Curcumin (Turmeric) and cancer

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Summary

Curcumin is a substance obtained from the root of the turmeric plant, which has the feature of being a yellow or orange pigment. It is also the main component of curry powder commonly used in Asian cuisine. Curcumin, a substance that has had an important place in traditional Indian and Chinese medicines for thousands of years, has been the center of interest for scientific studies especially in the field of cancer treatment for several years. Laboratory studies have presented some favorable results in terms of curcumin's antioxidant, antiinflammatory and anticancer properties in particular. However, since such findings have yet to be confirmed in clinical studies, its effect on humans is not clearly known. Therefore, when its advantages in terms of toxicity, cost and availability as well as the favorable results achieved in laboratory studies are considered, it would not be wrong to say that curcumin is a substance worth being studied. However, for now the most correct approach is to abstain from its use for medical purposes due to lack of adequate reliable evidence obtained from clinical studies, and because of its potential to interfere with other drugs.

Key words: *alternative medicine, cancer, complementary medicine, curcuma longa, curcumin, turmeric*

Introduction

Turmeric (curcuma longa), also known as 'curcuma domestica', is a perennial herbaceous plant of the ginger family (Zingiberaceae) [1]. Although it has more than 300 active components, a substance obtained from its root that has the feature of being a yellow or orange pigment is the main biologically active component constituting the basis for the medicinal properties of this plant [2,3]. This substance called curcumin, is also the main component of curry powder commonly used in Asian cuisine. It is also used as a food colorant with the code E100 [3,4].

Curcumin usage dates back more than 2,500 years in Asia, especially in traditional Indian Medicine (Ayurveda) [2]. It has been used for the treatment of many health problems such as wounds, acne, burns, various skin diseases, eye infections, sinusitis, rheumatism, depression, stress, and dyspepsia [5-7]. The first scientific study on the use of curcumin for the treatment of diseases was published in 1937; later on, the studies gained speed with the promising results of a study on its antibacterial activity, published in 1949 [8]; more than 6,000 studies on curcumin have been included in PubMed database to date [9].

The effects of curcumin, having a polyphenol structure, on certain cytokines, kinases, enzymes, transcription factors, growth factors and receptors have been studied [10], and it has shown some antimicrobial [11], antiinflammatory [12], antiox-

idant [13,14], immunomodulatory [15], renoprotective [16], hepatoprotective [17] and hypoglycaemic [18] effects. The fact that its antiinflammatory effect has been shown in some studies, and that inflammation is one of the factors for cancer development suggested that curcumin could be used for the prevention and treatment of cancer [19]. In 1985, Kuttan et al. showed the possibility of curcumin having anticancer properties; thereupon, studies turned towards this attribute [20]. Recently, particularly its chemopreventive activity has been the focal point in the field of cancer treatment [21]. Being an easily accessible, low cost and low toxicity substance, curcumin could be an ideal chemopreventive agent. Since 1987, the U.S. National Cancer Institute tested more than 1,000 agents for chemopreventive purposes. Among them, approximately 40 promising agents were moved to clinical trials. Curcumin is one of these agents. However, its poor bioavailability and high potential to interfere with other drugs, combined with lack of evidence showing its efficacy, constitute barriers at this point [22,23].

Laboratory studies carried out on the effects of curcumin in cancer

Some anticancer properties of curcumin, in terms of both treatment and chemoprevention, are to be found in many laboratory studies and there have been efforts to describe them with different mechanisms. In one study, it was alleged to be an interaction with the arachidonic acid metabolism and association with its antiangiogenic characteristics [24]; in another study, it was attributed to the inhibition of STAT-3 (signal transducer and activator of transcription-3) pathway [25]. Then, there are some other studies in which it was associated with various mechanisms such as matrix metalloproteinase, vascular endothelial growth factor [26], and caspase and mitochondria-dependent apoptosis [27]. Moreover, in various laboratory studies, curcumin inhibited cyclooxygenase-2, lipoxygenase, ornithine, c-Jun/AP- 1, nuclear factor-kappa B, c-Jun N-terminal kinase, protein kinase C, and epidermal growth factor activities in a variety of tumor cells [28].

