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ARTICLE

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ALSUntangled reviews alternative therapies are presented on behalf of persons with ALS (PALS). Here we review the use of curcumin for ALS, for which we have had over 100 requests (1). Curcumin is a chemical compound in the spice turmeric, accounting for ~0.5–5% of the dry weight of turmeric powder (2–4). It is also found in the curry powder used in Middle Eastern and Asian cuisine; however, the use of other spices in curry powder dilutes curcumin to signficantly lower levels than in pure tumeric powder (3). Because curcumin is a small component of tumeric and an even smaller component of curry powder (3,4), we focus our review on curcumin dietary supplements.

Overview

Curcumin comprises the majority of several structurally similar compounds in tumeric called curcuminoids, which belong to a chemical class called polyphenols (2). Curcumin is most commonly administered orally. The medicinal utility of oral curcumin has been questioned, because it is poorly absorbed from the gut, rapidly metabolized, has been reported to inhibit several proteins important for normal physiology, and is toxic to several healthy cell lines (5,6). Different curcumin formulations have been created to try and optimize perceived problems with absorption and/or distribution within the body; these will be discussed in the "Dosing" section below. It has also been suggested that orally administed curcumin might act primarily by altering the fecal microbiome (7), which would be possibly independent of absorption. Curcumin is reported to have multiple downstream biological effects (6–10) and as a result has been tested in animal models and/or clinical trials for many different diseases, including Alzheimer's disease, arthritis, cancer, hyperlipidemia, Parkinson's disease, Charcot-Marie-Tooth disease, spinal cord injury, and stroke. *In vitro* studies on curcumin have been criticized, because the compound itself is unstable in common *in vitro* testing conditions and could potentially interfere with a variety of *in vitro* assays through several mechanisms, potentially leading to false interpretations due to real bioactivity of degradation products or assay interference (5). Nonetheless, many published clinical trials with curcumin in varying formulations show clinical benefits in various diseases, suggesting that curcumin warrants further study (11).

Mechanisms

At least four of curcumin's purported mechanisms of action might be relevant in treating ALS: modulation of neuroinflammation, reduction of oxidative stress, amelioration of protein aggregation, and alteration of the fecal microbiome.

Neuroinflammation

Neuroinflammation is thought to have a role in ALS pathogenesis, possibly through activation of the nuclear factor-κB (NF-κB) pro-inflammatory cellular pathway (12). Patients with sporadic ALS have elevated NF-κB expression in microglia (13). Reduced expression of NF-κB in microglia slows progression and extends survival in multiple mouse models of ALS (14–16). Curcumin can reportedly decrease NF-κB pathway activation in rat and mouse microglial cell cultures (17–19) and in rat brain when delivered to the animals via intraperitoneal injection (20) or orally (21). Curcumin also reportedly decreases NF-kB activation in human cell lines (22–25). Despite the promising preclinical data, a clinical trial, with cancer patients, utilizing a high bioavailability oral form of curcumin (Theracurmin) could not find a change in NF-kB levels in peripheral blood monocytes (26).

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Oxidative stress

Oxidative stress may also be a key player in ALS pathology (27). PALS have elevated oxidative species and decreased antioxidants in their blood (28). Increased oxidative stress in the motor cortex correlates with worse ALS disease severity (29). Compounds that induce Nrf2-ARE, a molecular antioxidant pathway, delay disease progression in a SOD1 mutant mouse model of ALS (30–32). Curcumin reportedly neutralizes free radicals *in vitro* (33) and activates the Nrf2-ARE pathway in the brain of rats (34–36), skeletal muscle of mice (37) and rats (38), and isolated rat astrocytes (39). A single very high oral dose of curcumin (Theracurmin formulation) was able to partially prevent acute oxidative stress induced damage to the brain of mice (40). In multiple human trials, oral curcumin treatment was associated with biomarkers of increased antioxidative effect in the blood (41–51) including NrF2 activation (51).

Protein aggregation

Misfolded proteins ("aggregates"), such as SOD1, are present in the motor neurons of PALS with familial and sporadic forms of the disease and some believe these play a pathogenic role (52). Treatments targeting protein aggregates can delay progression in ALS animal models (52,53). Curcumin can reportedly inhibit SOD1 aggregation *in vitro* (54), however, the concentrations of curcumin used in this experiment are so high that these concentrations would be virtually impossible to obtain in humans. Curcumin can also promote the expression of genes related to the clearance of protein aggregates in isolated blood cells from PALS and people with Alzheimer's disease (55). Unlike neuroinflammation and oxidative stress, we found no human trials testing curcumin's ability to affect protein aggregation.

