Turmeric for Spicy Health

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Turmeric: *from: Wynn & Fougere: Veterinary Herbal Medicine; Mosby, 2007.*
Curcuma longa L.
Family:
Zingiberaceae
Other names:
Indian saffron, yellow ginger
Part used:
Dried rhizome, tuber
Distribution:
Cambodia, China, India, Indonesia, Madagascar, Malaysia, Philippines, Vietnam. Cultivated throughout the tropics including Africa.
Selected Constituents:
Volatile oil (6%) composed of monoterpenes and sesquiterpenes, including zingiberone, curcumene, and α-and β-turmerone. The bright yellow color is due to the curcuminoids, 50-60% are a mixture of curcumin, monodesmethoxycurcumin, and bisdesmethoxycurcumin

Introduction:
Turmeric (*Curcuma longa* L.), a member of the Zingiberacea plant family which includes ginger and cardamom, is a spice and food coloring found primarily in India, but also grown in China, Thailand and Indonesia. For centuries it has been used for its culinary and medicinal properties in these countries. Turmeric is the base found in most Indian curries; it has a bright yellow color and is used to enhance the flavor of foods. As is true of most culinary spices, their purpose is not just flavoring, but also as a food preservative due to their antioxidant properties. This is how they helped to keep food fresh in a world before refrigeration.

Curcuminoids are found in the rhizome of the *Curcuma longa* plant. A rhizome is a "creeping rootstalk, growing underground in horizontal stems, like its cousin, ginger". The rhizome of this plant, in addition to the curcuminoids found in it, also contains sesquiterpenes (turmerone, atlantone, zingiberone, turmeronol, germacrone and bisabolene), carbohydrates, proteins, resins and caffeic acid. The active molecules in the plant are considered to be the brightly yellow-colored polyphenolic curcuminoids. Curcuminoids make up 2%-5% of the rhizome.

Naturally-occurring curcuminoids are: Curcumin (diferuloylmethane), demethoxycurcumin, and bisdemethoxycurcumin. The distribution of these curcuminoids in commercially available turmeric is: 75-85% curcumin, 10-15% demethoxycurcumin and 5-10% bisdemethoxycurcumin. (8) (9) (10)

Biological Activity
Historically, turmeric has been used in both the Ayurvedic and Traditional Chinese Medicine systems of Ethnobotany for the treatment of skin disorders, pulmonary and gastrointestinal ailments, pain, wounds and liver disorders. (1)

Over 3000 preclinical and clinical studies have found many medical applications for this common Indian spice. It has been found to have a benefit in the treatment of cancer, immune deficiencies, cardiovascular health, Alzheimer's disease, diabetes, arthritis, and Crohn's disease, as well as psoriasis and a number of other diseases.

Curcumin works by modulating multiple molecular targets, cell signaling proteins, cell cycle proteins, cytokines and chemokines, enzymes, receptors and cell surface adhesion molecules. Curcumin works "upstream" to down-

regulate inflammation, and modulates the pro-inflammatory enzymes (cyclooxygenase and lipoxygenase), the inflammatory transcription factors nuclear factor kappa B (NFκB) and signal transducer and activator of transcription 3 (STAT3) and their genomic expressions.

Curcumin has been found to be a neuroprotectant as a result of its polyphenolic antioxidant properties. These antioxidant properties also protect DNA from single strand breaks induced by singlet oxygen. Curcumin suppresses the mutagenicity of several common mutagens including cigarette smoke and benzopyrene. Curcumin also has potent anti-inflammatory effects by inhibiting neutrophil function, inhibiting platelet aggregation, inhibiting lymphocyte activity, promoting fibrinolysis, and stabilizing lysosomal membranes. (1) (10)

Curcumin has cancer-preventative activity (chemoprevention) which results from the ability of curcumin to: 1) inhibit phase 1 cytochrome P450 activation of pro-carcinogens; 2) enhance phase 2 detoxification activity, including glutathione transferase; and 3) inhibits multiple signal transduction pathways that trigger cancer proliferation, angiogenesis and tissue invasion. The inhibition of NFκB activation by curcumin down-regulates multiple inflammatory genes which in turn result in decreased proliferation, signaling, anti-angiogenic effects and decreased cell invasiveness. Turmeric has been found to sensitize only cancer cells to the cytotoxic effects of chemotherapy agents. (11)

