Review

Curcumin in cancer management: Recent results of analogue design and clinical studies and desirable future research

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The ability of the curry constituent curcumin to delay the onset of cancer has been the topic of extensive research for many years. Abundant literature is devoted to mechanisms by which curcumin may mediate this activity. These insights have prompted investigations in which curcumin as lead molecule serves as a scaffold for synthetic chemical attempts to optimize pharmacological potency. Among the published analogues with notable efficacy are dimethylcurcumin, 1,5-bis(3-pyridyl)-1,4-pentadien-3-one and 3,5-bis-(2-fluorobenzylidene)-piperidinium-4-one acetate. Results of a small number of clinical pilot studies conducted with curcumin at doses of up to 12 g suggest tentatively that it is safe in humans. Prevention of adenoma recurrence constitutes a clinical paradigm worthy of further investigation for curcumin. Future clinical study should include measurement of mechanism-based pharmacodynamic parameters.

Keywords: Chemoprevention / Clinical trial / Curcumin

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1 Introduction

Epidemiological evidence hints at the possibility that certain phytochemicals consumed as constituents of the diet, exemplified by resveratrol in red grapes, genistein in soybeans and curcumin in curry spice, possess cancer chemopreventive properties. Such suspicions have been supported by experiments in preclinical models of carcinogenesis. Research into diet and cancer is of considerable concern to the general public and raises a lot of interest from the media. Among current cancer-related areas of research into dietary phytochemicals, the elucidation of anti-oncogenic mechanisms stands out as particularly fertile and exciting (for review, see [1]). A recent research approach is the search for synthetic analogues with optimized pharmacological properties. In contrast, robust data on chemopreventive efficacy and pharmacodynamics of dietary phytochemicals in humans gained in controlled clinical trials remain scarce.

This issue of *Molecular Nutrition & Food Research* underpins the notion that curcumin is one of the most thoroughly researched dietary phytochemicals from the standpoint of potential value in cancer management. Literally hundreds of papers have been published devoted to the exploration of anti-neoplastic mechanisms of curcumin, it has been tested extensively in a considerable number of preclinical models of cancer, and there are a handful of papers on its early clinical evaluation. This short review aims to explore the extent to which the currently available information on curcumin permits the assessment of its usefulness in cancer management. An attempt is made to determine from the recent literature – at least in outline – some strategies which may help reach this verdict. Evidence published during the past 10 years has been reviewed, focussing on novel curcumin analogues and on results of clinical trials of curcumin. The following two questions are addressed: (i) Are any as yet known curcumin congeners superior to the parent molecule? (ii) Do we know enough about the effects of curcumin in humans to warrant the initiation of large clinical studies of its role in cancer management?

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2 New curcumin congeners

Other contributions in this issue highlight the impressive multitude of mechanisms which curcumin has been suggested to engage. On the basis of its anti-proliferative,

apoptosis-inducing, anti-oxidant and anti-angiogenic properties, curcumin has been postulated to be of potential use not only in cancer chemoprevention but also in treating existing disease. Therefore, screens used to compare pharmacological properties of newly synthesized curcumin analogues with those of the parent lead compound, in terms of inhibitory potency, include proliferation and survival of cancer cells, carcinogen-induced preneoplastic lesion formation [2], angiogenesis [3], redox activity in cell-free systems [4], activity of the transcription factor NFκB [5, 6], inhibition of COX-1 activity [7] and expression of the COX-2 and iNOS genes [2]. In one approach the ability of curcumin and ten derivatives to inhibit human platelet 12-lipoxygenase was compared with their goodness of fit into an enzyme model [8]. In a few cases, screening of analogues included cursory observation of toxicity in rodents after intraperitoneal administration [9, 10].

Prominent among the pharmaceutical properties of the curcumin molecule, which medicinal chemists have attempted to change, are its low bioavailability and high susceptibility towards hepatic and gastrointestinal drug metabolism *via* enzyme-catalysed conjugation and reduction. Chemical strategies governing curcumin analogue discovery have encompassed varying degrees of molecular change. Almost all of these alterations furnished molecules that retained the Michael acceptor nature of the parent. Therefore this feature seems to be considered an important curcumin pharmacophore element, albeit proof for this contention is scarce. An example of a subtle but apparently pharmacologically advantageous molecular modification performed is the methylation of the two phenol functions generating dimethylcurcumin [11] (for structures, see Fig. 1). This congener possessed increased systemic availability in mice compared to parent curcumin, probably due to reduced extent of metabolism. In human-derived colorectal cancer cells, dimethylcurcumin had anti-proliferative and apoptosis-inducing properties superior to those of curcumin [11], but it has to be borne in mind that these results may reflect increased non-specific toxicity, an issue which remains to be explored. Desmethoxycurcumin and bisdesmethoxycurcumin, two curcuminoids that always accompany curcumin in its plant source, and tetrahydrocurcumin and hexahydroxcurcumin, products of reductive curcumin metabolism, have also been the subject of cancer pharmacological studies, but in general their efficacy seems inferior to that of curcumin proper. Analogue synthesis attempts have incorporated parts of the curcumin structure into an elaborate chemical scaffold [2, 3, 5, 9, 12] guided by design rationales which are often not instantaneously plausible. Synthetic approaches entailed the shortening or lengthening of the aliphatic chain linking the two curcumin phenyl moieties. One study focussed on diarylpentadienones [10]. Part of the chain has been incorporated into cyclic structures including cyclohexanone, piperidinone or naphthalene, the latter manipulation imparting increased rigidity to