In the literature, there are many laboratory studies, in which the antiproliferative effects of curcumin on various tumor cells were investigated. In one of them curcumin inhibited the proliferation in uterine leiomyosarcoma cell lines through AKT-mTOR (RAC-alpha serine-threonine-protein kinase; mammalian target of rapamycin) [29]. In

another study carried out on mice, curcumin significantly inhibited the proliferation in prostate cancer cells [30]. In a study carried out on mice, some of them were fed with curcumin, and then the esophageal carcinogen N-nitrosomethylbenzylamine was injected into all. As a result, cell proliferation biomarkers (5-bromo-2'-deoxyuridine) were found to be significantly lower in the mice fed with curcumin [31].

In a study involving the investigation of the effect of curcumin on triple negative breast cancer (TNBC), known to have poor prognosis, the administration of curcumin to TNBC cell cultures was found to inhibit TNBC cell proliferation. The inhibition of EGFR (epidermal growth factor receptor) pathway was thought to be the underlying mechanism of this result [32].

Another study on the antimetastatic potential of curcumin showed that it inhibited metastasis of prostate cancer cells by reducing CXCL1 and CXCL2 expression which play an important role in metastasis [33]. In another study, curcumin also showed an antimetastatic effect on breast cancer [34].

A study performed on mice showed that the dietary curcumin treatment significantly reduced the incidence of lung metastases of breast cancer, by inhibiting NF-κB and COX2 expression [35].

The effect of curcumin on chemosensitivity and radiosensitivity was also assessed. In two studies published on this subject, curcumin increased the sensitivity of 5-Fluorouracil (5-FU) in colorectal cancer cell lines [36,37], while in another study published in 2014, a newly developed curcumin analog (H-4073) enhanced the efficacy of cisplatin in head and neck cancer cell lines [38]. It has also been reported that curcumin enhances the efficacy of cisplatin in ovarian cancer cells [39]. Another study carried out on mice showed that curcumin reinforced the effectiveness of paclitaxel in cervical cancer cells [40] and it was also reported that it increased the sensitivity to radiotherapy in lymphoma [41].

Curcumin was shown to create a synergistic effect with the chemotherapeutic agent vinorelbine, used for inhibiting the growth of squamous cell lung carcinoma H520 cells. Both agents lead to apoptosis by increasing the caspase-9 and caspase-3 activities and reducing the Bcl-2 and Bcl-X (L) expressions. It was observed that when administered alone, vinorelbine led to 38% apoptosis in H520 cells, while curcumin led to 23.7% apoptosis. However, their combined use increased the vinorelbine-induced apoptosis to 61.3% [42].

An *in vivo* study carried out on mice investigated the use of curcumin in conjunction with oxaliplatin. Their combined administration was found to cause increased growth inhibition of colorectal cancer cells, compared to use of oxaliplatin alone. It was observed that curcumin's combined use with oxaliplatin induced apoptosis and led to the death of cells at S and G2/M phases [43]. In another study on the use of curcumin in conjunction with other agents intended for cancer treatment, the combined use of curcumin with dasatinib in chemotherapy-resistant colon cancer cell lines was found to create a synergistic effect and cause a reduction in cancer stem cells [44].

Chemoprevention is one of the most studied anticancer properties of curcumin. In one of these studies, it was reported that curcumin could suppress oral carcinogenesis through insulin-like growth factor binding protein-5 (IGFBP-5) and CCAAT/enhancer-binding protein alpha (C/EBPalpha), which are suppressors of head and neck carcinogenesis [45]. In a study carried out on mice with familial adenomatous polyposis, it was reported that when administered orally it might show a chemopreventive effect against colorectal cancer APC mutation, by preventing adenoma development in the intestinal tract [46] (Table 1).

Clinical studies carried out on the effects of curcumin in cancer

There is a limited number of clinical studies investigating the effects of curcumin in the prevention or treatment of cancer. Except for these few, there were others at the initial stage, which included a limited number of cases. In one of the studies that involved a relatively high number of cases, it was stated that curcumin given orally to 126 colorectal cancer patients in the preoperative period decreased their weight loss, increased the p53 expression and apoptotic tumor cells in the tumor tissue, and reduced the serum TNF-a levels [47]. In a phase II study of 44 patients with colon cancer lesions, the use of 4 g curcumin a day for a period of 30 days provided a 40% reduction in the number of lesions [48].