Other properties for curcumin include altering serum lipids such as cholesterol, LDL and HDL cholesterol as well as LDL peroxidation. Curcumin has been shown to increase HDL cholesterol (the "good" cholesterol) in humans. Curcumin interferes with intestinal cholesterol uptake, increases the conversion of cholesterol into bile acids by increasing the activity of hepatic cholesterol-7-alpha-hydroxylase, which is the rate limiting step in bile acid synthesis. Curcumin, for the reasons just stated also increases bile acid secretion, increasing bile output by almost 100%. (13)

And if all of these properties weren't enough, curcumin has been found to have hepato-protective and cholerectic properties. It prevents lipid peroxidation *in vivo* due to its potent anti-oxidant properties. Historically, turmeric has been used to improve digestive function, in part due to its ability to stimulate the digestion of fats and carbohydrates. (1) (10)

Absorption

In spite of having all of these beneficial health properties, turmeric, and its active ingredients, the curcuminoids, are very poorly absorbed from the digestive tract. It is a lipophilic molecule, and in ethnobotanical use turmeric is commonly cooked with oils and other spices like black pepper, all of which improve its absorption and slow down GI transit time.

There have been a number of attempts to chemically modify the curcuminoid molecules to improve their intestinal absorption, but before pharmaceutical technology was applied to this plant extract, there was "Yellow Paste". This is a home cooking way to improve the absorption of the curcuminoids in this healthy spice.

Recipe for Turmeric Paste (AKA Yellow Paste or Turmeric Bomb):
4 oz. organic turmeric
1/4 cup water
Mix together and heat slowly on low heat until thickens.
Add 1/4tsp ground black pepper
Add 2 tablespoons virgin coconut oil
Slow heat 5-10 minutes. Let cool. Put into glass. Store in fridge.

Curcumin is very unstable at the pH of the GI tract, decomposing in less than 10 minutes, and has a very low oral absorption. Doses as high as 12 grams daily only resulted in plasma levels of less than 50 ng/ml in one study (12)

Currently there are several patented curcumin modifications in the marketplace that are using pharmaceutical technology to increase the absorption of curcuminoids. Curcuminoids have poor solubility, low absorption from the gut, rapid metabolism and rapid systemic elimination. The major amount of curcumin ingested orally is excreted unchanged in the feces.

Molecular Strategies to Increase Absorption
Co-administration of curcuminoids (AKA: simple curcumin complex) with black pepper extract (piperine) has been shown to increase absorption 1.5 times over simple curcumin complex. The combination of curcuminoids and volatile oils of the turmeric rhizome resulted in a 6.9-fold increase in the absorption of curcumin (BCM-95™) over turmeric in animal models (8). The lipophilic matrix of curcumin with phosphatidylcholine and microcrystalline cellulose (Meriva™) has been shown to increase the oral absorption of curcumin in the human by 19.2 times over the simple curcumin complex.

One of the most highly absorbable formats for oral curcumin absorption studied utilizes a water-soluble complex in which the curcuminoids are dispersed with the anti-oxidants tocopherol and ascorbyl palmitate and combined with the water-soluble carrier molecule polyvinyl pyrrolidone. This complex, called Curcuwin™, in a pharmacokinetic study using human subjects, comparing its oral absorption with that of the simple curcumin complex, BCM-95™ and Meriva™, was found to be 45.9 times better absorbed.

When compared to the relative absorption of BCM-95 to simple curcumin complex, Curcuwin™ was 34.9 times more orally absorbable, and 5.8 times more absorbable relatively than Meriva™. This study used each subject as its own control, by having a washout period between administration of each different test material. Its very rare to find “head to head” studies that compare different proprietary products in the same experimental subject, using them as their own control such as with this study (8).