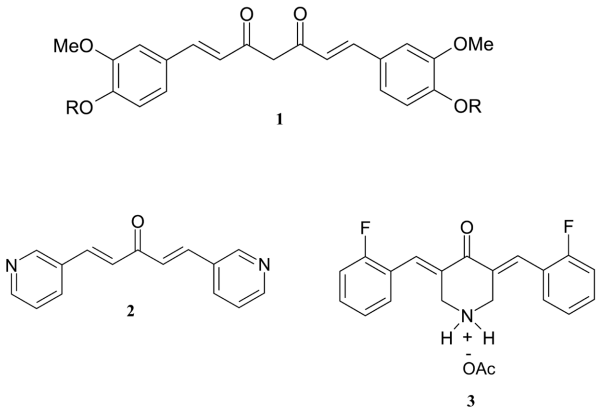

Figure 1. Structures of curcumin (1, R = H), dimethylcurcumin (1, R = Me), 1,5-bis(3-pyridyl)-1,4-pentadien-3-one (2) and EF24 (3).

the molecule [2, 3]. The phenyl rings have been replaced by heterocycles or methylenedioxyphenyls [2]. The keto-enol nature of curcumin has been exploited in reactions with aromatic aldehydes to yield Knoevenagel condensation products on carbon 4 of the bridge, or with thiosemicarbazide to furnish Schiff bases [6].

These curcumin analogue discovery efforts furnished several compounds which in specific tests showed efficacy superior to that of curcumin. Two congeners appear particularly notable because of their potency: 1,5-bis(3-pyridyl)-1,4-pentadien-3-one and 3,5-bis-(2-fluorobenzylidene)-piperidinium-4-one acetate (EF24) (for structures, see Fig. 1). The former inhibited TNF-a-induced activation of NFκB in NFκB reporter-expressing human kidney-derived cells with an IC_{50} of 3.4 μM, as compared to 8.2 μM for curcumin [5]. EF24 inhibited cell proliferation and angiogenesis in cell line-based screens encompassing a wide range of tumour types at concentrations which were consistently a fifth or a smaller fraction of those necessary for curcumin to exert these effects [3]. Subsequently, EF24 in the 1 – 20-μM concentration range was shown to induce apoptosis and G_2/M cell cycle arrest *via* redox-dependent mechanisms in human-derived breast and prostate cancer cells [13]. The putative Achilles heel of all these chemical manipulations of the curcumin scaffold is the fact that they may compromise the safety of the parent molecule. Extensive and elaborate long-term toxicity studies will be necessary to prove the safety of the congeners, an issue particularly pertinent if they are to be considered to serve as potential cancer chemopreventive agents. Intuitively, minor alteration, such as conversion of the two phenols to methoxy moieties, might stand a better chance of retaining the safety features of the parent than more complex alterations, such as incorporation of the aliphatic chain into piperidinone.

Table 1. Recent clinical trials of curcumin

Dose [g/day]	Subjects [*n*]	Reference
0.5 – 12 single	Healthy volunteers (24)	[15]
0.02 single	Healthy volunteers (12)	[21]
2 daily, 6 months	Patients with ulcerative colitis (43)	[16]
1.1 – 1.65 daily, 2 – 3 months	Patients with ulcerative colitis/ Crohn's disease (10)	[17]
0.5 – 12 daily, up to 6 months	Patients with preneoplasia (25)	[14]
0.45 – 3.6 daily, up to 4 months	Patients with cancer (15)	[20]
0.45 – 3.6 daily 7 days	Patients with colorectal cancer (23)	[18, 19]

