Turmeric for Osteoarthritis in Veterinary Medicine: a Review.

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Abstract

Curcumin, a compound derived from Curcuma Longa, commonly known as turmeric, is widely used as an anti-inflammatory. It targets a number of pathways that are central to osteoarthritis pathogenesis. The bioavailability of curcumin is low, but new formulations are being developed. Curcumin has an excellent safety profile but consideration should be given to the possible interactions and side effects when assessing patients who are supplemented with curcumin. There is a pressing need for large-scale clinical trials in dogs and horses, along with clinical veterinary studies to identify ways to increase the bioavailability and the clinical efficacy of supplementary curcumin in the management of osteoarthritis.

Keywords
Osteoarthritis, Curcumin, Veterinary, Safety, Anti-inflammatory

Introduction

Turmeric, Curcuma longa, is a member of the Zingiberaceae family of plants. Other members include ginger, Javanese ginger and galangal. The rhizome of turmeric is used in herbal medicine. Rhizomes, also called creeping rootstalks, are underground horizontal stems. Turmeric is extensively cultivated in China, India, Indonesia, Thailand and throughout the tropics. Curcumin, one of the constituents of turmeric, was described more than two centuries ago as a yellow coloured matter derived from the rhizomes of Curcuma longa. Turmeric is used to flavour food in South East Asian cuisine (Gupta, et al., 2013). In Asian medicine, more specifically in Ayruvedic medicine, curcumin is used for the treatment of skin disorders, pulmonary and gastrointestinal ailments, pain, wounds and liver disorders (Aggarwal, et al., 2007).

A search of the American website www.clinicaltrials.gov in September 2015 showed 124 recruiting, active or completed clinical trials on the use of curcumin in a wide variety of diseases. In July 2009 a total of 34 clinical trials were recorded. This change is indicative of the dramatic increase in interest and research into the effects of curcumin, and its bioavailability, over the last decade. Anecdotally, enthusiasm for curcumin-based supplements for horses has increased so significantly in recent years that wholesale supply cannot always keep up with demand. Veterinary professionals are asked on a regular basis whether curcumin would be an appropriate adjunct treatment for osteoarthritis. This review is aimed at giving them the knowledge to effectively and safely advise owners who treat, or plan to treat, their animals with curcumin. This article is a narrative review of the use of curcumin as an anti-inflammatory agent. It focuses on papers published in the last decade on curcumin and its application in osteoarthritis although some of the material discussed also applies to other inflammatory pathologies.

Components

In addition to curcumin more than 300 different components, including phenolic compounds and terpenoids, have been identified in turmeric. Plant terpenoids are used extensively for their aromatic qualities and play a role in traditional herbal remedies. Terpenoids contribute to the scent of eucalyptus, the flavours of cinnamon, cloves, and ginger, the yellow colour in sunflowers and turmeric, and the red colour in tomatoes. Curcumin is one of the major active components. However, research during the past decade has revealed that some of the activities of turmeric are independent of curcumin, and some studies suggest that whole turmeric exhibits activities superior to curcumin alone (Gupta, et al, 2013). The idea of using the whole plant rather than the extracted active ingredients in order to counteract side effects or achieve greater effect is very well known among herbal practitioners in Western herbal, Ayruvedic and Traditional Chinese medicine.

The selective constituents of turmeric are a volatile oil (6%) composed of monoterpenes and sesquiterpenses, including zingiberene, curcumene, α-turmerone and β-turmerone. The colouring principles (3 to 5%) are polyphenolic curcuminoids, 50% to 60% of which are a mixture of curcumin, monodesmethoxy curcumin and bisdesmethoxycurcumin (Wynn, 2007). Most research is centred around these polyphenolic components. Most commercially available curcumin is not pure but a mixture of curcumin (77%), desmethoxycucrcumin (18%) and bisdesmethoxy curcumin (5%). Curcumin is readily soluble in dimethylsulfoxide, ethanol or acetone but is sparingly soluble in water (Basnet & Skalko-Basnet, 2011).

