



# Efficacy and Safety of *Curcuma longa* L: Relevant Results for Cancer Treatment

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## Abstract

Cancer represents an important public health challenge, and its occurrence has been increasingly observed at human and veterinary medicine. However, despite of the significant results published by the scientific community, the use of medicinal plants for cancer treatment is not properly widespread. Thus, considering that *Curcuma longa* Linn. has demonstrated an important antitumor activity, the objective of this study was to present the main results of *in vitro* and *in vivo* studies. The anticancer activity of turmeric was found by the capability to induce apoptosis, reduce metastatic potential and inhibiting different tumor types of proliferation. In addition, other activities such as immunomodulatory, anti-inflammatory, and the inhibitory effect on modulating proteins of drug resistance are relevant for tumor therapy. Therefore, the results demonstrated by *in vitro* and *in vivo* studies showed that *C. longa* presents important evidence of prophylactic and curative effect for cancer treatment.

## Keywords

Antitumor, Medicinal plants, Neoplasms *Curcuma longa*, Turmeric

## Introduction

Cancer represents an important public health challenge, and its occurrence has been increasingly observed in both human and veterinary medicine [1,2]. Several modalities of natural medicine have been used as complementary therapy in oncological treatment, emphasizing the use of medicinal plants [3]. The diffusion of these natural therapies among cancer patients is mainly due to the dissatisfaction with the results of conventional medicine and the ability to reduce the usual side effects of chemotherapy and radiotherapy [3]. In addition, the affinity for the use of natural products and the search for lower cost treatments are considered [4].

The use of medicinal plants accentuated from the 90's, mainly due to aspects as safety, effectiveness, and low cost in comparison to chemical drugs. However, despite of the significant results published by the scientific community, an important obstacle to adequate use of medicinal plants is the fact that this knowledge is not properly widespread. In cases that cancer patients are not attended in their request

regarding the use of medicinal plants, it is often observed the independent use of these plants by themselves. So, the most patient adept at medicinal plants obtains the information from popular knowledge, using them in oncological treatments in an empirical way [5].

Empirical use may be detrimental to the health and

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efficacy of cancer treatment and may lead to hepatotoxicity, nephrotoxicity, and cardiovascular toxicity [6]. Therefore, the development and dissemination of research related to the use of medicinal plants in oncology is justified not only by the growing interest but also especially by the need to sensitize health professionals to the possibility of effective complementary therapy. Thus, considering that *C. longa* has been shown to present an important antitumor potential, the objective of this study was to discuss the main relevant results of *in vitro* and *in vivo* studies about the antitumor activity of *Curcuma longa* Linn.

## Review Methodology

The studies presented in this review were identified through a literature review conducted on Google Scholar, Scielo, Medline and Science Direct. The key terms used were: Antineoplastic, antitumor, medicinal herbs, neoplasms, saffron and turmeric.

In spite of the intense effort on the conduction of research aimed to cancer therapies, many patients continue to receive an unfavorable prognosis. Thus, the effort for finding anticancer treatments with better efficacy and lesser side effects has been continued. This review was focused on the beneficial effects of *C. longa* for various types of cancer. The main findings of these results were also summarized and discussed.

## Historical Background

### Compounds and antitumoral activity

*C. longa* or zerdeçal, is also known as turmeric in English-speaking countries, jiang huang in eastern countries, and curcuma or saffron in latin-speaking countries. Belonging

to the family *Zingiberaceae*, turmeric is herbaceous plant, perennial that present large and long leaves and ovoid rhizomes. It is native to India and southeast of Asia, but it is spread throughout Europe and America.

The turmeric anticancer activity was evidenced by the ability to induce apoptosis (Table 1) [7-16], inhibit proliferation of different tumor types and favor metastasis reduction (Table 2) [17-27].