In addition to the advantages of the improved absorption of the Curcuwin™ complex over the other two patented products evaluated, peak serum levels of curcuminoids from Curcuwin™ persisted for at least 12 hours in this pharmacokinetic study in humans. These peak serum levels of curcuminoids may actually persist longer, but the study duration was only 12 hours. The authors note that future studies will carry the curve out to 24 hours. The duration of therapeutic serum levels of curcuminoids with Curcuwin™ far exceeds the duration of therapeutic serum levels in the other absorption technologies described in this paper. It is still suggested to administer Curcuwin™ twice daily, but it may be that once daily administration could also have its benefits.

Another finding of this study was that the distribution of each of the three individual curcuminoids in the serum varied from product to product. It is known that the antioxidant potency of curcuminoids decreases according to the number of methoxy groups present on the curcuminoid molecule.

Decreasing Antioxidant Potency:
Curcumin>Demethoxycurcumin>Bismethoxycurcumin

Each curcuminoid has similar but different properties. For instance, the anti-ulcer and anti-inflammatory aspects of the curcuminoid curcumin has been found to be stronger than that of demethoxycurcumin. However, with respect to the growth-modifying activity of curcuminoids the methoxy groups do not play a role. (14)

It is interesting to note here that the phospholipid-curcumin complex increases the amount of demethoxycurcumin in the serum greater than the amount of curcumin. Demethoxycurcumin is not as anti-

inflammatory as curcumin. In the simple curcumin complex there is 4 times the amount of curcumin than demethoxycurcumin. The phosphatidylcholine-curcumin complex (Meriva™) has demethoxycurcumin as the major plasma curcuminoid in the serum. This comparison study found this to be true for the this complex, but it was not found to be true for either the BCM-95™ or Curcuwin™ formulations. (8)

Research in our Veterinary Species

As many studies as have been conducted studying curcuminoids, there are very few that are in our target veterinary species of dogs, cats and horses, and most of those are basic research versus interventional studies. There is an abundance of studies in laboratory animals, and there are studies from India, Iran and other countries where turmeric is widely consumed and widely used for medical purposes. Many of those studies use whole powdered turmeric which is very poorly absorbed, even in large dosages. Studies of the more bioavailable forms of curcumin in veterinary species exist only for the phosphatidylcholine bound format, and those were sponsored by the Italian company that owns the patent on this effective product.

One study in dogs measured the gene expression of peripheral white blood cells in dogs with osteoarthritis (OA). Two groups of dogs were studied, one group with OA and the other without this problem. They were administered either an NSAID (Previcox™) or Meriva™. The curcumin formula was administered at 4 mg/kg BID and the NSAID at 5 mg/kg/day. The response of genes involved in the inflammatory response was measured for the two groups after 20 days on the different treatments.

The study found that curcumin regulated the same molecular target of inflammation as has been found to be true in humans. Molecular targets of curcumin that were not similar to the targets of the NSAID were those related to the inhibition of macrophage proliferation, and strongly down-regulated TNFα and activated fibrinolysis. The authors feel that for these reasons curcumin can provide complementary support in the treatment of OA. (6)

This study was modeled on a parallel study in mares (4). In this study 7 mares aged 4-9 years were given 4 mg/kg of Meriva™ once daily for 15 days. Whole blood was analyzed for the effects of curcuminoids upon expression of COX-2, TNF-α, IL1β, IL1RN, and IL6 in the mares and the foals studied.

They found that curcumin inhibited the expression of all of these pro-inflammatory cytokines which play a role in the pathogenesis of osteoarthritis, with only IL1β, IL1RN having statistically significant values. In foals, curcumin significantly inhibited the expression of COX-2, TNF-α, IL1RN and significantly increased the expression of IL6. The authors conclude that curcumin has potential as a natural anti-inflammatory agent for treating osteoarticular disorders by suppressing pro-inflammatory cytokines and catabolic enzymes.

A 2009 Italian study compared the modulation of neutrophil function and apoptosis by standardized extracts of *Echinacea angustifolia*, *Butea frondosa* (an herb of the Ayurvedic tradition) and *Curcuma longa* (another herb from Ayurveda) in sheep neutrophils. This study was sponsored by the company that manufactures Meriva™.