Alteration in fecal microbiome

An altered fecal microbiome acting directly through a bacterial toxin or via a secondary effect on neuroinflammation through the "gut brain axis" was first postulated as a cause of ALS more than a decade ago (56). Two recent studies (57,58), but not another (59), found an altered microbiome in PALS. Altering the fecal microbiome in the mutant SOD1 mouse model of ALS prolongs survival (60) and in a worm model of ALS improves motor function (61). Oral curcumin (7) and oral Theracurmin (62) can alter the fecal microbiome in mice though it is not yet clear it can do this in a way that would help PALS.

The above-described mechanistic data are potentially exciting, but some experiments may need to be replicated given curcumin's ability to interfere with *in vitro* assays (5). Despite these limitations, the data are at least theoretically compelling, so ALSUntangled assigns a TOE "Mechanism" grade of C (Table 1).

Pre-clinical models

We found three studies, at a single institution, exploring the effect of chemical analogs of curcumin in a ALS cell model involving NSC-34 mouse spinal cord-neuroblastoma cells transfected with mutant TDP-43 or a fragment of wildtype TDP-43. In this model, either mutant TDP-43 or a fragment resulted in hyperexcitability, altered mitochondrial morphology and complex I activity, protein aggregation, and elevated a marker of oxidative stress (63–65). These studies show that certain chemical analogs of curcumin can reduce hyperexcitability (63), rescue mitochondria morphology and complex I activity (64), reduce a marker of oxidative stress and decrease protein aggregation (65). None of these studies have been independently replicated and not all experiments were adequately controlled given curcumin's ability to interfere with *in vitro* assays (5). It is unclear how the chemical analogs that were used would perform in human trials or whether any experimental results obtained in this non-human cellular model will translate into a treatment for PALS.

Based on these three flawed published studies showing benefits of curcumin chemical analogs in an ALS cell model, ALSUntangled assigns a TOE "Pre-Clinical Models" grade of C (Table 1).

Cases

In the online community PatientsLikeMe, 28 PALS report taking curcumin at doses ranging from 500–1500 mg daily, and eight of these completed detailed evaluations. Only one perceived "slight" effectiveness for their ALS; the others perceived no effectiveness or could not tell that it was helping (66).

We are aware of three other PALS who experienced substantial and sustained functional improvement on cocktails of treatments that included curcumin at some point. Members of the ALSUntangled team obtained their medical records and independently validated their diagnoses and motor improvements (67). There are multiple possible explanations for their improvements, including one of the other supplements or drugs they took, endogenous resistance to ALS, or an unrecognized ALS mimic syndrome (67).

Based on the three PALS with validated diagnoses who experienced validated improvements on regimens containing curcumin, ALSUntangled assigns a TOE "Cases" grade of B (Table 1).

Table 1. Table of evidence.

	Grade	Explanation
Mechanism	C	Curcumin can theoretically act on at least four plausible ALS mechanisms.
Pre-Clinical	C	In three flawed studies using a TDP43 transfected mouse cell model of ALS, chemical analogs of curcumin have been shown to be beneficial.
Cases	B	Three PALS with validated diagnoses experienced substantial and sustained functional improvements on different multi-compound regimens that all included a form of curcumin.
Trials	C	One small published randomized, double blinded, placebo-controlled pilot trial showed some benefit with a nanoparticle formulation of curcumin.
Risks	B (oral)/D (intravenous)	Oral curcumin is associated with only rare, minor side effects. Intravenous curcumin is associated with severe adverse events including death.

Trials

There has been one published pilot trial of curcumin in PALS which used a proprietary formulation of curcumin called Sina Curcumin (68). This was a 12-month double blinded randomized placebo-controlled trial that enrolled 54 PALS. The Sina Curcumin group took one capsule by mouth per day that contained 80 mg curcuminoids. All patients, regardless of the assigned group, took riluzole and an antacid. The results showed that the Sina Curcumin group was less likely to experience a major event, defined as death or mechanical ventilation dependency, even when controlling for other factors such as age. Despite the difference in major events, there was no significant difference found between groups in progression of ALSFRS-R score or tests of arm and leg muscle strength (MMT). The results of this study are difficult to interpret because of significant differences in age and motor testing between the placebo and Sina Curcumin groups at baseline.

