Effectiveness of Curcumin for Treating Cancer During Chemotherapy

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Abstract

Oncologists tend to avoid the use of supplements during chemotherapy. To understand the safety issue, a literature review was conducted to evaluate safety and possible benefits of taking curcumin during chemotherapy. Curcumin was chosen because of its wide use in the public and because of the availability of clinical trials utilizing curcumin during chemotherapy. Curcumin is considered a "pan-assay interference compound," creating false leads in drug discovery assays. The pharmacodynamics of curcumin presents many challenges for a therapeutic agent, including poor bioavailability and rapid metabolism and excretion. The proposed molecular targets for curcumin include inhibition of nuclear factor kappa B and inhibition of cyclooxygenase-2. Clinical trials investigating the efficacy of curcumin treatment for cancer have been conducted in patients with colorectal cancer (CRC), pancreatic cancer, breast cancer, prostate cancer, multiple myeloma, lung cancer, and head and neck cancer. Outcomes revealed that while curcumin was not effective, it was well tolerated and safe. Recently, there have been several Phase I and Phase II trials combining curcumin with chemotherapeutic agents. Two trials investigated the effect of curcumin given concurrently with gemcitabine for advanced pancreatic cancer patients. One trial investigated the effect of curcumin given concurrently with docetaxel in advanced breast cancer patients. Another trial investigated the role of curcumin given concurrently with docetaxel and prednisone in castration-resistant prostate cancer patients. The results again indicate the safety of curcumin, but no added benefit of adding curcumin to the chemotherapy regimen. The literature review demonstrated that curcumin is well tolerated up to 6–8 g in research. While there are many promising in vivo and in vitro trials on the potential benefits of curcumin for treatment of cancer in conjunction with chemotherapy, to date there is no evidence that combining curcumin with chemotherapeutic agents is effective for treating cancer in humans. The lack of effect may be due to the target diseases that are treatment resistant such as advanced pancreatic cancer and advanced breast cancer. Also, curcumin has many difficult properties such as poor solubility and rapid metabolism. Currently, there are developments of analogues, liposomal products, and nanoparticles that may overcome the current challenges of curcumin. Future studies should utilize these evolving technologies.

Keywords: curcumin, chemotherapy, cancer

Introduction

While most oncologists recommend to their patients to refrain from using supplements during chemotherapy, the literature reveals wide use of supplements during chemotherapy. It has been estimated that more than 50–60% of cancer patients use herbs, and most herbal use occurs during chemotherapy.[1,2] Interest in exploring botanical sources to treat cancer is not new. Examples of chemotherapeutic agents originating from plant sources are listed in Table 1. In recent years there has been an increasing interest in naturally occurring plant-based supplements for treatment of disease.[3] Among these supplements, curcumin stands out because of extensive scientific inquiry.

Turmeric (*Curcuma longa*) is a member of the ginger family and is widely used as a kitchen spice and food colorant. Although turmeric is originally from South Asia, it is now cultivated in many tropical areas around the world. Turmeric has been used for more than 4,000 years to treat a variety of ailments. While curcumin is considered to be the active ingredient of turmeric, other curcuminoids such as desmethoxycurcumin and bisdemethoxycurcumin are being investigated. A study by Zhang et al. demonstrated that while all three curcuminoids were equally potent in inhibition of microglia activation, desmethoxycurcumin exhibited the strongest inhibitory activity on tumor necrosis factor alpha (TNF-α) production.[4] Further research on curcuminoids other than curcumin for treating cancer is needed.

The popularity of curcumin has grown, as evidenced by the sales of curcumin supplements in the United States, which exceeded $20 million in 2014. Studies have shown that curcumin is nontoxic to human subjects. In fact, one study

Table 1. Examples of Chemotherapeutic Agents of Plant Origin

Chemotherapeutic agent	Source
Taxol	Pacific yew tree (*Taxus brevifolia*)
Vinca alkaloids	Madagascar periwinkle (*Catharanthus roseus*)
Irinotecan, Topotecan (analogues)	Happy tree (*Camptotheca acuminata*)

documented that oral doses of up to 12 g per day were well tolerated.[5] However, the authors also concluded that doses > 8 g per day were difficult due to its bulky nature, resulting in gastrointestinal discomfort. In the United States, turmeric products and curcumin have been classified as "Generally Recognized as Safe" by the Food and Drug Administration.