Inhibitory effect against angiogenesis, growth factor receptors and cell adhesion molecules involved in tumor growth was associated to the potential to reduce metastasis. Curcuminoid compounds such as demethoxycurcumin, bisdemethoxycurcumin, and tetrahydrocurcumin were isolated from turmeric root. Among the commonly isolated curcuminoids, curcumin is the most abundant, highlighting that 13 curcuminoids with anticancer activity were described [28].

Comparing the cell growth inhibition effect by pure curcumin and turmeric methanolic extract, it was presented much more effective inhibition by curcumin (half maximal inhibitory concentration ( $IC_{50}$ ) =  $41.69 \pm 2.87 \mu\text{g mL}^{-1}$ ) than the turmeric methanolic extract ( $IC_{50}$  =  $196.12 \pm 5.25 \mu\text{g mL}^{-1}$ ) [15]. But factors such as tumor type [7,29,30] and dose-time-dependent action [7,27,30-32] appear to interfere in anticancer activity.

Curcumin (2  $\mu\text{M}$ ) decreased mesenchymal cell proliferation while cell death was detected only at 50  $\mu\text{M}$ . Highly migratory cells decrease on migration speed and directionality about 50% and 40% when treated with 2 or 5  $\mu\text{M}$  of curcumin, respectively. In addition, the curcumin decreased cell adhesion with dose dependence, especially on tumor-derived spheroids [27].

**Table 1:** Induction of apoptosis by turmeric, its mechanisms of action, and their respective references.

Mechanisms of action	Affection	References
reduction of anti-apoptotic Bcl-2 protein, and increase of pro-apoptotic Bax protein (dose-dependent effect)	Hepatoma (HepG2) and breast cancer (MCF-7, MDA-MB-231)	YUE, et al. [7]
Bcl-2 reduction, increase protein Bax and cell apoptosis by activating the PI3K/Akt.	Pulmonary carcinoma (NCI-H460)	WU, et al. [8]
Reduction of Bcl-2 and transcription factor STAT-3 associated with the cell cycle genes	Glioblastoma cells	SENFTE, et al. [9]
Bcl-2 reduction	Metastatic melanoma (A375, FO1, Hs294T, 1106 MEL)	BILL, et al. [10]
	Breast adenocarcinoma	IBRAHIM, et al. [11]
	Cholangiocarcinoma	PRAKOBWONG, et al. [12]
	Thyroid cancer (K1 cells)	SONG, et al. [13]
Kill SPC-A1 cells (high doses), apoptosis SPC-A1 cells (small doses)	Cancer cells (HeLa)	SANTOS, et al. [14]
Apoptosis and inhibition of cell proliferation	Hepatocellular carcinoma HepG2 cell lines	ABDEL-LATEEF, et al. [15]
Increased caspase-3 activity, decreased Bcl-2 and PI3K protein expression, and decreased the phospho (p)-Akt protein expression and activated miR-15a expression.	Laryngeal cancer cells	MOU, et al. [16]

**Table 2:** Antimetastatic and antiproliferative action by turmeric, its mechanisms of action, and their respective references.

Mechanisms of action	Affection	References
Inhibition Notch-1 transcription fator	Osteosarcoma cell lines	LI, et al. [17]
Wnt pathway inhibition	Prostate cancer	LU, et al. [18]
Reduction in the expression of cyclin D1 (protein involved with G1-S cell cycle)	Gastric cancer	CAI, et al. [19]
Inactivation of cyclin-dependent kinases (CDK), and increased mRNA of inhibitory genes p21 and p27	Pulmonary carcinoma (NCI-H460)	SAHA, et al. [20]
Inhibition of the cell cycle in phase G2/M	Colon cancer (Rko and HCT116)	MUDDLURU, et al. [21]
Inhibition of the production of three proteins (Tcf-4, CBP and P300), related to Wnt transcription	Prostate cancer (22rv1)	TEITEN, et al. [22]
Reduced expression of MMP-9	Breast cancer (metastasis)	KIM, et al. [23]
decrease in apoptotic sunburn cells, and decrease expression of proliferation nuclear antigen (PCNA)	Skin cancer induced by ultraviolet radiation	TSAI, et al. [24]
inhibition of Notch-1 transcription factor (associated with increased proliferation and tumor invasion)	Three osteosarcoma cell lines	LI, et al. [25]
Antiproliferative effects in SPC-A1 ( <i>in vitro</i> and <i>in vivo</i> test)	Human lung adenocarcinoma	WANG, et al. [26]
Decrease adhesion, migration, and proliferation ( <i>in vitro</i> and <i>in vivo</i> test)	Oral squamous cell carcinoma (OSCC), fibroblast cell lines and xenograft model of OSCC	CAMPOS, et al. [27]