In another study that included 199 patients with localized prostate cancer, who were under follow-up after primary intervention, the median increase in PSA was found to be 63.8% lower in the 6-month period after radical treatment in patients who were given a mixture of green tea, pomegranate, broccoli and curcumin [49].

In some early-stage studies, certain favorable results were achieved in the reduction of side effects and symptoms associated with radiotherapy. In an initial study that enrolled 50 patients with head and neck cancer, who were given radiotherapy, a cream containing sandalwood oil and curcumin was found to be effective in the prevention of radiodermatitis [50]. In a similar study carried out on 30 breast cancer patients, who were given radiotherapy, taking curcumin orally decreased the severity of radiation dermatitis and moist desquamation [51]. Curcumin provided symptomatic relief again in a study of 62 patients, who had cancer lesions on their skin, vulva, breast, or oral cavity [52].

In some studies, curcumin was administered in combination with other agents, and as a result, the specific effects of curcumin could not be assessed. In a study involving 50 patients with chronic myeloid leukemia, the effect of turmeric - known to play a role in tumorigenesis - on nitric oxide levels was assessed. As a result, turmeric was observed to reduce nitric oxide levels more than imatinib. However, since turmeric itself was used instead of curcumin in the study, it is not known whether that effect belonged to curcumin or another component in turmeric [53]. In a study carried out on men, who had no detectable prostate cancer, the combination of curcumin and isoflavone reduced the PSA levels in men who had a PSA level higher than 10. These results suggested that these substances might have an antiandrogenic effect, yet, it is difficult to say whether this effect was from curcumin or from isoflavone [54].

In a phase II study published in 2008 25 patients with advanced pancreatic cancer taking curcumin were enrolled, and the results showed that the disease was stable for a period of more than 18 months in a patient, and the tumor showed 73% regression in another patient. No positive responses could be achieved in the remaining patients [55]. In another clinical study, curcumin in combination with gemcitabine was given to 17 patients with advanced pancreatic cancer but no favorable results could be achieved; moreover, 5 patients had increased abdominal pain [56].

In a phase I study that involved the assessment of the combined use of curcumin with FOLFOX chemotherapy in patients with colorectal cancer and liver metastases, the combined use of curcumin with FOLFOX was found to enhance the antiproliferative and proapoptotic activities of oxaliplatin and 5-FU [57]. Contrary to this study, a phase I study carried out by Somasundaram et al. showed that curcumin led to reduced apoptosis induced by cyclophosphamide used in breast cancer [58] (Table 2).

