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Invited Review

Clinical potential of curcumin in the treatment of cancer: a minireview of clinical trials

Olga Leal-Hernandez, Jose M. Moran, Jesus M. Lavado-Garcia, Raul Roncero-Martin, Ignacio Aliaga, Maria Pedrera-Canal, Juan D. Pedrera-Zamorano

Metabolic Bone Diseases Research Group, University of Extremadura, Cáceres, Spain

Address for correspondence:
Jose M. Moran,
Metabolic Bone Diseases Research Group, University of Extremadura, Avd. Universidad s/n, 10003- Cáceres, Spain.
jmmorang@unex.es

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ABSTRACT

Curcumin is derived from turmeric (*Curcuma longa*) and is a natural polyphenol. Curcumin has long been used as a food, a coloring agent, and a traditional medicine. It has been shown to possess potent anti-inflammatory and antioxidative properties and has a long history of dietary use as a food additive. Many patients suffering from different types of cancer have received curcumin in several preparations and at different dosages.

Fifteen clinical trials focused on cancer patients receiving different dosages of curcumin have been reviewed systematically and critically to compare the effect of this antioxidant in the different groups. This minireview primarily focuses on the application of curcumin in the treatment of various forms of cancer *in vivo* and does not consider data from *in vitro* and experimental studies that are out of such focus. To establish direct evidence of a potential effect of curcumin treatment and its anti-tumor activity, further investigations should be conducted.

KEY WORDS: Cancer, clinical trial, *Curcuma longa*, curcumin, turmeric

CURCUMIN: USE AND PROPERTIES

Curcumin is derived from turmeric (*Curcuma longa*) and is a natural polyphenol. Curcumin has long been used as a food, a coloring agent, and a traditional medicine. It has been shown to possess potent anti-inflammatory and antioxidative properties and has a long history of dietary use as a food additive [1]. Increasing evidence supports the idea that this chemical could be a promising anti-cancer drug [2]. Curcumin induces apoptosis in several cell lines [3-6] and, in combination with chemotherapy, was proven to be a safe and feasible treatment in patients with cancer [7].

In the course of publishing the results of intervention trials, many authors have provided information on curcumin's effect in the treatment of several types of cancer. Curcumin has been often used in combination with ordinary cancer treatment, but a lack of a comparator group, problems with placebo composition [8] and an absence of groups in the study design [9-12] have often been observed. Pediatric patients have also received curcumin but yielded uncertain results, again because of the absence of a control group and due to the small sample size for the patients treated with curcumin [13].

The antioxidant curcumin has also been used as a prevention therapy in healthy patients and has been shown to suppress prostate-specific antigen (PSA) production in prostate cells [14]. In healthy patients, it has also been proven that curcumin can protect against oxidative stress [15]. In general, no problems or side effects have been described in patients who received curcumin as a preventive treatment, so it seems to be well tolerated [16].

This minireview primarily focuses on the application of curcumin in the treatment of various forms of cancer in vivo. The aim of this study was to systematically and critically review clinical trials on the application of curcumin in the treatment of various forms of cancer.

METHODS (SEARCH STRATEGY)

To identify the pertinent data from clinical trials performed in cancer patients, we performed a review of the scientific literature available in Medline. In vitro and experimental studies based on the efficacy of curcumin in cancer research are out of the focus of this study. All relevant clinical trials published in English were retrieved. The words "curcumin AND cancer" and the limit "clinical trial" were used, and we obtained 36 results. After carefully reading the abstracts, 8 of 36 papers were excluded because they did not focus on curcumin or cancer research. The other 28 papers were thoroughly reviewed. This minireview was designed using the following inclusion criteria:

1) Clinical trial design using at least two groups.

2) Patients with any type of cancer.

3) Patients receiving any type or dosage of curcumin.

Ultimately, 13 papers did not meet the inclusion criteria; 15 did and were analyzed.