**Table 3:** Anti-inflammatory and immunomodulatory activities presented by turmeric, its mechanisms of action, and their respective references.

Activity	Mechanisms of action	Affection	References
Anti-inflammatory	Stimulation enzymes caspases 3, 8, 9	Hepatoma (HepG2) and breast cancer (MCF-7, MDA-MB-231)	YUE, et al. [7]
	Activation of caspases	Pulmonary carcinoma (NCI-H460)	WU, et al. [8]
	NF-κB inhibition associated with cyclooxygenase-2, prostaglandin E <sub>2</sub> , and NO	Several cells	BASNET; SKALKO-BASNET [37]
	protective effect involved thymine dimer, PCNA, apoptosis, transcription factors NF-κB, inhibition of COX-2, PGE2, NO, and upregulation of p53 and p21/Cip1 to prevent DNA damage and facilitate DNA repair	Skin cancer induced by ultraviolet radiation	TSAI, et al. [24]
Immunomodulatory	Inhibition of NF-κB associated with reduction of metastasis in mice	Prostate cancer (PC-3M)	HUANG, et al. [38]
	Inhibition of NF-κB, protection of thymic cells to reactive species of oxygen and tumor-induced TNF-α-induced apoptosis	Renal carcinoma (SK-RC-45 and SK-RC-26B)	BHATTACHARYYA, et al. [39]
	increased production of TNF-α, IL-2 and INF-γ	Peripheral blood mononuclear cells	YUE, et al. [7]
	Inhibition of NF-κB associated with urokinase suppression	Lung Cancer (MCF-7)	ZONG, et al. [40]

Although the curcumin antitumor activity has been demonstrated to be important, in the same way the antitumor effect of turmeric-has also been observed both in the form of extracts [23,33,34] and essential oil [14].

Studies that evaluated curcumin-free turmeric observed suppression of benzo[a] pyrene-induced tumorigenesis in mice [33] and inhibition of 7,12-dimethylbenz[a]anthracene-induced mammary tumorigenesis in rats [34]. Antiproliferative

activity between curcumin and turmeric was compared in seven cancer cell lines. Both treatments presented similar amounts of curcumin, with a higher inhibition percentage for turmeric in all cell lines tested [23]. Therefore, other components than curcumin also contribute to the turmeric anticancer activities.

Curzerene is a sesquiterpene that presented dose-dependent antiproliferative effect both *in vitro* and *in vivo* test

[32]. The crude turmeric methanolic extract was evaluated by gas chromatography-mass spectrometry analysis (GC-MS). 50 compounds were detected, and the major compounds were ar-turmerone (20.50%),  $\beta$ -sesquiphellandrene (5.20%) and curcumenol (5.11%) [15]. Recently evaluating turmeric ethanolic extract, four new sesquiterpenes were isolated [35].

Concerning the form of essential oil obtained from rhizomes, sesquiterpenes and oxygenated monoterpenes such as ar-Turmerone (33.2%),  $\alpha$ -Turmerone (23.5%) and  $\beta$ -Turmerone (22.7%) were recorded using CG-MS and nuclear magnetic resonance (NMR) spectroscopy [14].