Table 1. Laboratory studies examining the effects of curcumin in cancer

First author (year) [ref]	Study design	Cell lines	Main results	Conclusion
Wong (2011) [29]	Laboratory study	Human leiomyosarcoma cells	Both rapamycin and curcumin significantly reduced SKN cell proliferation. Curcumin inhibited mTOR, p70S6 and S6 phosphorylation similar with rapamycin. Cleaved PARP, caspase-3 activity and DNA fragmentation increased proportional with curcumin concentration. At a high concentration, curcumin significantly induced apoptosis in SKN cells, but not rapamycin.	Curcumin inhibited uterine leiomyosarcoma cells' growth by targeting the AKT-mTOR pathway for inhibition. However, rapamycin, a specific mTOR inhibitor, did not induce apoptosis in SKN cells unlike curcumin that also had a pro-apoptotic potential in SKN cells.
Dorai (2001) [30]	Laboratory study	Human prostate cancer cells	Curcumin caused a marked decrease in the extent of cell proliferation as measured by the BrdU incorporation assay and a significant increase in the extent of apoptosis as measured by an in situ cell death assay. Moreover, a significant decrease in the microvessel density as measured by the CD31 antigen staining was also seen.	Curcumin could be a potentially therapeutic anti-cancer agent, as it significantly inhibited prostate cancer growth, as exemplified by LNCaP *in vivo*, and had the potential to prevent the progression of this cancer to its hormone refractory state.
Ushida (2000) [31]	Laboratory study	Male rats' esophageal cells	In curcumin group, esophageal neoplasms and esophageal preoplastic lesions were significantly lower.	These findings indicated that curcumin inhibited NMBA-induced esophageal carcinogenesis when given during the post initiation as well as initiation phase. This inhibition may be related to suppression of the increased cell proliferation induced by NMBA in the esophageal epithelium.
Sun (2012) [32]	Laboratory study	Triple-negative human breast cancer cells	After treatment with different concentrations of curcumin, the growth inhibition rates of the MDA-MB-231 breast cancer cells of the 30 μmol/ml curcumin-treated group were significantly different from those of the other groups. The level of apoptosis of the curcumin-treated group (26.34%) was significantly different from that of the control group (2.76%). The expression levels of pERK1/2 and pEGFR in the curcumin-treated group were significantly decreased compared with those of the control group.	These results indicated that curcumin was able to inhibit the proliferation of TNBC cells. Inhibition of the EGFR signaling pathway was the likely underlying molecular mechanism.
Killian (2012) [33]	Laboratory study	Human prostate cancer cells	Curcumin inhibited translocation of NFκB to the nucleus through the inhibition of the IκB-kinase (IKKβ, leading to stabilization of the inhibitor of NFκB, IκBα), in PC-3 prostate carcinoma cells. Inhibition of NFκB activity reduced the expression of CXCL1 and -2 and abolished the autocrine/paracrine loop that links the two chemokines to NFκB. Treatment with curcumin inhibited significantly the formation of lung metastases.	Chronic inflammation can induce a metastasis prone phenotype in prostate cancer cells by maintaining a positive proinflammatory and prometastatic feedback loop between NFκB and CXCL1/-2. Curcumin disrupted this feedback loop by inhibition of NFκB signaling leading to reduced metastasis formation *in vivo*.
Bachmeier (2007) [34]	Laboratory study	Human breast cancer cells	Curcumin strongly induced apoptosis in MDA-MB-231 cells in correlation with reduced activation of the survival pathway NF kappaB, as a consequence of diminished IotakappaB and p65 phosphorylation. Curcumin also reduced the expression of major matrix metalloproteinases (MMPs) due to reduced NF kappa B activity and transcriptional downregulation of AP-1. Reduced NF kappa B/AP-1 activity and MMP expression led to diminished invasion through a reconstituted basement membrane and to a significantly lower number of lung metastases in immunodeficient mice after intercardiac injection of 231 cells.	68% of curcumin treated but only 17% of untreated animals showed no or very few lung metastases, most likely as a consequence of down-regulation of NF kappa B/AP-1 dependent MMP expression and direct apoptotic effects on circulating tumor cells but not on established metastases. Dietary chemoprevention of metastases appeared therefore feasible.

