxicity in the long term.

Beta-carotene is the classic example to show that supplementation of dietary agents at high doses may produce toxic and carcinogenic effects in the long term. Because the antioxidant agent β-carotene is found in vegetables and fruits and because eating vegetables and fruits is associated with a reduced risk of cancer, it seemed plausible that taking high doses of β-carotene supplements might reduce cancer risk. Preclinical studies also supported the potential cancer preventive activity of β-carotene. In three major clinical trials, people were given high doses of β-carotene (20–30 mg, which are approximately 10-times higher than those found in a diet rich in fruits and vegetables) in an attempt to prevent lung cancer and other cancers. These trials were stopped ahead of schedule because two of them found β-carotene supplements to be associated with a higher risk of lung cancer [198, 199]. The pro-oxidant activity of β-carotene may account for its carcinogenic properties observed in these trials. Like curcumin, β-carotene can behave as a pro-oxidant agent [200, 201], and pro-oxidant agents can increase the cellular level of ROS and produce toxic and carcinogenic effects. It is important to mention that, before the trials were stopped, β-carotene had not shown any apparent toxicity or carcinogenic activity during the 4–6 years of the studies. This lack of visible toxic and carcinogenic effects is understandable, as carcinogenesis is a long process that remains silent until its final stages. This example suggests that, although short-term studies can show that chemopreventive agents (e.g., curcumin) do not produce apparent toxicity at doses that largely exceeded those taken in the diet, these doses may produce carcinogenic effects in the long term. Therefore, which doses of curcumin should be used for future cancer chemoprevention clinical trials? Since a diet rich in turmeric is considered safe and has been associated with a lower cancer risk, it seems appropriate to use doses of curcumin equivalent to those found in diets rich in turmeric. Although higher doses of curcumin may be more effective, it seems prudent to test the safety of such doses in long-term studies in humans before large cancer chemoprevention clinical trials are implemented.

Although cancer chemoprevention clinical trials can be aimed at healthy populations and at populations with cancer predisposition (people with precancerous lesions or who are at high risk for developing cancer), most cancer chemopreventive studies are implemented in those with cancer predisposition. In addition, the limited bioavailability of curcumin suggests that its cancer preventive activity may be limited to the gastrointestinal tract. Therefore, it is usually considered that the cancer chemopreventive activity of curcumin should be focused on people with colon cancer predisposition. Evidence suggests, however, that curcumin may also exert chemopreventive effects in healthy people on different organs and tissues. For instance, the antioxidant effects of curcumin following oral administration are not restricted to the gastrointestinal tract, as they have also been observed in other organs or tissues such as the liver [39–44], kidneys [40, 41, 45] or the brain [41, 46–49]. In addition, oxidative stress is known to play an important role not only in cancer progression, but also in cancer initiation. Overall, this suggests that the evaluation of the cancer chemopreventive activity of curcumin should not be restricted to people with colon cancer predisposition.

The duration of the trials and follow-ups is a crucial aspect to consider in the design of cancer chemoprevention clinical trials. A short trial or follow-up may hide the true effectiveness of a cancer chemopreventive agent. For example, a prospective epidemiological study assessed the influence of multivitamin use in colon cancer risk. Women who used multivitamins had no benefit with respect to colon cancer after 4 years of use (RR, 1.02) and had only non-significant risk reductions after 5–9 (RR, 0.83) or 10–14 (RR, 0.80) years of use. After 15 years of use, however, the risk was clearly lower (RR, 0.25 [CI, 0.13–0.51]) [202]. These data agree with the fact that cancer takes several years or decades to develop completely; for instance, it is estimated that 5–20 years are necessary for normal colon cells to form adenomas and that these adenomas require 5–15 additional years to become an invasive colon cancer [203]. In addition, the fact that cancer is not usually detected until it reaches its final stages suggests that we may need to wait several years after a trial finishes (follow-up) in order to observe a chemopreventive effect. Since the
most reliable endpoint for a cancer chemopreventive intervention is the presence or absence of cancer, we may need long follow-up periods. It should also be noted that the follow-ups of cancer chemoprevention clinical trials aimed at healthy populations should be longer than those conducted in people with premalignant lesions. Future validation of reliable surrogate endpoint biomarkers of carcinogenesis may reduce the duration of the follow-ups. In short, the duration and follow-up of any clinical trial evaluating the chemopreventive activity of curcumin should be designed long enough to let this dietary agent demonstrate its putative anticancer activity.

5.2 Development of curcumin as a cancer chemotherapeutic agent

Many in vitro studies have demonstrated that curcumin is an efficient inducer of apoptosis in different types of cancer cells. Some of these studies have shown that specific concentrations of curcumin can induce apoptosis in cancer cells without affecting nonmalignant cells. Several reports have also revealed that curcumin may sensitize cancer cells to the anticancer effects of radiotherapy and chemotherapy. These data indicate that curcumin has potential to be developed as a cancer chemotherapeutic agent.