The bioavailability of oral curcumin is low due to factors including poor gastrointestinal absorption, fast metabolism, rapid elimination, and poor aqueous solubility. In fact, after oral intake of curcumin, the serum concentration peaks at one to two hours and is undetectable by 12 hours. Studies have shown that combining curcumin with phospholipids such as lecithin can increase its absorption. For example, Meriva® (Indena S.p.A.) is a formulation of a standardized curcuminoid mixture and lecithin. Cuomo et al. demonstrated that the total curcuminoid absorption was about 29-fold higher for Meriva® than unformulated curcuminoid mixture.[6] Also, pairing curcumin with black pepper (piperine) helps boost its absorption from the digestive system to the bloodstream. Shoba et al. published that 2 g of curcumin with concomitant administration of 20 mg of piperine resulted in much higher concentration, demonstrating a 2,000% increase in bioavailability.[7] Lastly, nanoparticle encapsulation of curcumin improved oral bioavailability of curcumin by at least ninefold when compared to curcumin administered with piperine as an absorption enhancer.[8]

Curcumin offers multiple biological targets and results in numerous cellular effects. The various cellular mechanisms make it a seemingly appropriate therapy for the treatment of cancer, a multifactorial disease. Properties attributed to curcumin include anti-inflammatory, antiangiogenic, and neuroprotective.[9] Recent studies have sought to explore and elucidate the role of curcumin for treatment and prevention of cancer. As such, curcumin may hold promise as an effective adjunct to chemotherapy.

Molecular Mechanisms of Curcumin for Treating Cancer

Curcumin has been shown to target several cell signaling pathways involved in carcinogenesis. During carcinogenesis, curcumin can suppress cancer cell activation.[10] Once carcinogenesis occurs, curcumin can block the continuation of malignant cell spread.[11] The most studied molecular mechanisms of curcumin are listed below:[12]

- Suppression of cyclooxygenase-2 (COX-2);
- Inhibition of inflammatory cytokines (interleukin [IL]-6, IL-1β);
- Inhibition of signal transducers and activators of transcription (STAT);
- Inhibition of growth factors (epidermal growth factor receptor, human epidermal growth factor receptors 2 and 3); and
- Suppression of transcription factors (nuclear factor kappa B [NF-κB] and activator protein 1).

While it is beyond the scope of this review paper to describe all molecular targets of curcumin, the authors have chosen to focus on the role of curcumin as an inhibitor of the transcription factor NF-κB. NF-κB is involved in chronic and acute inflammation, as well as cancer development. It can play a critical role in regulating many genes that participate in different signal transduction pathways involved in carcinogenesis.[13] Notably, the inhibition of NF-κB is being investigated as a target for new cancer drug development.

Inflammatory cytokines IL-1β, IL-6, TNF-α, oxidative stress, and other carcinogens play an active role in activating NF-κB.[14] NF-κB normally exists in an inactivated form in the cytoplasm. Once activated, NF-κB is translocated into the nucleus, resulting in a change of cell function.[15,16] Curcumin blocks the activation of NF-κB, thereby allowing NF-κB to remain in the cytoplasm in its inactive form.