Aggarwal (2005) [35]	Labo- ratory study	Human breast can- cer cells	In a human breast cancer xenograft model, dietary administration of curcumin significantly decreased the incidence of breast cancer metastasis to the lung and suppressed the expression of NF-kappaB, cyclooxygenase 2, and matrix metalloproteinase-9.	Curcumin, which is a pharma- cologically safe compound, had a therapeutic potential in preventing breast cancer metastasis possibly through suppression of NF-kappaB and NF-kappaB-regulated gene products.
Shakibaei (2013) [36]	Labo- ratory study	Human colorectal cancer cells	Curcumin potentiated 5-FU-induced expression or cleavage of pro-apoptotic proteins (caspase-8, -9, -3, PARP and Bax), and down-regulated anti-apop- totic (Bcl-xL) and proliferative (cyclin D1) proteins. Although 5-FU activated NF-κB/PI-3K/Src pathway in CRC cells, this was down-regulated by curcumin treatment through inhibition of IκBα kinase activation and IκBα phosphorylation.	Combining curcumin with conventional chemotherapeutic agents such as 5-FU could provide more effective treatment strategies against chemoresistant colon cancer cells. The mechanisms involved may be mediated via NF-κB/ PI-3K/Src pathways and NF-κB regulated gene products.
Shakibaei (2014) [37]	Labo- ratory study	Human colon cancer cells	Pre-treatment with curcumin significantly enhanced the effect of 5-FU on HCT116R and HCR116+ch3R cells, in contrast to 5-FU alone as evidenced by increased disintegration of colono- spheres, and enhanced apoptosis by inhibiting their growth. Curcumin and/or 5-FU strongly affected MMR-deficient CRC cells in high density cultures, however MMR-proficient CRC cells were more sensitive.	The results illustrated novel and previously unrecog- nized effects of curcumin in enhancing chemosensitization to 5-FU-based chemotherapy on DNA MMR-deficient and their chemo-resistant counterparts by targeting the CSC sub-pop- ulation.
Kumar (2014) [38]	Labo- ratory study	Human head and neck squa- mous cell carcinoma cells	A novel curcumin analog (H-4073) significantly enhanced the anti-tumor and anti-angiogenesis effects of cisplatin, with no added systemic toxicity. Interestingly, H-4073 inhibited tumor angiogenesis by blocking VEGF production by tumor cells as well as directly inhibiting endothelial cell function.	The results suggested that H-was a potent anti-tumor agent and it could be used to overcome chemotherapy resistance in head and neck squamous cell carcinomas.
Selvendi- ran (2011) [39]	Labo- ratory study	Human ovarian cancer cells	HO-3867 (a curcumin analog)/cisplatin combina- tion treatment significantly inhibited cisplatin-re- sistant cell proliferation in a concentration-depen- dent manner. The inhibition was associated with increased expression of p53 and p21, and decreased expression of cdk5 and cyclin D1. The combination treatment significantly inhibited the growth of cis- platin-resistant xenograft tumors with significant downregulation of pSTAT3, and without appar- ent toxicity to healthy tissues. The combination treatment exhibited synergistic anticancer efficacy, which appeared to be largely due to HO-3867-in- duced downregulation of pSTAT3.	The results, combined with the previously-reported safety features of HO-3867, suggested the potential use of this com- pound as a safe and effective adjuvant for the treatment of ovarian cancer.
Sreekanth (2011) [40]	Labo- ratory study	Human cervical cancer cells	The combined treatment of curcumin and paclitaxel induced a synergestic reduction in the tumor inci- dence as well as tumor volume of animals com- pared with the individual treatments of paclitaxel or curcumin, although curcumin alone could not induce any significant effect at the concentration used. The results suggested that a suboptimal con- centration of curcumin augmented the antitumor action of paclitaxel by downregulating the activa- tion and downstream signaling of antiapoptotic factors and survival signals such as NF-κB, Akt and mitogen-activated protein kinases that have signif- icant roles in proliferation, survival, angiogenesis and metastasis.	The findings of this preclini- cal study provided a strong rationale for the validation of this combination through cli- nical trials. As curcumin could effectively downregulate all these survival signals induced by paclitaxel, it was suggested as a potent chemosensitizer to improve the therapeutic index of paclitaxel.