In vitro studies have clearly established that curcumin-induced cancer cell death occurs in a dose and time-dependent manner. Cancer cells do not undertake apoptosis in the presence of curcumin unless this dietary agent is at concentrations of approximately 5–50 μM during several hours. These concentrations of curcumin are not achieved outside the gastrointestinal tract through the oral route. In the gastrointestinal tract, these concentrations cannot be kept during several hours, suggesting that the therapeutic effects of oral curcumin are limited. Indeed, when patients with advanced colorectal cancer were treated with curcumin at relatively high doses, no partial responses to treatment were observed [84]. High oral concentrations of curcumin may produce pro-oxidant effects that, although may not be high enough to exert a potent therapeutic effect, may sensitize cancer cells to the effects of radiotherapy and some anticancer drugs. It would be interesting to test whether the combinations of curcumin with radiation or these anticancer drugs can improve the efficiency of the standard therapies.

Intravenous (i.v.) infusion seems to be an appropriate route of administration to overcome the low oral bioavailability and extensive metabolism of curcumin in the human body. A continuous and prolonged administration of curcumin through the i.v. route would allow high concentrations of curcumin to be reached and maintained in plasma and tissues for longer periods of time. Curcumin has already been administered through the i.v. route to animals [55, 204–206], yet none of these experiments studied the safety and chemotherapeutic effect of curcumin under these conditions. It may be useful to evaluate the possible toxicity and therapeutic effectiveness of administering cytotoxic concentrations of curcumin through i.v. infusion to animals with cancer.

Although i.v. infusion seems to be the most straightforward route of administration to overcome the low oral bioavailability and extensive metabolism of curcumin, other delivery strategies are worth exploring [207–209]. For example, in order to overcome the low oral bioavailability of curcumin, Li et al. [208] encapsulated curcumin in a liposomal delivery system and tested its anticancer activity. In vitro studies revealed that liposomal curcumin inhibited the growth and induced apoptosis in pancreatic carcinoma cell lines. In vivo, liposomal curcumin (40 mg/kg, administered intravenously three times a week) suppressed in vivo growth of pancreatic tumor xenografts without showing significant toxicity to the host [208]. These encouraging results have also been observed by the same research group in colorectal cancer [209].

During the last decade, a high number of in vitro studies have clearly established that curcumin is an efficient inducer of apoptosis in cancer cells. In order to develop curcumin as a chemotherapeutic agent, now we need to evaluate its toxicity and therapeutic effectiveness in animals with cancer. In these studies, curcumin needs to be administered through the appropriate route or delivery system (e.g., i.v. infusion, liposomal or sustained release technologies) in order to achieve and maintain cytotoxic levels in the target tissues. The next step would be the evaluation of the possible toxicity and therapeutic activity of curcumin in a group of patients with cancer (Phase I/II clinical trial). Phase III clinical studies would be required to compare the anticancer efficiency of curcumin with that of standard anticancer therapies. These studies would reveal whether or not curcumin can be developed as a useful drug for the treatment of cancer.

6 Conclusions

Epidemiological studies suggest that populations that live on a diet rich in curcumin have a lower cancer risk. Accumulating preclinical studies have shown that curcumin can interfere with an increasing number of molecular targets, pathways and processes involved in cancer. Since a high consumption of curcumin in the diet is considered safe, it is commonly believed that the cancer chemopreventive and therapeutic properties of curcumin may be accompanied by a lack of toxicity. This belief is supported by short-term Phase I clinical studies that have shown that oral curcumin is well tolerated. This lack of toxicity is probably due to the low bioavailability of oral curcumin and to the extensive metabolism that this dietary agent undergoes in the human body. However, these pharmacokinetic parameters also suggest that many of the anticancer effects shown by curcumin
in vitro cannot be achieved in vivo. In addition, despite insufficient recognition, evidence strongly suggests that curcumin can exert toxic and carcinogenic effects under specific conditions. Although a high number of mechanisms have been proposed to participate in the anticancer and carcinogenic properties of curcumin, many of these properties seem to be mediated by the antioxidant and prooxidant activities of this dietary agent. After a critical analysis of the cancer-related properties of curcumin, several considerations that may help develop curcumin as an anticancer agent can be made. As far as cancer chemoprevention is concerned, evidence suggests that oral supplementation of curcumin at relatively high doses may produce carcinogenic effects in the long term, that the cancer chemopreventive potential of curcumin is not restricted to the gastrointestinal tract, and that future cancer chemoprevention clinical trials need to be designed long enough to let curcumin show its putative chemopreventive effects. Regarding cancer chemotherapy, evidence suggests that the therapeutic potential of oral curcumin is low even in cancers from the gastrointestinal tract, and that other routes of administration (e.g., i.v. infusion) or other formulations (e.g., liposomal or sustained release technologies) need to be considered to evaluate the potential of curcumin as a chemotherapeutic agent.

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7 References


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