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A novel Curcumin Complex with Superior Efficacy to Indomethacin and Native Curcumin in an Inflammatory Model

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Abstract

Turmeric and its active ingredients, curcuminoids, have long been used to treat inflammatory, bacterial, dermatological, and neurological diseases. However, they are constrained by their poor bioavailability as therapeutics. A new complex of curcumin and cyclodextrins has been formulated that has been shown to enhance the bioavailability of curcumin by about 40 times. This paper shows that the complex also is superior to curcumin and positive control, indomethacin, in an inflammatory model. This is the only complex to show both a superior bioavailability as well as efficacy and thus it could be a new therapeutic to treat inflammatory diseases such as Rheumatoid Arthritis.

Keywords:

Curcumin; Cyclodextrin, Rheumatoid Arthritis; Psoriasis; Ankylosing Spondylitis; Alzheimer's Disease; Cancer; Oncology; Carrageenan; Anti-infective

Introduction

Turmeric and turmeric extracts have long been active ingredients in compositions for oral and topical application to treat diseases and conditions. *Curcuma longa* (Family Zingiberaccae), or turmeric, is a spicy plant that is a common ingredient in curry powder [1]. Turmeric is one of the oldest herbs in Ayurveda, the traditional Indian system of medicine. Turmeric has been applied topically to wounds to stop bleeding, speed healing and reduce scarring. Ground turmeric has been used as a topical salve to prevent and treat a variety of skin diseases and conditions [1].

The significance of turmeric in medicine has changed in modern times with the scientific observation of turmeric's therapeutic properties. Curcuminoids have scientifically documented anti-oxidant, anti-inflammatory, anti-bacterial, anti-fungal, anti-parasitic, anti-mutagen, and anti-cancer properties. Significant data are available on the safety, toxicity, dose range, pharmacokinetics, and other biological properties of turmeric and its components, including curcuminoids and turmeric peptide. As detailed below, turmeric components are well tolerated while providing anti-oxidant benefits, inhibit microbial growth, inhibit several enzymes, and inhibit abnormal cell growth in studies of cells, animals, and humans.

Turmeric reduces arachidonic acid-induced rat paw and mouse skin edema and markedly inhibits epidermal lipoxygenase and cyclooxygenase activity in vitro [2, 3, 4]. Phosphorylation events can also be influenced by curcumin, as it has been reported that curcuminoids inhibit protein kinase C activity induced by 12-O-tetradecanoyl-phorbol-13-acetate in NIH 3T3 cells [5].

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Turmeric can fight against microbial infections and parasitic infestations. In humans, ingestion of turmeric has been used to treat biliary infections where it demonstrates bacteriostatic or bactericidal effects against organisms involved in cholecystitis [6, 7]. Topical application of a turmeric paste for the treatment of scabies has also shown satisfactory results [8].

The potential use of turmeric and turmeric extracts in the prevention of cancer is the subject of intensive laboratory and clinical research. The addition of turmeric to the diet has been shown to inhibit azoxymethanol-induced colonic epithelial cell proliferation and focal areas of dysplasia [9]. It has also been shown to interfere with the formation of covalent carcinogen-DNA adducts [10].

Curcumin can moderate the immune system as well as smooth muscle cell proliferation. Curcuminoids had a greater inhibitory effect on platelet derived growth factor-stimulated proliferation than serum stimulated proliferation [11].

Curcuminoids were shown to inhibit the 5-lipoxygenase activity in rat peritoneal neutrophils as well as the 12-lipoxygenase and the cyclooxygenase activities in human platelets [12] Curcuminoids had no significant effect on quercetin-induced nuclear DNA damage, lipid peroxidation and protein degradation, and thus it has the unique potential of acting as both pro- and antioxidants, depending on the redox state of their biological environment [13]. Administration of curcuminoids in mice exhibited antioxidant properties by significantly reducing the scavenging of peroxides and other activated oxygen species [14].

Curcumin (diferulomethane) is not only a potent natural antioxidant and anti-inflammatory agent, acting on NFkB and AP-I regulated pro-inflammatory mediators including COX-2, iNOS, il-1 and TNFα, but it has multiple useful activities and has shown therapeutic potential in many pre-clinical in-vitro and animal models for diseases, often related to aging. These include cancers of colon, prostate, breast, skin, leukemia, etc. [15]. Based on its outstanding safety profile and efficacy in multiple disease models with oxidative damage and inflammatory factors, curcumin has shown excellent potential for disease pathogenesis in Alzheimer models. Curcumin has passed several Phase II trials for cancer and is currently in further clinical trials for cancers at multiple sites in the US and abroad (clinicaltrials.gov).