Qiao (2012) [41]	Laboratory study	Human Burkitt's lymphoma cells	Pretreatment of curcumin sensitized lymphoma cells to ionizing radiation (IR)-induced apoptosis and increased G2/M phase arrest in the cell cycle distribution. Accordingly, the antiapoptotic Bcl-xL protein, cell cycle modulating protein CDC2, and cyclin B1 were downregulated by the curcumin treatment. Pretreatment with curcumin significantly decreased the nuclear translocation of p65 and cytoplasmic IκBα degradation. Survivin and hexokinase II, downstream effectors of NF-κB that mediate the antiapoptotic effect of NF-κB, were suppressed by the pretreatment of curcumin.	The activated NF-κB pathway played a prosurvival role in Burkitt's lymphoma in response to ionizing radiation. Curcumin blocked this pathway and has therapeutic potential for improving the antitumor effects of radiotherapy.
Sen (2005) [42]	Laboratory study	Human squamous cell lung carcinoma cells	Human squamous cell lung carcinoma H520 cells treated with curcumin were sensitized to the cytotoxicity caused by the chemotherapeutic agent vinorelbine. Both caused apoptosis by increasing the protein expression of Bax and Bcl-xs while decreasing Bcl-2 and Bcl-X(L), releasing apoptogenic cytochrome C, and augmenting the activity of caspase-9 and caspase-3. Expression of Cox-2, NF-kappaB, and AP-1 was also affected. 23.7% apoptosis was induced in the H520 cells by treatment with curcumin while vinorelbine caused 38% apoptosis. Pre-treatment with curcumin enhanced the vinorelbine induced apoptosis to 61.3%.	The findings suggested that curcumin had the potential to act as an adjuvant chemotherapeutic agent and enhance chemotherapeutic efficacy of vinorelbine in H520 cells *in vitro*. Thus, curcumin offers the prospect of being beneficial in the above-mentioned patient groups.
Guo (2015) [43]	Laboratory study	Human colorectal cancer cells	Combinatorial administration of curcumin and oxaliplatin evidently inhibited the growth of colorectal cancer cells in nude mice, which was significantly more effective than either agent alone. Curcumin combined with oxaliplatin treatment induced apoptosis, accompanied by ultrastructural changes and cell cycle arrest in S and G2/M phases.	This study demonstrated that administration of combined curcumin and oxaliplatin effectively suppressed colorectal carcinoma *in vivo* through inducing apoptosis and thus may provide an effective treatment for colorectal carcinoma.
Nautiyal (2011) [44]	Laboratory study	Human colon cancer cells	The residual tumors from APCMin +/- mice treated with dasatinib and/or curcumin showed 80-90% decrease in the expression of the CSC markers ALDH, CD44, CD133, CD166. The colon cancer CR cells showed a higher expression of CSCs markers, cell invasion potential and ability to form colonospheres, compared to the corresponding parental cells. The combination therapy of dasatinib and curcumin demonstrated synergistic interactions in CR HCT-116 and CR HT-29 cells, as determined by Calcusyn analysis.	The combination therapy of dasatinib and curcumin may be a therapeutic strategy for re-emergence of chemo-resistant colon cancer by targeting cancer stem cells sub-population.
Chang (2010) [45]	Laboratory study	Human oral cancer cells	Curcumin increased nuclear C/EBPalpha expression and IGFBP-5 expression through p38 activation and this was abrogated by SB203580 treatment. Furthermore, MKK6 expression activated p38 and C/EBPalpha, increasing IGFBP-5 promoter activity and expression. Finally, curcumin-induced IGFBP-5 expression was associated with the suppression of xenograft tumorigenesis in mice due to oral cancer cells.	Curcumin activated p38, which, in turn, activated the C/EBPalpha transactivator by interacting with binding elements in the IGFBP-5 promoter. The consequenting upregulation of C/EBPalpha and IGFBP-5 by curcumin was crucial to the suppression of oral carcinogenesis.
Perkins (2002) [46]	Laboratory study	A model of familial adenomatous polyposis in mice	A dietary concentrations of 0.2 and 0.5%, curcumin reduced intestinal tumor load significantly by 39 and 40%, respectively. Inspection of adenomas revealed a flattened morphology in the case of mice that had received curcumin at 0.5%, compared with untreated mice or mice on the lower doses of curcumin (result not shown). There were only a few adenomas in the colon of untreated Min/+ mice (3.5 ± 3.8, n = 22) although dietary curcumin (0.2 and 0.5%) reduced their number by 30 and 27%, respectively.	Curcumin may be useful in the chemoprevention of human intestinal malignancies related to Apc mutations. The comparison of dose, resulting curcumin levels in the intestinal tract, and chemopreventive potency suggested tentatively that a daily dose of 1.6 g was required for efficacy in humans. A clear advantage of curcumin over nonsteroidal anti-inflammatory drugs was its ability to decrease intestinal bleeding linked to adenoma maturation.

Soma-sundaram (2002) [58]	Labo-ratory study	Human breast carcinoma cells	Curcumin exhibited antioxidant properties and inhibited both JNK activation and mitochondrial release of cytochrome C in a concentration-dependent manner. Using an in vivo model of human breast cancer, dietary supplementation with curcumin was found to significantly inhibit cyclophosphamide-induced tumor regression. Such dietary supplementation was accompanied by a decrease in the activation of apoptosis by cyclophosphamide, as well as decreased JNK activation.	Dietary curcumin could inhibit chemotherapy-induced apoptosis through inhibition of ROS generation and blockade of JNK function, and suggested that additional studies are needed to determine whether breast cancer patients undergoing chemotherapy should avoid curcumin supplementation, and possibly even limit their exposure to curcumin-containing foods.