In Vitro and In Vivo Studies Demonstrating Synergy of Curcumin with Chemotherapy

Colon Cancer Cells

Patel et al. showed the combination of curcumin with 5-fluorouracil and oxaliplatin (FOLFOX) significantly inhibited cell growth and increased apoptosis in two different human colon cancer cells (> 10-fold in HCT-116 and 3.7-fold in HT-29), lending support to the conclusion that curcumin can potentiate the effects of FOLFOX.[17]

Pancreatic Cancer Cells

Kunnumakkara et al. demonstrated in vitro and in vivo that curcumin has a synergistic effect when combined with gemcitabine.[18] Four pancreatic cancer cell lines (MIA PaCa-2, MPanc-96, Panc-1, and BxPC-3) were used to measure the effects of curcumin as an inhibitor of cell proliferation and as an apoptotic agent. Curcumin showed apoptotic effects in the four cell lines, with greatest effect seen in the MIA PaCa-2 cells.

Du et al. conducted a study in mice using MIA PaCa-2 cells to measure the antiproliferative and antiangiogenic effect of curcumin with gemcitabine. The mice receiving curcumin and

gemcitabine combination therapy showed significantly decreased tumor volume when compared to the control group and when compared to the gemcitabine alone group.[19]

Results

Clinical Trials Utilizing Curcumin to Treat Cancer

CRC—Carroll et al. evaluated the role of curcumin for prevention of CRC in a non-randomized, open-label clinical trial where doses of 2 or 4 g of pure curcumin powder (Sabinsa Corp.) were given to 20 subjects in each group.[20] Results showed a significant reduction (40%; $P < 0.005$) of the number of aberrant crypt foci (ACF) in the 4 g group. This effect was not seen for the 2 g group. Overall, the dose of 4 g of curcumin was without toxicity, safely tolerated, and displayed evidence of therapeutic efficacy.

Tumor invasion involves the suppression of immunity via upregulation of T regulatory cells (Tregs).[21] A randomized placebo controlled study regarding curcumin and the immune system in 40 individuals with colon cancer was conducted in 2016 by Xu et al.[22] In those with advanced colon cancer, 3 g of oral curcumin powder (Biomart) resulted in a markedly reduced frequency of Tregs, with a significant increase in type 1 T helper (Th1) cells ($P < 0.01$). Curcumin appeared to repress gene transcription of Tregs and increase their conversion to Th1 cells, the latter being important antitumor effector cells. The mechanistic effects of curcumin in CRC are not only anti-inflammatory and p53 upregulating, but also appear to be immune modulating in nature.

Dose response and pharmacodynamics of curcumin for treating CRC—Two dose–response studies have elucidated the importance of curcumin dose and biochemical response. The first of these studies, by Plummer et al., sought to elucidate the role of COX-2 and curcumin in CRC.[23] Doses of curcumin (P54FP by Phytopharm plc; 80% pure curcumin, 11% desmethoxycurcumin, 9% bisdesmethoxycurcumin) ranged from 440 to 2,200 mg. There was no significant difference compared to values from pretreatment measurements. It is possible that the study failed to reach a critical concentration of 4 g observed by Carrol et al.[20]

Another dose–response study was performed by Sharma et al. in 2004 where oral intake of curcumin (C3 by Sabinsa Corp.; 450 mg of curcumin, 40 mg of desmethoxycurcumin, and 10 mg of bisdesmethoxycurcumin) at doses ranging from 0.45 to 3.6 g per day for up to four months were evaluated.[24] Notably, the 3.6 g dose resulted in a significant 62% decrease ($P < 0.05$) in prostaglandin E2 (PGE2) on day 1 and a 57% significant decrease ($P = 0.01$) in PGE2 on day 29. It has been well studied that COX-2 suppression is associated with CRC prevention and management.[25] PGE2 is a product of the COX-2 enzyme and served as a proxy measure for COX-2 enzyme activity. Once again, the dose required to produce measurable effect is about 4 g of curcumin per day.

Additional studies seemed to confirm the need for higher doses of curcumin (C3 by Sabinsa Corp.; 450 mg of curcumin, 40 mg of desmethoxycurcumin, and 10 mg of bisdesmethoxycurcumin). Garcea et al. observed the effect of taking 3.6 g of curcumin daily in patients with CRC.[26] A significant decrease ($P < 0.05$) of oxidative DNA adduct levels were observed. Once again, the lower doses did not produce this result. Furthermore, although curcumin metabolites were apparent within the biopsy tissue, only trace levels of curcumin were found in peripheral circulation, indicating that poor absorption may not have provided optimal dosing of curcuminoids.