Due to its action on NFkB and its anti-oxidative properties, in addition to its many other effects, curcumin has been proposed to treat various inflammatory, central nervous system and coronary artery diseases. Although curcumin is an effective medication in multiple animal models for human diseases when given with food at high doses (typically 2,000-5,000 PPM in diet in cancer trials), the current understanding is that it is so poorly bioavailable that it cannot be used for treatment outside the colon in humans. Curcumin is very hydrophobic and typically is not dissolved when delivered as a powder extract in common nutraceuticals. Most curcumin activities require 100-2,000 nanomolar (0.1-2 micromolar) levels in vitro, but current supplements result in negligible, low nanomolar blood levels. A group at Leicester had tried repeatedly and been unable to achieve significant blood levels beyond the low nanomolar range[16]. They and others conclude that delivery of effective concentrations of oral curcumin to systemic tissues (outside the GI tract) is "probably not feasible [16]. Most of the literature supports this view, leading the National Cancer Institute to focus on colon cancer. In addition, curcumin has very poor bioavailability, with T_{max} of only 3-5 minutes.

Curcumin has been extensively studied in various diseases ranging from phase I to phase IIb. In Phase-I clinical studies, oral administration of curcumin is well tolerated at pharmacological concentration. Cheng et al conducted a phase I study in patients with Bowens Disease and found that doses up to 8000 mg/day for 3 months were well tolerated [17]. Serum concentrations peaked at 1-2 hours and then gradually declined. Maximum serum concentrations ranged from 0.5 +/- 0.11 mM at 4000 mg/day to 1.77 +/- 1.87 mM at 8000 mg/day. No difference was observed with repeated dosing (on day 30). Many other Phase I and phase II studies have come to similar conclusions - that while there is a lot of scientific merit to the use of curcumin, its poor bioavailability limits its use 1. Two factors limit curcumin absorption: 1) rapid glucuronidation/sulfation of curcumin's phenolic hydroxyl groups with high "first pass" clearance; 2) curcumin is very hydrophobic and typically is not water soluble at acidic pH and when delivered as a dry powder in existing supplements. Cancer patients take huge doses, typically up to 8 gms a day. Diarrhea is a common side-effect [17]. Garcea, G. et al report that with patients taking 3.6 gms of curcumin a day (as a standard powder extract capsule supplied by Sabinsa Corporation), blood and liver levels achieved are negligible [16]. They conclude that "the results suggest that doses of curcumin required to furnish hepatic levels sufficient to exert pharmacological activity

are probably not feasible in human".

Cyclodextrins are cyclic oligomers of glucose. These compounds form inclusion complexes with any drug whose molecule can fit into the lipophilic cavities of the cyclodextrin molecule. They make an excellent vehicle for carrying other molecules, especially insoluble compounds such as curcumin [18].

Cyclodextrin can be alpha, beta, or gamma-cyclodextrin. Alpha-cyclodextrin contains six glucopyranose units; beta-cyclodextrin contains seven glucopyranose units, and gamma cyclodextrin contains eight glucopyranose units. The molecules are believed to form a truncated cone having a core opening of 4.7-5. 3 A, 6.0-6. 5 A and 7. 5-8. 3 A in alpha, beta, or gamma cyclodextrin respectively. Cyclodextrins have been used to improve delivery of existing drugs such as itraconazole, nimesulide, indomethacin, etc.

In order to improve the solubility of curcumin, a complex of curcumin and cyclodextrin was created and tested in the carrageenan model of inflammation [19]. The subcutaneous injection of carrageenan into the foot paw of a mouse or rat produces local inflammation, designated by the 5 cardinal signs: hypersensitivity, redness, swelling, heat, and loss of function. Edema (swelling) can be used to assess inflammation in an animal model, thus providing a method to monitor inflammatory responses and the reversal or prevention of these responses with anti-inflammatory compounds, such as non-steroidal anti-inflammatory drugs (NSAIDs). Indomethacin was used as the comparator as it is the most potent NSAID in this model.

Materials

Hydroxy Propyl β-cyclodextrin was obtained from Sigma Aldrich (catalogue number 332593) and a 20% solution created. Curcumin was obtained from Sigma Aldrich (catalogue number C7727) and a 15 mg/ml curcumin stock solution created. Cyclodextrin Curcumin (VOLT03) was created by mixing curcumin stock to cyclodextrin stock in a proprietary method.

Indomethacin (Sigma I8280, lot #098K1500) 10 ml dosing solution was made by suspending 5 mg in 10 ml of sterile water with stirring, and then adding 0.1 N NaCO3 drop wise until pH was 7-8.

Gamma Carrageenan 1% (Fluka 22049, lot #1408463) 2 ml was made by dissolving 20 mg in 2 ml of saline at 4 °C and then vortexing, warming and sonicating. It was tested for injection resistance by 27G and 28 G needles.

35 male CD-1 mice, weighing 20-30 g were obtained from Harlan Sprague Dawley Inc

Methods

Carrageenan Mouse Paw Edema Model:

1. The mice were acclimatized for 4 days after receipt and weighed within 24 hours of dosing to calculate dosing volume. Food was removed 2 hours before dosing and restored 2 hours after dosing.