CURCUMIN AND CANCER

Curcumin in combination with chemotherapy

Most of the studies used different types of curcumin as a supplement to increase the effectiveness of chemotherapy. The studies compared chemotherapy in combination with placebo or curcumin during 8 weeks to 6 months of treatment, and all reached positive conclusions; this antioxidant seems to make chemotherapy more effective, with fewer side effects and improved quality of life. Although curcumin was safe and well tolerated in all patients and was recommended as an adjuvant in these patients, all studies recommended further investigation with a larger sample size, a longer time and different dosages [17-21] (Table 1).

Alternatives to oral intake

There are results related not only to oral intake of curcumin but also to intravaginal application via capsules and cream in patients with human papilloma virus. A polyherbal vaginal cream, namely Basant™, developed in India was composed of extracts of curcumin, reetha, amla and aloe vera, and curcumin vaginal capsules containing 500 mg of curcumin per capsule were compared in a study by Basu et al [22]; these treatments attained better outcome compared with placebo groups, but the results were not statistically significant. The studies had a large sample size but divided this sample into four groups.

Results in animals and healthy patients

In addition to the results obtained with patients with any type of cancer, certain papers included results related to the use of curcumin in animals [17] or in healthy patients [23] and provide another view of the use of curcumin. These studies all concluded that curcumin is well tolerated and has positive effects in different groups, even though further investigation was also recommended.

Groups and curcumin dosages

Another way to compare groups is crossing over the placebo group and the curcumin group. In these cases, researchers can observe the effects of different treatments in the same patient. The results were positive, but not in all patients, and further investigation was also recommended [24, 25].

Comparing different dosages was a very popular approach in the papers reviewed. In these studies, the sample was divided into three to five groups to observe the effects at several different dosages. When using the same type of curcumin, the studies reached similar conclusions and recommended that future investigations use the better dosage [23, 26-29] (Table 2).

Cancer and curcumin preparations

The most frequent cancer suffered by the studied patients was colorectal cancer [17, 23, 26, 28-30], but different types of cancer were also combined in the same paper in certain cases [18, 25, 27, 31].

Different curcumin preparations were used in the clinical trials reviewed. Meriva® (Indena, Milano, Italy), a patented delivery form of *Curcuma longa* L, at different dosages (300 mg and 500 mg) was used. The 500 mg preparation was composed of 100 mg curcuminoids (ratio of curcumin:demethoxycurcumin:bis-demethoxycurcumin of 33:8:1), 200 mg soy lecithin and 200 mg microcrystalline cellulose; and the 300 mg Meriva® preparation contained also 20% curcuminoids [18, 20].

P54FP, an extract of Indian and Javanese turmeric, is another preparation form used in two studies but consisted

Table 1. Curcumin in combination with radio and chemotherapy

Author and year	Curcumin preparation	Dosage	Route	Time	Main outcome
Chen *et al* 2014 [17]	MB-6 composed of fermented soybean extract, green tea extract, Antrodia camphorata mycelia, spirulina, grape seed extract, and curcumin extract (*Curcuma longa L*)	6 capsules of 320 mg; each administered 3 times daily	Oral	16 weeks	Increase the effectiveness of chemotherapy
Panahi *et al* 2014 [18]	Meriva® 300 mg (curcuminoids content is 20%)	3 capsules of Meriva® 300 mg per day; 180 mg of curcuminoids per day	Oral	8 weeks	Safe and well tolerated
Belcaro *et al* 2014 [20]	Meriva® 500 mg (composed of 100 mg curcuminoids; ratio curcumin:demethoxycurcumin:bis-demethoxycurcumin 33:8:1, 200 mg soy lecithin and 200 mg microcrystalline cellulose)	1 capsule of Meriva® 500 mg per day	Oral	At least 60 consecutive days	Curcumin might alleviate the burden of side effects associated to chemo- and radiotherapy
Ryan *et al* 2013 [19]	500 mg Curcumin C3 Complex® (each capsule contained 390 mg curcumin, 75 mg demethoxycurcumin and 12.5 mg bisdemethoxycurcumin)	6 grams of Curcumin C3 Complex® per day	Oral	16-33 radiotherapy sessions	Reduced radiation dermatitis severity and moist desquamation
Ghalaut *et al* 2012 [21]	Turmeric is a spice derived from the rhizomes of *Curcuma longa*	Tumeric powder 5 g three times/day dissolved in 150 ml of milk	Oral	6 weeks	Adjuvant to chemotherapy treatment in decreasing the nitric oxide (NO) levels