Bioavailability

Curcumin is well tolerated but its bioavailability is poor because of poor absorption, poor solubility in aqueous solution, rapid metabolism and rapid systemic elimination (Noorafshan and

Ashkani-Esfahani, 2013). Yang, et al., (2007) reported a bioavailability of 1% in rats when curcumin extract at dose of 500 mg/kg as administered orally. Several formulations have been used to increase curcumin's bioavailability, provide longer circulation, improve resistance to metabolic processes and increase its permeation to a cellular level.

Metabolic enzymes can be bypassed by dissolving curcumin in oil before ingestion. Dissolution in oil does not modify the structure of curcumin but allows it to be directly absorbed into chylomicrons and subsequently into the lymphatic system, bypassing the liver and the first pass effect metabolism (Anand, et al., 2007). It has been suggested that ruminants and horses should absorb curcumin relatively well because the microbial fermentation in the rumen produces short chain fatty acids, which should dissolve curcuminoids, and prevent fast excretion. The hindgut of the horse may act in a similar way, but clinical studies of this hypothesis are yet to be investigated (English, 2016).

Piperine, the alkaloid responsible for the pungency of black pepper, inhibits hepatic and intestinal glucuronidation of curcumin (Patil, et al., 2011). The effect of piperine on the pharmacokinetics of curcumin was much greater in humans than in rats. In humans, curcumin bioavailability was increased by 2000% at 45 minutes after co-administering curcumin orally with piperine, whereas in rats it only increased by 154 % for a short period after administering (Shoba, et al., 1998). It is unclear whether piperine can facilitate such significant increases in curcumin bioavailability in herbivores or dogs.

It has been found that after oral administration of polylactic-co-glycolic acid (PLGA) encapsulated curcumin nanoparticles, the relative bioavailability was increased 5.6-fold and had a longer half-life compared with plain curcumin extract. This is due to improved water solubility, higher release rate and residence time in intestinal flora and enhanced absorption by improved permeability (Xie, et al., 2011). In vivo pharmacokinetics revealed that curcumin entrapped nanoparticles demonstrate at least 9-fold increase in oral bioavailability when compared to curcumin administered with piperine as a absorption enhancer (Shaikh, et al., 2009). Liposomes are able to solubilise hydrophobic components such as curcumin and hence alter pharmacokinetic properties (Takahashi, et al., 2009; Basnet, et al., 2012). Liposomal encapsulation of curcumin has been used to improve bioavailability. Encapsulation of curcumin with cyclodextrine both improved in vitro and in vivo bioavailability (Prasad, et al., 2014). Cyclodextrins are cyclic oligosaccharides arising from the degradation of starch. The most important property of the cyclodextrines is the ability to establish specific interactions (molecular encapsulation) with various types of molecules through the formation of non-covalently bonded entities, either in the solid phase or in aqueous solution (Marques, 2010). One recent equine study used a lysine salt of curcumin in beta-cyclo dextrine NDS27, which had higher bioavailability and could be inhaled (Sandersen, et al., 2015).

Safety and toxicity

Curcumin is consumed daily in the spice turmeric in many Asian countries. In India the average intake of turmeric can be as high as 2000 to 2500 mg per day (corresponding up to approximately up to 100 mg of curcumin) but no toxicities or adverse effects have been reported or studied at population level (Chainani-Wu, 2003). Doses administered in clinical trials are, however, expected to be much higher than a normal dietary intake. A phase I human trial with 25 subjects using up to 8000 mg of curcumin extract orally per day for 3 months found no toxicity for curcumin (Cheng, et al., 2001).