Table 2. Clinical studies examining the effects of curcumin in cancer

First author (year) [ref]	Study design	Participants (number, diagnosis)	Main results	Conclusion
He (2011) [47]	Randomized controlled trial	126 patients with colorectal cancer	This study provided evidence that curcumin administration improved weight loss, reduced serum levels of TNF-α, increased cancer cell apoptosis, upregulated p53 molecules, and modulated apoptosis-related Bax and Bcl-2 molecules in cancer cells.	The curcumin treatment improved the general health of patients with colorectal cancer via the mechanism of increased p53 molecule expression in tumor cells and consequently sped up tumor cell apoptosis. Thus, the curcumin administration could be a supplemental remedy for the treatment of cancer.
Carroll (2011) [48]	Clinical trial, phase II	44 eligible smokers with 8 or more aberrant crypt foci (ACF) on screening colonoscopy	A significant 40% reduction in ACF number occurred with the 4 g dose ($p < 0.005$), while ACF were not reduced in the 2 g group. This reduction was associated with a significant change in plasma curcumin/conjugate levels pre- and post-treatment (5-fold increase; $p = 0.009$) in the 4 g group. Curcumin was well tolerated at both 2 g and 4g. Data suggested that curcumin could decrease ACF number.	A short duration of curcumin treatment reduced ACF number, and this is potentially mediated by curcumin conjugates delivered systemically.
Thomas (2014) [49]	Randomized controlled trial	199 men with localized prostate cancer,	The median rise in PSA in the food supplement group was 14.7%, as opposed to 78.5% in the placebo group (difference 63.8%;p=0.0008).	This study found a significant short-term, favorable effect on the percentage rise in PSA in men managed with active surveillance and watchful waiting following ingestion of this well-tolerated, specific blend of concentrated foods.
Palatty (2014) [50]	Randomized controlled trial	50 patients with head and neck cancer	A significant reduction in grades of dermatitis was seen in cohorts applying wood oil-containing turmeric cream (VTC) at all time points, including 2 weeks post radiotherapy. The occurrence of grade 3 dermatitis was lower in the cohorts using VTC and was statistically significant. Additionally, follow-up observations 2 weeks after the completion of radiotherapy also showed a reduced degree of radiodermatitis in cohorts applying VTC, which was significant.	VTC was shown to be effective in preventing radiodermatitis and needs to be validated in larger double-blind trials.
Ryan (2013) [51]	Randomized controlled trial	30 adult patients with breast cancer	Standard pooled variance t-test showed that curcumin reduced RDS at the end of treatment compared to placebo. Fisher's exact test revealed that fewer curcumin-treated patients had moist desquamation.	In conclusion, oral curcumin, 6 g daily during radiotherapy, reduced the severity of Radiation dermatitis in breast cancer patients.