2. Groups: Mice were grouped as shown in the table 2

3. Procedure: The thicknesses of each paw of each mouse were measured with calipers, holding the mouse vertical and paw out with forceps. It was ensured that the right and left front paws were of same thickness. The mice were dosed orally with water (vehicle), indomethacin, curcumin, or VOLT03 30 minutes before carrageen an injection. Both foot pad of the mice was anesthetized with ketamine/xylazine (100/12 mg/kg, i.p.) 15 minutes before carrageen injection. At t=0, the left footpad of each mouse was injected with 25 µL of 1% carrageen, using a 27 or 28 G needle. At 3 hours, the thickness of each paw was measured. The edema was calculated by subtracting the right paw thickness from left paw thickness.

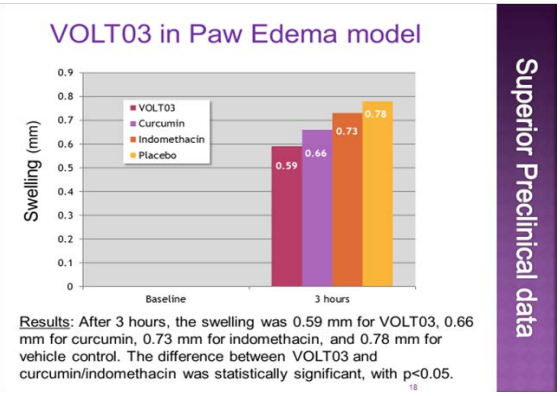
Results

The paw was measured at 3 hours after oral gavage of curcumin (30mg/kg), Indomethacin (5mg/kg), and VOLT03 (30mg/kg) to mice. After 3 hours, the mean swelling was 0.59 mm for VOLT03, 0.66 mm for curcumin, 0.73 mm for indomethacin, and 0.78 mm for vehicle control (Figure 1). The difference between VOLT03 and curcumin/indomethacin was statistically significant, with $p<0.05$.

Table 1: Group Variables

Group No.	No. of Animals	Test Article	Dose Route	Dose Level (mg/kg)	Dose Volume (mL/kg)	Dose Conc. (mg/mL)
1	8	Vehicle	p.o.	N/A	10	N/A
2	8	Curcumin	p.o.	30	10	3
3	8	VOLT03	p.o.	30	10	3
4	8	Indomethacin	p.o.	5	10	0.5

Figure 1: Paw swelling in left foot pad with VOLT03, indomethacin, vehicle and curcumin 3 hours after carrageenan injection



Discussion/Conclusion

Curcumin has demonstrated significant anti-inflammatory and anti-cancer properties both in –vitro and in-vivo. However, the poor absorption of native curcumin negates its utility as a therapeutic or nutritional entity. Many methods have been tried to increase the absorption of curcumin. One approach involves the use of nanoparticles [20]. However, this approach has not been shown to have superior human pharmacokinetics or better efficacy than native curcumin in inflammatory models. Other techniques include Polyethylene-glycol (PEG) albumin curcumin nanoparticles [21] but they have also not been shown to have better absorption in human studies, nor superior efficacy. One commonly used technique is to combine curcumin with BioPerine which is found in black pepper. Black pepper is not necessary for turmeric to be effective, but it can be helpful. Black pepper contains a compound, piperine, which inhibits the metabolic breakdown of turmeric compounds in the gut and the liver. This allows higher levels of turmeric compounds to remain in the body (i.e., it increases its bioavailability), which may increase the effects of turmeric. However black pepper does not significantly help with absorption. In animals, co-administration of curcumin with an extract obtained from the black pepper has been shown to increase the absorption (Area under the Curve or AUC) of curcumin by 1.5-fold. A complex of curcumin with phospholipids increased absorption by 3.4-fold [22]. Other strategies have been pursued to improve the absorption of curcumin including emulsions, liposomes, self-assemblies and nanogels [23]. A formulation of curcumin with a micellar surfactant (polysorbate) has been shown to increase the absorption of curcumin in mice 9.0-fold [24]. A micro emulsion system of curcumin, which consists of Capryol 90 (oil), Cremophor RH40 (surfactant), and Transcutol P aqueous solution (co-surfactant) has been shown to increase the relative absorption in rats by 22.6-fold [25]. Polylactic-co-glycolic Acid (PLGA) blend nanoparticles increased curcumin absorption by 15.6-, compared to an aqueous suspension of curcumin in rats [26,27].

The complex of curcumin and cyclodextrin is a new way to increase the absorption of curcumin. A recent paper has shown that the complex of curcumin to cyclodextrin increases human PK of curcumin by a factor of almost 40 over native curcumin, better than any other approach to deliver curcumin [28]. In the present paper, it is shown that the complex of curcumin with cyclodextrin is also associated with better efficacy. In the carrageen an mouse foot paw model, a commonly used model for inflammation, VOLT03 was superior to both the active control, indomethacin, which behaved as expected, but also native curcumin. VOLT03 thus has the rare advantage of being not only the most potent curcumin formulation but also the one that has the best PK coverage. It can be used not only as a nutritional supplement for neurological and oncology prophylaxis, but also in the clinic for inflammatory diseases such as Rheumatoid Arthritis, Ankylosing Spondylitis and Psoriasis.

Competing Interests: The author has substantial ownership of LeVolta Pharmaceuticals

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