Table 2. Groups and curcumin dosage

Author and year	Curcumin preparation	Dosage groups	Route	Time	Main outcome
Garcea *et al* 2005 [26]	Curcumin C3 Complex® (contained of 450 mg curcumin, 30 mg desmethoxycurcumi and 20 mg bisdesmethoxycurcumin)	450, 1800 or 3600 mg of curcumin daily	Oral	7 days before surgery	A daily dose of 3.6 g curcumin achieves pharmacologically effective levels
Sharma *et al* 2004 [28]	Curcumin C3 Complex® (contained of 450 mg curcumin, 40 mg desmethoxycurcumi and 10 mg bisdesmethoxycurcumin)	450, 900, 1800 or 3600 mg of curcumin daily	Oral	Maximum 4 months	The systemic pharmacological properties of a daily dose of 3.6 g of curcumin are suitable for its evaluation.
Plummer *et al* 2001 [23]	P54FP (contained of 18 mg curcumin and 2 mg desmethoxycurcumin suspended in 200 mg of *Curcuma* essential oils)	36, 72, 108, 144 or 180 mg of curcumin daily	Oral	At least 29 days	The results of the pilot study of oral curcumin suggest that measuring blood monocyte PGE2 production may be a useful and feasible proposition in clinical trials of other putative chemopreventive agents that inhibit COX-2
Cheng *et al* 2001 [27]	Diferuloylmethane (each tablet contained 500 mg of curcumin; the purity was 99.3%)	500, 1000, 2000, 4000 or 8000 mg of curcumin daily	Oral	3 months	A dose-dependent effect was not observed since histological improvement was seen at almost all dose levels; the recommended oral dose of curcumin for future phase II studies is 6000-8000 mg/day
Sharma *et al* 2001 [29]	P54FP (contained of 18 mg curcumin and 2 mg desmethoxycurcumin suspended in 200 mg of *Curcuma* essential oils)	36, 72, 108, 144, and 180 mg of curcumin daily	Oral	Maximum 4 months	Doses of up to 180 mg of curcumin per day can be administered to patients with cancer, such treatment was safe

of the same dosage. Each 220 mg capsule of P54FP contained 18 mg curcumin and 2 mg desmethoxycurcumin suspended in 200 mg *Curcuma* essential oils [23, 29]. The most common curcumin preparation is Curcumin C3 Complex®, but the papers do not agree about the recommended dosage, which ranged from 3.6 to 8 g; Each capsule of this preparation contained 500 mg curcuminoids (450 mg curcumin, 40 mg desmethoxycurcumin, and 10 mg bis-desmethoxycurcumin) [19, 24-26, 28].

The studies were conducted in Australia [24, 25]; England [23, 26, 28, 29]; and, most commonly, in Asia [17, 18, 21, 22, 27, 30, 31], where curcumin is widely consumed by most of the population.

CONCLUSION

Over the last several years, we have broadened our knowledge about and understanding of the role of the antioxidant curcumin in the promotion of apoptosis in cancer cell lines. Most recently, knowledge has increased further due to contributions that include translational research studies supporting the therapeutic potential, safety profile, optimal route, optimal timing, optimal dose, and potential efficacy of curcumin therapies alone or combined with chemotherapy for cancer treatment. Moreover, clinical trials have been conducted successfully, proving curcumin's safety and feasibility as a treatment in several cancer types. Use of the antioxidant curcumin as an adjuvant in the treatment of cancer is a very exciting prospect, but there are a number of unresolved issues. To more conclusively assess the relative efficacy of curcumin treatment, future research is likely to be necessary.

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