Safety precautions and contraindications for therapeutic curcumin include:

1. Inhibition of drug metabolism.
Curcumin has been shown to inhibit the activity of drug metabolising enzymes such as cytochrome P450 (CYP450), glutathione-S-transferase (GST) and UDP-glucuronosyltransferase (UGT) in vitro and in animal models (Burgos-Morón, et al., 2010; Cho & Yoon, 2015). Consequently animals taking drugs such as digoxin, anticoagulants, cyclosporine, and non-steroidal anti-inflammatories may be at risk of accumulation of drug concentrations in the plasma, which may be toxic (Gupta, Kismali & Aggarwal, 2013). CYP450 are the most important enzymes in phase I metabolism (modification) in mammals. Phase I results in small changes that make a compound more hydrophylic, so it can be effectively eliminated by the kidneys. More drugs affected by CYP450 are listed on the University of Medicine of Indianapolis website: (www.medicine.iupui.edu/clinpharm/ddis/clinical-table). GST and UGT are transferase enzymes, which are responsible for some phase II reactions. Phase II reactions (conjugation) involves the attachment of an ionised group to make the metabolite more water-soluble. This facilitates excretion as well as decreasing pharmacological activity (McDowall, 2016) (Rolfe, 2016).

2. Iron chelation.
Curcumin has been shown to be an active iron chelator in vivo. In rodents fed diets poor in iron curcumin induced a state of overt iron deficiency (Jiao, et al., 2008; Badria, et al., 2015). It is not clear how much this would affect facultative carnivores such as dogs, or herbivores.

3. DNA damage.
Several studies have shown that curcumin at concentrations similar to those reported to be beneficial can cause DNA damage and chromosomal alterations both in vivo and in vitro. For example, Burgos-Morón, et al, (2010) cite a report by the National Toxicology Program (USA) that an increase in carcinogenic activity in rats and mice in the small intestine was seen when curcumin was administered at an average daily dose of ~0.2 mg/kg body weight over periods ranging from 3 months to 2 years. However, epidemiological data

suggests a relatively low incidence of gastrointestinal cancers in India may be due to diet rich in curcumin. The estimated dose of curcumin ingested in the diet is ~ 0.15 g/day. This dose is up to 10 times lower than the therapeutic dose recommended by some health professionals (Burgos-Morón, et al., 2010).

4. Gastrointestinal inflammation.
Curcumin has been associated with nausea, diarrhoea and increases in alkaline phosphatase and lactate dehydrogenase in humans (Gupta, Kismali & Aggarwal, 2013). It has been observed also in clinical practice with dogs. Canine patients with pre-existing inflammatory gastrointestinal conditions like eosinophilic plasmacytic lymphocytic enteritis, exocrine pancreatic insufficiency and gastritis or stomach ulcers tend to suffer adverse reactions more rapidly. However, once the underlying inflammation, irritation or liver dysfunction has been settled by other means, low doses of curcumin may be tolerated.

5. Gall bladder contraction
Rasyid & Lelo, (1999) found that curcumin extract induces gallbladder contraction. This shows that use of any curcumin supplement in dogs with known gallbladder issues could be contraindicated if there is existing cholelithiasis. Certain dog breeds like Poodles, Schnauzers and Shetland Sheepdogs are more prone to these problems. A study by Li et al, (2015) showed that curcumin has the potential to decrease the formation of gallstones so in those predisposed breeds the use of curcumin might have preventive value if there are no pre existing gallstones.

6. Hypoglycaemia enhancement.
Some animal studies have shown that curcumin may enhance the hypoglycaemic effect of anti diabetic medication via inhibition of the CYP enzyme system or by reducing the low-density lipoprotein fraction in the blood (Basnet & Skalko-Basnet, 2011; Grynkiewics & Slifirski, 2012). Therefore glucose levels should be closely monitored in diabetic patients.

7. Zingiberaceae extracts have been reported to have anti-coagulant properties and could exacerbate clotting disorders (Kim, Ku & Bae, 2012; Lakhan, Ford & Tepper, 2015). Clotting disorders are relatively uncommon in dogs, cats and horses, but turmeric discontinuation prior to any surgical intervention should be considered. In dog breeds with suspected Von Willebrand disease (from Type 1 to Type 3) such as German Shepherds, Dobermans, Standard Poodles, Golden Retrievers and Shetland Sheep dogs it is standard to do a Buccal Mucosal Bleeding Test (BMBT) preoperatively. Interestingly, these very same anticoagulant properties indicate that curcumin may have a preventative effect for disseminated intravascular clotting associated with colic in horses and thrombosis associated with inflammatory disorders.