We also found an unpublished pilot trial of a supplement called Brainoil (69). Brainoil is said to be a blend of curcumin, piperine, and several herbs which is processed and combined with oil into a gel. This was a six-month trial that was initially double-blind and placebo controlled and enrolled 42 PALS. After the first three months, the placebo group was crossed over to Brainoil and the trial was open-label for the remaining three months. The results showed a trend toward slower progression on ALSFRS-R scores from 0 to 6 months in the Brainoil group compared with the placebo group, but these did not reach significance. The trial was likely underpowered to detect significant changes on this scale and additionally may have suffered from a placebo effect given that it was open-label for three months, so in our opinion, the results are inconclusive.

Based on the above trials, ALSUntangled assigns a TOE "Trials" grade of C (Table 1).

Risks

Despite the *in vitro* data suggestive that curcumin could have toxic functions (5,6), more than 120 human clinical trials have been conducted with orally administered curcumin at doses of up to 12 g per day. We found no serious adverse events attributed to curcumin in these trials. Meta-analyses suggest that side effects of any kind are rare, affecting less than 10% of patients participating in oral curcumin trials; the most common reported side effects include abdominal pain, nausea, indigestion, constipation, diarrhea, and hot flashes (5, 70–72). Intravenous curcumin, which is far less commonly studied, is associated with at least one severe allergic reaction and one death (73). Since curcumin can affect enzymes involved in drug metabolism (5,74), it may interact with other drugs or supplements (74–77).

Based on this information, ALSUntangled assigns a TOE "Risks" grade of B for oral curcumin and D for intravenous curcumin (Table 1). It is important to note that there are many ways of formulating oral or intravenous curcumin and that these different forms could have different safety profiles. Also, while curcumin has been tested for safety in the general population, there is minimal specific experience with it in PALS.

Dosing and costs

Although oral curcumin studies have utilized a wide range of different dosages, most were unable to detect curcumin in the serum of participants (5). Different oral formulations have been developed to try and improve blood concentrations of curcumin. The two most common strategies tested in clinical trials are creation of water soluble nanoparticles and the addition of compounds ("bioenhancers") that improve curcumin bioavailability (78); some of these formulations with references for pharmacokinetic data are listed in Table 2. However, in light of the fact that curcumin may not need to be absorbed from the gut to work (7), it is difficult to select an optimal product for future ALS trials based on absorption data. Besides the above described trial in PALS utilizing Sina Curcumin (68), we only found one other successful trial in neurological diseases. In a trial on mild cognitive impairment (MCI), 21 patients with MCI were randomized to receive "Theracurmin" at 90 mg twice daily had significantly improved blinded measures of memory and

Table 2. Selected curcumin formulations purported to increase serum concentrations.

Product category	Product name	Description	Supporting references
Nanoparticle	Sina Curcumin	Curcuminoids in nanomicelles	No pharmacokinetic data found.
Nanoparticle	Theracurmin	Curcumin dispersed with colloidal sub-micron particles	(79,80)
Nanoparticle	Meriva	Curcumin complexed with phospholipids	(80,81)
Addition of Bioenhancer	Bio-Curmin (BCM-95)	Curcuminoids with essential oils	(80,82)
Addition of Bioenhancer	BioPerine	Curcumin with piperine (a component of black pepper)	(83)

attention over 18 months, while 19 patients randomized to placebo worsened (84). This clinical study, along with the above mentioned study of Theracurmin partially preventing acute oxidative stress induced damage in the brain of mice (40), suggests that oral Theracurmin would be a promising formulation for a future ALS trial.

The cost of curcumin varies somewhat depending on the dose and specific formulation taken. One month's supply of Theracurmin at 90 mg twice daily currently costs $53 (85).

Conclusion

Oral curcumin is safe, inexpensive, and has at least four potential mechanisms by which it might theoretically be useful in treating PALS. Flawed preclinical studies showed benefits of a curcumin chemical analog in a cell model of ALS, three PALS experienced validated motor improvements on regimens including curcumin (although there are several alternative explanations for these improvements) and there is one small pilot trial showing some benefit of curcumin in PALS. Based on the evidence presented in this review, some of us are planning a trial of Theracurmin at 90 mg twice daily in PALS.

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