3 Clinical trials of curcumin

We and others have argued for years that curcumin might constitute a viable alternative to non-steroidal anti-inflammatory drugs or COX-2 inhibitors as a potential colorectal cancer chemopreventive agent. Would curcumin be safe when administered in trials in which this hypothesis was to be tested? The evidence from small human trials (Table 1) which has emerged thus far seems to suggest tentatively that this is indeed the case. The most extensive clinical evaluation has been conducted in Taiwan, where patients with preneoplastic lesions received up to 12 g curcumin daily, apparently without ill effect and with indications of efficacy in terms of delay of progression to full-blown malignancy, even though the pharmacodynamic arm of the study was not properly controlled [14]. A recent study [15] underlines the notion that a single high dose of curcumin (0.5 – 12 g) is safe in healthy human volunteers. Results of a randomized placebo-controlled double-blind study of curcumin (2 g daily for 6 months) in patients with ulcerative colitis hint at the possibility that, when given in combination with sulphasalazine or mesalamine, it may prevent relapse [16]. Similarly, in another pilot study involving ten patients with ulcerative colitis or Crohn's disease, curcumin at between 1.11 and 1.65 g daily for 2 or 3 months appeared to delay disease progression, albeit interpretation of results from such a small number of trial participants is obviously difficult [17]. Pilot studies of curcumin at dose levels of up to 3.6 g *per* day in cancer patients conducted at Leicester University suggest – again tentatively – that curcumin is safe and may reduce oxidative DNA adduct levels in gastrointestinal target tissue [18], even though not in the liver [19]. Furthermore, there was a weak reduction in serum levels of prostaglandin E-2, reflecting COX activity, in patients who received curcumin at 3.6 g *per* day [20]. Interestingly, as little as 20 mg curcumin has been reported to exert a pharmacological effect in healthy volunteers, in that it seemed to induce gall bladder contraction [21]. In some of the clinical studies described above, plasma levels of curcumin were measured, and its systemic bioavailability was found to be very low. Metabolism, predominantly *via* glucuronidation and reduction, was abundant. In human volunteers, in whom curcumin was co-administered with the pepper constituent piperine, the extent of curcumin glucuronidation was significantly reduced [22]. Whilst in carcinogenicity and mutagenicity screens curcumin turned out to be innocuous, two reports on the interaction between curcumin and the p53 tumour suppressor in cultured cells suggest that it can induce degradation of p53 and impair the activity of this tumour suppressor [23, 24]. These results hint at a mechanistic rationale for potentially compromised safety, but they need to be confirmed in animal models *in vivo* before their putative relevance to humans can be assessed. Overall the preliminary clinical evaluation of curcumin conducted thus far is consistent with it being free of concerns related to safety.

4 Desirable future studies

The survey of the currently available literature on curcumin analogues suggests that there is not yet a synthetically generated curcumin congener, the efficacy and safety of which we understand as well as those of curcumin. One cannot help feeling that subjecting all of the published structures to judiciously chosen tests under comparable conditions in selected cancer cell types in one laboratory would be advantageous so as to acquire a comprehensive understanding of their comparative potencies. Future investigations are likely to generate additional bioactive molecules and more insights into the pharmacology and toxicology of the congeners outlined above. Among the molecules which currently seem to warrant additional experimental scrutiny with the view of advancing them to the stage of clinical evaluation are dimethylcurcumin, 1,5-bis(3-pyridyl)-1,4-pentadien-3-one and EF24. All three molecules seem to possess desirable pharmacological properties. For dimethylcurcumin, the close molecular similarity with curcumin signals that it may possess the favourable safety profile of its parent.

Whilst the ongoing congener discovery attempts are undoubtedly exciting and promising, it will probably take a long time until analogue candidates with robustly proven safety and efficacy will be at a stage of development that will allow planning of their early clinical evaluation. Therefore, it seems most unlikely that within the next few years a curcumin analogue will upstage the parent molecule in terms of promise for cancer management potential. Clinical results obtained thus far are consistent with the notion that curcumin remains an agent worthwhile of extensive clinical evaluation. A study paradigm, which will help adjudge its usefulness *vis-à-vis* non-steroidal anti-inflammatory drugs and coxibs, is the prevention of adenoma recurrence. The fact that curcumin possesses poor systemic availability renders the gastrointestinal tract a rational target site for intervention. Based on past experience, repeat doses of up to 3.6 g seem suitable to be used in such studies, as they were

well tolerated and afforded curcumin levels at the target site commensurate with pharmacological activity [18]. Future trials should include suitably planned pharmacodynamic measurements. Such studies might provide insights into curcumin mechanisms at the clinical level and help assess within a short time frame the potential success or failure of future long-term interventions. Among mechanism-based efficacy biomarkers which could be included are anti-oxidation, induction of apoptosis and inhibition of proliferation, NFκB activation and COX-2 and MDM2 expression. These biomarkers might be assessed in surrogate tissues such as blood and, whenever possible, in adenoma tissue. Another clinical paradigm worthy of exploration is the potential role which curcumin may play as part of chemotherapeutic combinations together with clinically used antineoplastic drugs. The rationale for this suggestion is the anticipation that the recently discovered intriguing anti-oncogenic signalling properties of curcumin may render it a suitable "cheap alternative" to molecular-targeted anti-cancer drugs exemplified by gefitinib (Iressa) produced expensively by the pharmaceutical industry. Examples of combinations which have thus far shown promise in experiments using cancer cells *in vitro* or preclinical models *in vivo* are those involving oxaliplatin [25, 26] and paclitaxel [27].

Many reviews contained in this issue of *Molecular Nutrition & Food Research* reflect the fact that curcumin is one of only a handful of diet-derived molecules which have been subjected to an enormous amount of research aimed at improving cancer management options. Does this work suggest unambiguously that curcumin is indeed useful in cancer management? Not quite yet. The answer will ultimately be provided by rationally designed phase II/III clinical trials. The information gathered above suggests that curcumin should be assessed in such clinical settings. It is a realistic prospect that in a few years time curcumin and perhaps some chemically synthesized analogues will play significant roles in cancer prevention and therapy.

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5 References

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