Irving et al. conducted another study, investigating the accumulation of daily curcumin dosing on colonic tissue, plasma, and urine.[27] Patients given 2.35 g of daily oral curcumin (C3 by Sabinsa Corp.; 450 mg of curcumin, 40 mg of desmethoxycurcumin, and 10 mg of bisdesmethoxycurcumin) demonstrated high levels of biopsy tissue curcuminoids persisting for up to 40 hours post administration. Again, there was limited detection of curcumin in plasma samples. This last point, in addition to the fact that higher doses of curcumin were not associated with higher tissue concentration, may reflect that curcumin is without the tendency to accumulate and may be less likely to interfere with the use of cytotoxic therapies at tissue levels.

Pancreatic cancer—A Phase II pilot study conducted by Dhillon et al. showed promise in the treatment of advanced pancreatic cancer with curcumin.[28] A daily dose of 8 g of curcumin (C3 by Sabinsa Corp.; 900 mg of curcumin, 80 mg of desmethoxycurcumin, and 20 mg of bisdesmethoxycurcumin) was given orally to 25 subjects, until disease progression. While the levels of cytokines (IL-6, IL-8, IL-10, and IL-1 receptor antagonists) were variable, the use of curcumin did result in an appreciable decrease in NF-κB, COX-2, and a statistically significant decrease of pSTAT3 ($P = 0.009$). Notably, two patients in this study had a marked antitumor response, with one acquiring ongoing stable disease for > 18 months. To date, the use of 8 g in patients with pancreatic cancer does appear to be the advisable dose, is well tolerated, and is without toxicity.[29]

Head and neck cancer—Kim et al. set out to ascertain the potential therapeutic effect of curcumin on inflammatory markers (IL-6, IL-8) in 21 patients with head and neck squamous cell carcinoma (HNSCC).[30] Saliva was collected prior to and post mastication of two 1,000 mg curcumin caplets (Jarrow Formulas Curcumin 95 manufactured by Sabinsa Corp.; 900 mg of curcumin, 80 mg of desmethoxycurcumin, and 20 mg of bisdesmethoxycurcumin) for 5 minutes. The use of curcumin had a statistically significant inhibitory effect on IKKB kinase activity ($P < 0.05$; a precursor to NF-κB production). The authors hypothesized that this, in turn, was associated with reduced HNSCC tumor-cell proliferation. Furthermore, an overall decrease in pro-inflammatory cytokines was seen in all patients with HNSCC. However, the results did not reach statistical significance.

Plasma cell dyscrasias and multiple myeloma—The first clinical trial evaluating the use of curcumin on monoclonal gammopathy of unknown significance (MGUS) was performed by Golombick et al. in a randomized crossover study of 24 patients.[31] Curcumin (C3 by Sabinsa Corp.; 900 mg of curcumin, 80 mg of desmethoxycurcumin, and 20 mg of bisdesmethoxycurcumin) was given at a dose of 4 g daily. In those patients with baseline paraprotein levels ≥ 20 g/L, a statistically significant paraprotein decrease of 12–30% ($P < 0.05$) occurred. Additionally, urinary N-telopeptide (uNTx), type I collagen bone turnover marker, decreased in seven out of nine patients taking curcumin. Notably, this decrease coincided with a decrease in serum paraprotein. While results were promising, further investigation was warranted.