Likewise, using GC-MS to evaluate the essential oil, turmerone (35.9%) was the majority component among the 23 compounds identified [36]. Complementarily, it should be noted that beyond the direct antineoplastic effects, the indirect effects such as immunomodulatory and anti-inflammatory activities are relevant for tumor therapy (Table 3) [37-40].

Pre-clinical and clinical assays also demonstrated promising results (Table 4) [41-49]. But, although these tests

were performed in mice, rats, dogs and other experimental animals, the development of research directly for veterinary medicine is scarce.

### The use of curcumin associated with other cancer therapies

The combination of curcumin and cisplatin in the treatment of lung adenocarcinoma cells (A549) was favorable due to reversing tumor resistance. It was demonstrated (*in vitro*) the inhibition of factor induced by hypoxia-1 (FIH- $\alpha$ ) and reduction of P-glycoprotein, these proteins are related to tumor resistance [50]. Furthermore, curcumin reduced neurotoxicity [51] and cisplatin nephrotoxicity [52].

The use associated with radiotherapy indicated that curcumin favored the action of radiation on colon cancer cells (HCT116 and HT29), increased sensitivity to this type of treatment by inhibiting nuclear factor kappa B (NF- $\kappa$ B) [47].

Promising results were found regards the effect of curcumin as a sensitizing agent to enhance the apoptotic potential of doxorubicin [31]. These researchers evaluated  $IC_{50}$  dose (5 nM) of doxorubicin and a lower dose (2.5 nM).

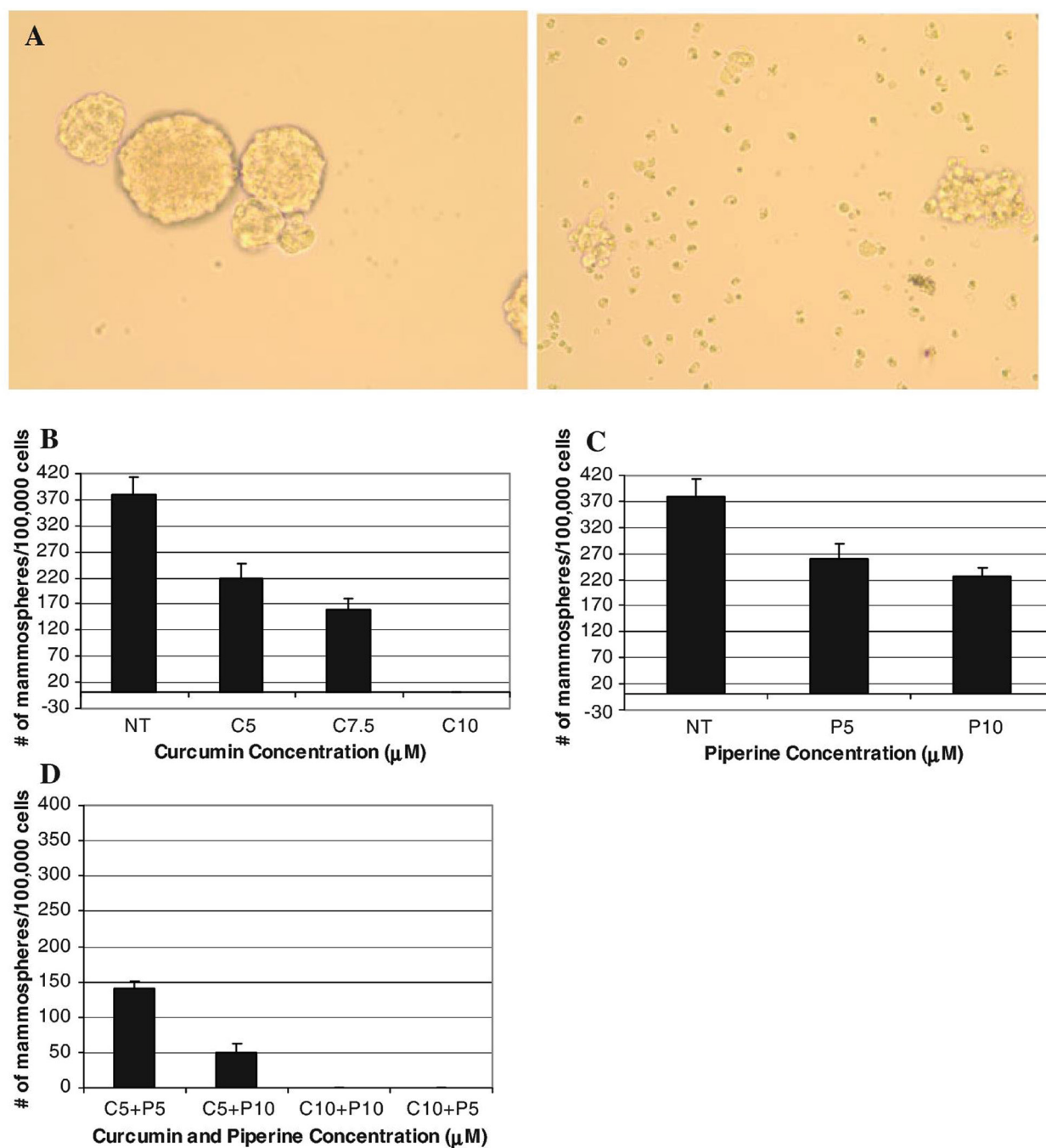
**Table 4:** Pre-clinical and clinical studies with curcumin.