Kuttan (1987) [52]	Single arm clinical trial	62 patients, who had cancer lesions on their skin, vulva, breast, or oral cavity	An ethanol extract of turmeric ("Curcuma longa") as well as an ointment of curcumin (its active ingredient) were found to produce remarkable symptomatic relief in patients with external cancer lesions. Reduction in smell were noted in 90% of the cases and reduction in itching in almost all cases. Dry lesions were observed in 70% of the cases, and a small number of patients (10%) had a reduction in lesion size and pain. In many patients the effect continued for several months.	Curcumin provided symptomatic relief in patients with external cancer lesions.
Ghalaut (2012) [53]	Randomized controlled trial	50 patients with chronic myeloid leukemia	Turmeric was observed to reduce nitric oxide levels more than imatinib. However, since turmeric itself was used instead of curcumin in the study, it is not known whether that effect belonged to curcumin or another component in turmeric.	Nitric oxide levels were found to be significantly decreased in both the groups, but more significantly in group B (receiving turmeric powder) after receiving the respective treatments. Thus, curcumin acted as an adjuvant to imatinib in decreasing the NO levels and might help in the treatment of chronic myeloid leukemia patients.
Ide (2010) [54]	Randomized controlled trial	85 men with no detectable prostate cancer	The production of PSA was markedly decreased by the combined treatment of isoflavones and curcumin in prostate cancer cell line. The expression of the androgen receptor was also suppressed by the treatment. PSA levels decreased in the patients group with PSA≥10 treated with supplement containing isoflavones and curcumin.	The results indicated that isoflavones and curcumin could modulate serum PSA levels. Curcumin presumably synergized with isoflavones to suppress PSA production in prostate cells through the anti-androgen effects.
Dhillon (2008) [55]	Clinical trial, phase II	25 patients with advanced pancreatic cancer	Two patients showed clinical biological activity. One had ongoing stable disease for >18 months. Interestingly, one additional patient had a brief, but marked, tumor regression (73%) accompanied by significant increases (4- to 35-fold) in serum cytokine levels (IL-6, IL-8, IL-10, and IL-1 receptor antagonists). No toxicities were observed.	Oral curcumin was well tolerated and, despite its limited absorption, had biological activity in some patients with pancreatic cancer.
Epelbaum (2010) [56]	Clinical trial, phase II	17 patients with advanced pancreatic cancer	Five patients (29%) discontinued curcumin after a few days to 2 wks due to intractable abdominal fullness or pain. One of 11 evaluable patients (9%) had partial response, 4 (36%) had stable disease, and 6 (55%) had tumor progression. Time to tumor progression was 1-12 mo (median 2.5), and overall survival was 1-24 mo (median 5).	Further studies should be conducted to evaluate the ability of other formulations of curcumin to enhance the effect of chemotherapy in cancer patients.
James (2015) [57]	Clinical trial, phase I	12 patients with colorectal liver metastases	Curcumin alone and in combination significantly reduced spheroid number in colorectal liver metastases cancer stem cell models, and decreased the number of cells with high aldehyde dehydrogenase activity (ALDH(high)/CD133(-)). Addition of curcumin to oxaliplatin/5-FU enhanced anti-proliferative and pro-apoptotic effects in a proportion of patient-derived explants, whilst reducing expression of stem cell-associated markers ALDH and CD133.	This phase I dose escalation study revealed curcumin to be a safe and tolerable adjunct to 5-fluorouracil (5-FU) and oxaliplatin (FOLFOX) chemotherapy in patients with CRLM (n = 12) at doses up to 2 gr daily. Curcumin might provide added benefit in subsets of patients when administered FOLFOX, and was a well-tolerated chemotherapy adjunct.

Potential side effects of curcumin

Curcuminoids have been characterized as "generally safe" by the FDA (Food and Drug Administration) [59]. Indeed, any serious side effects directly associated with curcumin use have not been reported in the literature. The cases reported were local, reversible side effects such as allergic dermatitis [60]. But there is strong evidence for drug interactions in the literature. There are studies on its interaction with some drugs such as antiplatelet drugs [61], camptothecin, mechlorethamine, doxorubicin, cyclophosphamide [58], celiprolol, midazolam [62] and tacrolimus [63]. Studies suggesting that curcumin generally affects cytochrome P450 enzymes have been reported. Curcumin was shown to affect cytochrome P450 enzymes in a clinical study carried out on 18 healthy volunteers, and in a laboratory study that involved the assessment of various components in spices [23,64]. In another laboratory study, it was stated that curcumin might antagonize the antitumor activity of chemotherapeutic drugs, by inhibiting the reactive oxygen species production and c-Jun NH(2)-terminal kinase (JNK) pathway [37].

Conclusion

Results obtained from animal studies and other laboratory studies indicate that curcumin may have antiinflammatory, antioxidant and anticancer properties, in particular. However, since there is a limited number of clinical studies, its effects on humans are not known clearly. Therefore, it is difficult to say that there is reliable evidence for the use of curcumin in any health condition. Indeed, its use for any health condition has yet to be approved. Although no serious side effects associated with the use of curcumin and curcumin-containing products have been reported, there are data on drug interactions, particularly with chemotherapeutic agents. For now, it would be preferable to abstain from the use of this product for medical purposes.

Conflict of interests

The authors declare no confict of interests.

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