Subsequently, Golombick et al. conducted a follow-up study. This time, a randomized, double-blind, placebo-controlled, crossover trial was performed, evaluating the use of curcumin (C3 by Sabinsa Corp.; 3,600 mg of curcumin, 320 mg of desmethoxycurcumin, and 80 mg of bisdesmethoxycurcumin) in 19 individuals with MGUS and 17 individuals with smoldering multiple myeloma on free light chain ratios and bone resorption.[32] Again, a 4 g daily dose was chosen. After a six-month intervention, doses of curcumin at 8 g daily were assessed. Notably, this higher dose decreased serum parathyroid concentrations by a statistically significant 19.8% ($P = 0.002$). Given Golombick's research, it is possible that curcumin may exert biological activity in select plasma cell dyscrasias, as well as decrease bone resorption.

Cervical cancer—A Phase II randomized trial by Basu et al. evaluated the topical use of curcumin in 287 women with cervical human papillomavirus (HPV) infection using a four-arm design.[33] The four arms included herbal combination cream (Basant cream), placebo cream, curcumin vaginal capsule, and placebo vaginal capsule. The formulation of Basant cream includes purified curcumin, purified extract of *Emblica officinalis* (amla), purified saponins from *Sapindus mukorrossi* (reetha), aloe vera, and rose water. On post-treatment evaluation, HPV infection was cleared by a statistically significant degree ($P = 0.03$) in women treated with Basant cream compared to placebo groups. Women treated with vaginal curcumin capsules also experienced HPV clearance compared to placebo. However, the latter did not reach statistical significance. Overall, results appeared to favor the use of vaginal curcumin and curcumin-containing cream. Further data are needed to confirm curcumin's efficacy in the clearance of HPV.

Additional high-risk, premalignant conditions—In 2001, Cheng et al. facilitated one of the first clinical trials regarding the use of curcumin as a chemopreventive agent in high-risk conditions.[34] A total of 25 patients were enrolled in this prospective Phase I trial exploring the role of curcumin as a chemopreventive agent for five conditions, including recently resected urinary bladder cancer, Bowen's disease of the skin, uterine cervical intraepithelial neoplasm (CIN), oral leukoplakia, and intestinal metaplasia of the stomach. Curcumin (Yung-Shin Pharmaceutical, 99.3% purity) was taken for three months and was dosed from 500 mg to 12,000 mg/day pending no adverse/toxic reactions. Histologic improvement was noted in one out of two patients with recently resected bladder cancer, two out of seven with oral leukoplakia, one out of six with intestinal metaplasia of the stomach, one out of four with CIN, and two out of six with Bowen's disease. Furthermore, it was discovered that doses of 8,000 mg of curcumin were well-tolerated and without toxicity. Given the small number of each arm, a replication with larger arms would be needed to demonstrate reliability of observation.

Clinical Trials Utilizing Curcumin in Addition to Chemotherapeutic Agents

Pancreatic cancer—Kanai et al. conducted a single-arm Phase II study of gemcitabine-based chemotherapy plus curcumin for patients with gemcitabine-resistant pancreatic cancer.[35] Twenty-one patients were given oral curcumin (C3 by Sabinsa Corp.; 3,600 mg of curcumin, 320 mg of desmethoxycurcumin, and 80 mg of bisdesmethoxycurcumin), 8 g/day in addition to gemcitabine 1,000 mg/m^2 i.v. weekly for three of four weeks. This study demonstrated 100% compliance of oral curcumin and reported that the median survival time after initiation of curcumin was 161 days (five months) and the one-year survival rate was 19%.

Epelbaum conducted a single-arm trial that assessed the use of oral curcumin (C3 by Sabinsa Corp.; 450 mg of curcumin, 40 mg of desmethoxycurcumin, and 10 mg of bisdesmethoxycurcumin) at 8 g/day, in addition to gemcitabine 1,000 mg/m^2 i.v. weekly for three of four weeks.[36] In this study, five patients discontinued curcumin due to abdominal complaints, and the dose of curcumin was reduced to 4 g/day for two other patients. Median survival time after initiation of curcumin was five months.

Given that both studies were of single-arm design, lacking a control group, it makes it difficult to draw conclusions. The literature estimates gemcitabine treatment in pancreatic cancer patients to be about six months.[37] Both studies documented a median survival time of about five months. The combination of curcumin and gemcitabine does not appear to increase overall survival time in those with pancreatic cancer.