Mechanisms of action/clinical action	Evaluation	References
Anti-inflammatory action: Decreased M1G levels from 4.8 F 2.9 adducts per 107 nucleotides to 2.0 F 1.8 adducts per 107 nucleotides	Human Patients colorectal cancer	GARCEA, et al. [41]
Phase I dose escalation: Toxicity at 8,000 mg/d	Human Patients Breast cancer	BAYET-ROBERT, et al. [42]
Association with PLGA Nanoparticles: Improve bioavailability, increased solubility, higher release rate in intestinal juice, enhanced absorption by improved permeability, inhibition of P-glycoprotein (P-gp)-mediated efflux, and increased residence time in the intestinal cavity	Rats	XIE, et al. [43]
Association with of Liposomal Curcumin and its Metabolite Tetrahydrocurcumin: Two-hour infusion levels were higher than eight-hour, and would be preferable for liquid malignancies; however, eight-hour infusion would be preferable for solid tumors.	Healthy Beagle Dogs	HELSON, et al. [44]
Association with Liposomal Curcumin and its Metabolite Tetrahydrocurcumin: Facilitate distribution and elevated tissue concentrations of curcumin may inhibit or saturate a putative reductase enzyme converting curcumin to THC	Healthy Beagle Dogs	MATABUDULm et al. [45]
Ameliorates Nephrotoxicity: Decrease levels of serum creatinine and urea, renal malondialdehyde, NO, tumor necrosis factor- $\alpha$ with a concurrent increase in renal glutathione peroxidase and superoxide dismutase activities.  Reduced cyclooxygenase-2 expression	Methotrxate-induced Nephrotoxicity Rats	MORSY, et al. [46]
Ameliorates Nephrotoxicity: Decrease serum concentrations TNF-alpha, renal TNF-alpha, and decreased MCP-1 and ICAM-1 mRNA expression in kidney	Cisplatin-induced Nephrotoxicity Mice	SANDUR, et al. [47]
Ameliorative Effect via Modulation of Inflammation, Oxidative Stress and Cell Death		MENG, et al. [48]
Apoptosis: Pathway PARP-, cleavage	Pre-B Acute Lymphoblastic Leukemia Cell Lines	MISHRA ,et al. [31]
Apoptosis and Renoprotective effects: Inhibiting oxidative stress through regulation of the AMPK and Nrf2/HO-1 signaling pathways, ameliorated RM-associated renal injury	Rhabdomyolysis-induced rats	WU, et al. [49]