This *in vitro* study determined that the curcumin-phosphatidylcholine complex stimulated spontaneous apoptosis of neutrophils and inhibited gene expression at T22 compared to the Echinacea and Butea extracts, suggesting to the researchers that curcuminoids have more of an anti-inflammatory activity as compared to the immunomodulatory effect of Echinacea and Butea extracts on neutrophil function. (5)

Another study in dogs with osteoarthritis used force plate measurements of limb placement, which is the best way to measure response to a pain relieving agent such as curcumin, and used a randomized placebo-controlled parallel group study of a proprietary turmeric product to determine if it had any better effect on their pain as measured by a force plate than a placebo. This turmeric product consisted of curcuminoid extracts of two

different Curcuma species combined with essential oils extracted from turmeric. It was administered at a dose of 4 mg/kg per day of curcuminoids.

No attempt was made to measure serum curcuminoid levels in this study. The study did not find a statistical difference in force plate values in the group treated with this enhanced turmeric formula as compared to those treated with the placebo. However, the investigator's assessment of the dogs' overall responses showed a statistically significant treatment effect in favor of the proprietary curcuminoid product. The owners' overall evaluation of the dogs' responses approached statistical significance. This is most likely due to the poor bioavailability of the curcuminoids in this particular proprietary product. This is why the bioavailability of curcuminoids is very important to demonstrate clinical effects. (3)

There is a recent study in beagles using a proprietary liposomal curcuminoid product that was designed for intravenous use, which doesn't apply to those products that are designed to be administered orally. This pharmacokinetic study used a 2 hour intravenous infusion of this liposomal curcuminoid product and found that the plasma half lives of tetrahydrocurcumin (THC) and curcumin both ranged from 0.4-0.7 hours, and was the consequence of both liver and renal clearance.

One take-away from this study is the short plasma half life of curcumin and THC when administered intravenously in a 2 hour liposomal infusion. For best clinical results plasma levels of curcuminoids need to be maintained at a therapeutic level for 24 hours, such as is found with the oral administration of Curcuwin™ (7).

Potential Veterinary Applications for Curcuminoids

- **Inflammatory conditions**
    - Osteoarthritis
    - Atopy
    - Inflammatory bowel disease
    - Autoimmune disease
- **Neoplastic diseases**
    - Both prevents and treats cancer
    - Inhibits metastasis
    - "Chemo-sensitizer"—improves effect of chemotherapy agents
    - Activates apoptosis
    - Inhibits proliferation and survival of almost all types of neoplastic cells
        - Cellular uptake of curcumin is higher in neoplastic cells than healthy cells
    - Prevents tumor-induced T-cell apoptosis
- **Metabolic diseases**
    - Improves symptoms associated with Type 2 diabetes
    - Improves glycemic control in mouse models of type 2 diabetes
    - Prevents alcohol-induced liver disease in laboratory rats
- **Neurologic disease**
    - Epilepsy
    - Senility
    - Head trauma

Empirically Determined Dosage of Curcuminoids in Veterinary Species

Curcuminoids bound to phosphatidylcholine (Meriva™ = 4 mg/kg qd)

- 3. Innes 2003 (dogs)
- 4. Farinacci 2009 (mares)
- 6. Colitti 2012 (dogs)

Curcumin (2)

- 50-250 mg TID dogs
- 1200-2400 mg daily for horses

Curcuwin™ (20% curcuminoids like Meriva™)

- No studies in target species yet
- Presumptive dose = 4 mg/kg daily
- Dosage may be less due to superior absorption of Curcuwin™ over Meriva™

Toxicology, Herb-Drug Interactions and Adverse Effects:

- Turmeric is classified as very safe.
  - The acute LD50 for turmeric in rats was 5 grams per kg .
- The only contraindications to its use are obstruction of the biliary tract and hypersensitivity to turmeric
  - Allergic reactions have occurred and contact sensitivity.
- Caution is advised with anti-platelet or anti-coagulation medication.
  - In rare cases it may affect bleeding times, but this is unlikely.
- No known herb or drug interactions or common adverse effects other than an unusual skin odor at higher dosages.

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