Breast cancer—Bayet-Robert et al. conducted a Phase I dose-escalation trial of docetaxel plus curcumin in patients with advanced and metastatic breast cancer.[38] Docetaxel (100 mg/m^2) was administered every three weeks on day 1 for six cycles. Curcumin (stated as 450 mg of curcumin; no other detail was provided by the authors) was given for seven consecutive days by cycle (from day -4 to day $+2$) starting at 500 mg and was dose escalated to 8,000 mg/day. The authors concluded that curcurmin at 6 g/day for seven consecutive days every three weeks in combination with a standard dose of

docetaxel was safe to administer to patients with advanced and metastatic breast cancer. Although the authors stated that a Phase II comparative trial of curcumin plus docetaxel versus docetaxel was ongoing in advanced and metastatic breast cancer patients, no publication was found. Of note, some of the authors (Barthomeuf, Chollet, and Bayet-Rober) obtained a patent (US20140128337A1) for curcuminoids in combination with docetaxel for the treatment of cancer and tumor metastasis.

***Prostate cancer*—**Muhammedi et al. conducted a Phase II trial combining docetaxel, prednisone, and curcumin in patients with castration-resistant prostate cancer (CRPC).[39] Thirty patients with progressing CRPC and rising prostate-specific antigen (PSA) received docetaxel/prednisone for six cycles in combination with 6 g/day of curcumin (day −4 to day +2 of docetaxel). The authors stated that each 500 mg capsule contained 450 mg of curcumin; no further details were provided. PSA response was defined by a 50% reduction in PSA. This was achieved in 59%, with a median survival time of 18 months. This study utilized a protocol developed by Bayet-Robert and others. As with previous studies, the lack of a control group makes it difficult to interpret the outcome. A literature review shows similar CRPC patients treated only with docetaxel and prednisone to have a PSA response rate of 54–58% and median survival time of 17–24 months.[40,41]

Discussion

Apparent reasons for investigating curcumin for medicinal purposes are obvious. For thousands of years, turmeric has been used safely in South Asia and other cultures. In addition, curcumin has shown positive results in many drug discovery assays and in vitro and in vivo trials. The latter have shown it to be a significant NF-κB inhibitor. As such, curcumin holds promise as a potentially effective therapeutic agent. Clinical trials utilizing curcumin in combination with chemotherapeutic agents have been mixed. However, curcumin does appear to be safe when used with gemcitabine or docetaxel. Clinical trials assessing the use of curcumin as a cancer treatment have not been as promising as in vivo and in vitro studies. A recent review by Nelson et al. of more than 120 studies concluded that curcumin's usage in clinical trials had not been found to reach statistical significance.[42] The authors subsequently declared "Curcumin is an unstable, reactive, non-bioavailable compound and, therefore, a highly improbable lead." While the conclusion by Nelson et al. seems harsh, there are some mitigating factors to consider. For example, in the practice of integrative medicine, supplements are used in combination to harness synergy. A popular anti-inflammatory combination frequently used by integrative medicine professionals includes curcumin, bromelain, and quercetin. Curcumin's therapeutic potential may be best when used in combination. It may also be best absorbed and therefore more bioavailable when used in a liposomal delivery system or in nano-particle form.

Unlike traditional pharmaceutical chemotherapeutic agents, curcumin has the ability to target cancer initiation, growth, and the tumor milieu in multiple ways via u-regulation of anti-carcinogenic pathways and downregulation of pro-carcinogenic mechanisms.[43] In addition, curcumin has unparalleled safety when taken as an oral supplement or in its whole-food form as turmeric. While the studies reviewed here do hold some promise in the safety of curcumin, it is clear that more long-term, rigorously designed, randomized controlled clinical trials are needed to establish the role of supplements firmly in the practice of evidence-based medicine.

Author Disclosure Statement

No competing financial interests exist. ■

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