They found that both curcumin (10  $\mu\text{M}$ ) and doxorubicin (5 nM) induced apoptosis. However, the association of curcumin (10  $\mu\text{M}$ ) with doxorubicin at a lower dose than its  $IC_{50}$  (2.5 nM) was able to induce a higher level of apoptosis in Pre-B acute lymphoblastic leukemia cell lines. It was also observed dose dependence which suggests enhanced level of apoptosis when curcumin was supplemented with doxorubicin in cell culture.

Unfortunately, unfavorable associations may occur

mainly if high doses of curcumin are used. It was verified that 6000 mg of curcumin per day represent the limit dose capable to induce adverse effects. Higher doses (8000 mg daily) demonstrated to affect negatively the association with docetaxel in breast cancer [42]. The same association was studied in MCF7 and MDA-MB-231 breast cancer cells [29]. Curcumin at 10 mg  $\text{L}^{-1}$  in cotreatment with docetaxel induced modifications in glutathione and lipid metabolisms and glucose utilization. Some of these changes were biphasic



**Figure 1:** A) Formation of primary multiple beads developed from normal human breast epithelial cells after treatment with 5  $\mu\text{M}$  curcumin (left image) and after treatment with piperine in the same dosage; B) Number of multiple spheres formation, formed from normal maternal undifferentiated epithelial cells in suspension culture with curcumin: C5 = 5  $\mu\text{M}$  curcumin and C10 = 10  $\mu\text{M}$  curcumin; C) Piperine treatment: P5 = 5  $\mu\text{M}$  and P10 = 10  $\mu\text{M}$ ; D) Treatment by the association curcumin + piperine.

depending on the exposure duration to curcumin. Thus, the continuity of research involving the use of curcumin to cancer treatment is increasingly justified. Despite the various publications in recent years, the mechanisms of action involved still need to be best clarifying, mainly when combining two active principles [29].

The association between medicinal plants may also determine benefits to oncological treatment. Curcumin associated with *Zingiber officinale* promoted growth inhibition of prostate cancer and presented superior results when compared to both treatments [53,54].

### Contribution of *C. longa* in drug resistance control

One of the major obstacles to the success of chemotherapy is the fact that some tumor cells develop multidrug pharmacological resistance (MDR) [55]. This process may be associated with overexpression of efflux pumps drug. P-glycoprotein is a drug efflux pump that is often found to be overexpressed in cases of acquired MDR. However, there are no P-glycoprotein inhibitors used in current clinical practice due to toxicity problems, drug interactions or pharmacokinetic problems. Thus, it has been carried out to search for natural products that can inhibit glycoproteins such as P-glycoprotein. Curcumin has shown important inhibition [56,57], emerging as a potential drug for the antitumor treatment response.

### Limiting factors of curcumin use: Bioavailability

The high metabolism and low half-life of curcumin impairs its absorption when administered orally [17,26,41,44,45,56]. Therefore, in order to increase the solubility, bioavailability and anticancer activity of curcumin, associations with liposomes [17,26,44,45], nanoparticles [43,58] and mainly piperine [59,60] have been proposed.

The incorporation of curcumin into liposomes promoted growth inhibition of pancreatic carcinoma cell lines [17]. Similarly, liposomal curcumin suppresses the growth of head and neck squamous cell carcinoma (HNSCC) cell lines CAL27 and UM-SCC1 *in vitro* and *in vivo* tests [26]. Association between curcumin and liposomes was also evaluated from intravenous infusion of 10 mg Kg<sup>-1</sup> in dogs [44]. These results indicated high plasma concentration of curcumin two hours after infusion, suggesting that this combination may be used in plasma cell and multiple myeloma tumors. This study was also performed by Matabudul, et al. [45] and after eight hours of infusion it was observed a significant increase of curcumin in lung, spleen and liver, demonstrating that the infusion time determined a better distribution of curcumin.