8. Oxalate uroliths
The consumption of supplemental doses of turmeric can significantly increase urinary oxalate levels, thereby increasing risk of kidney stone formation in susceptible individuals (Tang, Larson-Meyer & Liebman, 2008). This was seen in a human study but we know that Miniature Schnauzers, Lhasa Apsos, Yorkshire Terriers, Bichon Frises, Shih Tzus and Miniature Poodles are predisposed to form calcium oxalate uroliths. Both cats and horses can form calcium oxalate uroliths so questioning the owner of patients on supplement use when diagnosing urolithiasis is recommended.

9. Anecdotally, dogs receiving medicinal doses of curcumin may show a marked increase in body odour resembling that of cat urine. Some owners find the odour too offensive and stop giving the curcumin or reduce the dose significantly. In most cases the odour decreases over time, or it may be neutralised by adding cinnamon.

Anti-inflammatory activity of curcumin in vitro and in vivo

Many of the activities associated with curcumin are related to the suppression of inflammation. It targets a number of pathways that are central to osteoarthritis pathogenesis, as detailed below.

1. Decreased synthesis of inflammatory mediators
Curcumin induces down regulation of various inflammatory cytokines in vitro, such as TNF, Il-1, Il-6, Il-8, Interferon γ and other chemokines (Mathy-Hartert, et al., 2009; Aggarwal, Gupta & Sung, 2013; Comblain, et al., 2015). Cytokines are small soluble proteins that affect the activity of other cell types. TNF- α and Il-1β also induce the expression of matrix metallo proteases (MMP) and COX-2 (Shakibaei, et al., 2007). The involvement of pro inflammatory cytokines and MMPs in osteoarthritis is well documented. MMP-3 is produced by chondrocytes in cartilage tissues affected by osteoarthritis. MMP-3 has the capacity to degrade collagens and proteoglycans, and activate other collagenases. Curcumin suppresses the gene expression of a number of MMPs, preserving the integrity of the joint matrix and thus having an anti-katabolic activity (Peddada, et al., 2015). Curcumin tested on equine cartilage explants stimulated with Il-1β showed the suppression of glycosaminoglycan (GAG) release (Clutterbuck, et al., 2013). GAG release is one of the indicators of cartilage damage. Dietary administration of Curcuvet, a stabilized extract of turmeric associated to a phytosome complex, resulted in significant down regulation of IL-1β and up regulation of IL6 gene expression (Farinacci, et al., 2010). The stimulation of IL-6 could have a beneficial effect since it has a protective role with respect to cartilage integrity.

2. Selective COX-2 inhibition but also some COX-1 inhibition.
COX-2 is the inducible form of cyclo-oxygenase predominant at inflammatory sites. Curcumin down regulates the expression of COX-2 enzymes and inhibits the expression of pro inflammatory enzyme 5-LOX, reducing prostaglandins, leukotrienes and thromboxanes. Curcumin inhibits COX-2 but not COX-1 gene expression (Park, et al., 2007; Henrotin, Priem & Mobasheri, 2013). COX-2 appears to have also some important physiological functions, for

example in the kidneys. This role is greater in dogs than humans.
Apart from the well-known roles of COX-2, studies suggest that the COX-1 iso enzyme also plays a role in inflammation and carcinogenesis. COX-1 is over expressed in a significant number of ovarian cancers. One study suggests that curcumin and its analogues had significantly higher inhibitory effects on peroxidase activity of COX-1 than that of COX-2 (Handler, et al., 2007). This would potentially explain the occasional gastro intestinal irritation with curcumin seen in practice. The balance between the metabolic products of COX- 1 and COX-2 catalysis appears important in the physiological function and response to inflammation. There is some literature that suggests there is some cardiovascular protective role for the products of COX-2 and that not all COX-1 functions are good in terms of cardiovascular health (Parente, 2001; Vanhoutte, 2009). Perrone, (2010) suggests that there is definite scope to develop new drugs whose activities are COX-1 mediated. Maddison, (2015) however warns to not extrapolate results from one species to another.