The nanoparticles associated with curcumin favor physical stability with maintenance of the cytotoxic activity of this curcuminoid in cancerous cells [43,54,56].

By intravenous administration (2.5 mg Kg<sup>-1</sup>) in mice, this association increased the bioavailability of curcumin in almost two times [56]. These authors also confirmed the antiproliferative activity in human chronic myeloid leukemia (KBM-5), human T-cell leukemia (Jurkat), prostate cancer cells (DU145), breast tumor (MDA-MB-231), esophageal cancer

(SEG-1) and colon cancer (line HCT116). It was demonstrated that curcumin loaded nanoparticulate formulation based on poly lactide-co-glycolide (PLGA) has enhanced cellular uptake and increased bioactivity *in vitro* and superior bioavailability *in vivo* over curcumin. They also observed increased cellular uptake of curcumin and inhibition of nuclear factor- kappa B (NF-κB) expression level.

Rats submitted to curcumin with nanoparticles by the oral route demonstrated increased solubility and bioavailability in five to six times and had a longer half-life. The results showed that the effect in improving oral bioavailability of curcumin may be associated with improved water solubility, higher release rate in the intestinal juice, enhanced absorption by improved permeability, inhibition of P-glycoprotein-mediated efflux and increased residence time in the intestinal cavity [43].

The association of curcumin with piperine, a polyphenol isolated from black peppers, increased the curcumin oral bioavailability [58,61]. In order to determine the ability to modulate the self-renewal of normal and malignant breast cells, Kakarala, et al. [58,61,62] examined multiple spheres formation trait and the expression of the breast stem cells with aldehyde marker dehydrogenase (ALDH) signaled by Wnt pathway. Both curcumin and piperine were able to inhibit the formation of the multiple beads, however, the addition of piperine to curcumin potentiated this reduction compared to the compounds used separately (Figure 1).

In addition, it is important to consider that some compounds of piperine may be able to determine some synergic action mechanism with turmeric. Genotoxicity was evaluated in hamsters induced by single dose (30 mg Kg<sup>-1</sup>) intraperitoneal injection of 7,12-dimethylbenz[a]anthracene. The curcumin association with piperine was able to potentiate its antigenotoxic effect, evidenced by the decrease of polychromatic erythrocytes and acrosomal aberrations [61,62].

Considering the antitumoral effect of β-elemene derived from *Curcuma wenyujin*, it was synthesized five novel β-elements from the piperazine: 13-(3-methyl-1-piperazinyl)-b-elemene (DX1), 13-(cis-3,5-dimethyl-1-piperazinyl)-b (DX2), 13-(4-isopropyl-1-piperazinyl)-b-eel (DX4) and 13-piperazinyl-b-element (DX5) [7]. These researchers reported that activation of caspase-8 by these new β-elemene, piperazine derivatives, was correlated with the decrease of cellular FLICE-like inhibitory protein (c-FLIP) levels and H<sub>2</sub>O<sub>2</sub> production, which determined the activation of the apoptotic pathways mediated by mitochondria, suggesting the influence of a synergic action mechanism.

### Conclusion

Turmeric anticancer activity was evidenced by antiproliferative, apoptotic and antimetastatic activities. Its use associated with nanoparticles, liposomes and mainly piperazine, promoted greater bioavailability of curcumin when administered orally, signaling a promising future. Additionally, the anti-inflammatory and immunomodulatory activities presented by curcumin represent an important

adjuvant mechanism of control for neoplastic pathogenesis. Therefore, the results of *in vitro* and *in vivo* tests, and pre-clinical and clinical trials showed that *C. longa* presents evidence of prophylactic and curative effects in cancer treatment.

## Conflict of Interest

The authors declare that they have no financial or personal relationships that may have inappropriately influenced them in writing this article.

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