3. Activator Protein-1 (AP-1) and Nuclear Factor-κB (NF-κB) inhibition Nuclear factor κB (NF-κB) and activator protein 1 (AP-1) transcription factors regulate many important biological and pathological processes. Nuclear factor κ-B plays a critical role in signal transduction pathways that are involved in inflammatory diseases and various cancers. Curcumin has been shown to inhibit NF-κ-B and AP-1 pathways (Csaki, Mobasheri & Shakibaei, 2009). This in turn reduces the downstream inflammatory effects of COX-2 and inhibits PGE2 synthesis. Prostaglandins and degradation of extracellular macromolecules lead to cartilage degeneration and joint inflammation.

Clinical trials in horses and dogs

The majority of large scale clinical trials to examine the anti inflammatory effects of curcumin have studied humans or rodents. There are a few big trials involving horses and dogs.

One such trial, a randomised, double-blind, placebo-controlled parallel group study of turmeric extract for the treatment of osteoarthritis in dogs, failed to reach statistical significant effects (Innes, et al., 2003). A small study involving 12 osteoarthritic dogs found that curcumin resulted in inhibited macrophage proliferation, strongly down regulated TNFα and the activation of fibrinolysis (Colitti, et al., 2012). These positive findings need to be validated with larger trials. The pharmacodynamics of intravenous injection of liposomal curcumin in beagles has been studied, but this has no practical applications for the regular pet owner (Helson, et al., 2012).

A study in which a nutritional supplement containing curcumin and boswellia extract was fed to thoroughbred horses found a reduction in pro inflammatory cytokine expression and hence an enhanced adaptation to exercise (Horohov, et al., 2012). Once again, large-scale studies are required to validate these findings. A study at the University of Udine, Italy showed that administration of a phytosome complex of curcumin administered to seven mares with confirmed osteoarthritis and five foals with osteochondrosis changes for fifteen days had some significant results. Gene expression was monitored before the treatment and after four, eight, and fifteen days. In mares, curcumin inhibited the expression of COX-2, TNF-α, IL-1β, IL1RN, and IL6, even if only the down regulation of IL-1β and IL1RN were significant. In foals, curcumin significantly inhibited the expression of COX-2, TNF-α, IL1RN and significantly increased that of IL6. These results show that curcumin has potential but again this is a very small study (Farinacci, et al., 2010). Clutterbuck, et al, (2013) found that curcumin at concentrations lower than 25μM exerted a potent anti-inflammatory effect on cartilage explants in vitro. This study did, however, express caution of extrapolating this data and recommended further research to establish curcumin's bioavailability and physiologically relevant serum and synovial concentration in vivo in humans and animals.

Conclusion

There is a vast amount of clinical observational and anecdotal evidence, together with some promising in vitro and in vivo studies, in support of the use of curcumin in the treatment of joint inflammation (Moreau, et al., 2014, Ulbricht et al., 2011). However, there is a pressing need for large-scale clinical trials in dogs and horses, along with clinical veterinary studies to identify ways to increase the bioavailability and clinical efficacy of supplementary curcumin in the management of osteoarthritis. The relative safety of curcumin should allow it to be used as a supplement for the management of osteoarthritis in the majority of cases. Recommended dose ranges are broad, ranging from 50 to 250 mg curcumin three times daily for dogs and 1200-2400 mg of curcumin daily for horses (Wynn, 2007). A lack of standardisation in extraction processes and quality control means that there may be considerable variability in the active constituents of veterinary nutraceutical products. However, further veterinary clinical trials with more bio available forms of curcumin will provide more accurate dosage guides and standardised products.

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