Reflections about Osteoarthritis and Curcuma longa

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ABSTRACT

Osteoarthritis (OA) is a chronic inflammatory degenerative process that affects joints such as the hands, hips, shoulders, feet, spine, and especially knees in millions of people worldwide. Some authors have shown that Curcuma longa components may exhibit benefic effects in the treatment of degenerative diseases as OA. This plant belongs to the family Zingiberaceae and it is popularly known as turmeric or saffron. This review intended to perform a retrospective search to identify studies involving humans and animal models. This review was based on articles linking OA and C. longa. Databases as Medline, Science Direct, and Lilacs were consulted and a retrospective search was carried out in order to identify studies involving humans and animal models. The curcuminoids from C. longa exhibit actions at different locations in the pathogenesis of OA once it may play an important role as anti-inflammatory, down-regulating enzymes as phospholipase A2, cyclooxygenase-2, and lipoxygenases, and reducing tumor necrosis factor-alpha-and interleukins such as interleukin-1β (IL-1β), IL-6, and IL-8. They also act as inducer of apoptosis in synoviocytes, decreasing the inflammation process and may also reduce the synthesis of reactive oxygen species. For these reasons, new pharmaceutical technology and pharmacological studies should be proposed to determine the dose, the best delivery vehicle, pharmaceutical formulation and route of administration of this plant so its use as an adjunct in the treatment of OA may become a reality in clinical practice.

Key words: Curcuma longa, curcumin, inflammation, osteoarthritis

INTRODUCTION

Osteoarthritis (OA) is a chronic inflammatory degenerative disease that affects the joints of the body in millions of people worldwide.1‑3 The number of people affected by this pathology increases with age, and can reach several joints such as the hands, hips, shoulders, feet, spine, and especially knees, resulting in inflammation and pain.4‑6 OA has no cure and the conventional treatment is restricted primarily to the use of nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroid injections, and analgesics. However, therapy with NSAIDs and analgesics such as acetaminophen can lead to adverse effects as gastrointestinal and cardiovascular problems, especially if it is used for long periods. This situation shows the need for new agents that treat pain and reduce the progression of the disease.1,2,5

C. longa is a plant belonging to Zingiberaceae family and it is popularly known as turmeric or saffron.6‑8 Its therapeutic potential has been widely studied for the treatment of several diseases including cancer, HIV, and Alzheimer’s.9‑11 Several studies suggest that it may also exhibit hypcholesterolemice, anti-apoptotic, neuroprotective, anti-inflammatory, and anti-proliferative effects6,9,11‑14 and some authors have shown that C. longa components may exhibit benefic effects in the treatment of degenerative diseases as OA.2‑5

Due to the difficulties in the conventional treatment of OA, the aim of this review was to survey up the effects of C. longa in this inflammatory condition.

METHODS

This survey was based on articles linking OA and C. longa. Databases as Medline, Science Direct, and Lilacs were consulted and a retrospective search was carried out in order to identify studies involving humans and animal models.

CURCUMA LONGA

The C. longa is commonly used in cooking (the rhizome) as a seasoning and in traditional medicine in Asia and India.16,17 It possesses three main components named curcumin, demethoxycurcumin, and bisdemethoxycurcumin, that are curcuminoids known to produce different medicinal properties and therefore have been widely studied.15,18,19 The curcumin is a natural polyphenolic compound of low toxicity and is considered the main compound of the rhizome.20‑22 Thanks to its different pharmacological actions, curcumin and its analogs have been employed in different studies involving several pathologies such as cardiovascular and ophthalmic diseases, diabetes, depression, HIV, vitiligo, Alzheimer’s disease, endometriosis, osteoporosis, inflammatory bowel disease, epilepsy, Parkinson’s disease, and cancer [Figure 1].8,10,12,13,20‑30

Its pharmacological actions occur by different mechanisms in different cells.21 Among the various pathways, the curcumin can reduce inflammation due to its capacity of decreasing the production of interleukin-1 (IL-1), IL-6, IL-8, IL-12 and tumor necrosis factor-alpha...

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(TNF-α), inhibiting the activation of nuclear factor kappa-B (NF-κB) and declining the synthesis of reactive oxygen species.\textsuperscript{[13,16,22]}  
Due to its pharmacological potential, several authors point out a feature of curcumin and also bisdemethoxycurcumin that could jeopardize its use: They are highly hydrophobic. Molecules with this characteristic have a low oral bioavailability.\textsuperscript{[19]} Therefore, to improve this property of curcumin and bisdemethoxycurcumin, researchers have used delivery systems, including nanoparticles, micelles, liposomes, and phospholipid complexes.\textsuperscript{[22,31]} Szymusiak \textit{et al}.\textsuperscript{[19]} showed that when the curcumin is formulated in stable polymeric nanoparticles it is necessary to use a dose 20 times lower to achieve the same plasma concentration.  
There are numerous reports in the literature indicating that curcuminoids and its analogs can have positive effects on OA.

**PATHOPHYSIOLOGY OF OSTEOARTHRITIS**

Commonly, the chondrocytes possess an equilibrium among the production and degradation of extracellular matrix such as Type II collagen and aggrecan, which are the main proteoglycan in the articular cartilage.\textsuperscript{[32]}  
OA occurs due to multiple factors, which include genetic and environmental factors.\textsuperscript{[16,34]} The pathophysiology of OA is not completely understood but it is believed that different pathways could lead to the disease. The pathogenesis involves processes as oxidative stress and inflammation, osteoclastogenesis and proteolytic degradation of cartilage.\textsuperscript{[11,35-37]} Figures 2 and 3 show some aspects involved in OA.

Osteoclasts are derived from hematopoietic cells that also originate macrophages and monocytes. The Receptor Activator NF-κB Ligand (RANKL) is produced by osteoblasts, stromal cells, and chondrocytes. After RANK biding to RANKL in the membrane of osteoclasts precursor cells, there is activation of I Kappa B Kinase (IKK), phosphorylation, and degradation of I Kappa B alpha (IkBα); thus, the Activator of NF-κB is activated. Then, these precursor cells differentiate into osteoclasts, which are activated by starting the osteoclastogenesis.\textsuperscript{[11,35,36,39]}

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**Figure 1:** *Curcuma longa* compounds may positively influence several pathologies

**Figure 2:** In the Osteoarthritis it is possible to observe a disruption in the matrix homeostasis and consequent loss of cartilage, expansion of chondrocytes leading to increase in the release of pro-inflammatory cytokines and increase in the production of reactive oxygen species. This scenario is related to the breakdown of matrix components and cell apoptosis resulting in pain and physical disability. Modified from Lee \textit{et al}.\textsuperscript{[32]}
To prevent the activation of osteoclasts, the osteoprotegerin (OPG), also produced by osteoblasts acts as a “decoy receptor” and binds to RANKL, thereby preventing RANKL binding to RANK, and thus avoids the osteoclastogenesis. The OPG also has a role in inducing apoptosis of mature osteoclasts. Thus, the RANKL/OPG ratio is a good index to analyze the occurrence of osteogenesis or osteoclastogenesis. When there is an increase in RANKL/OPG ratio there is predominance of bone destruction, and when there is a decrease of this index, there is protection of subchondral bones.[38-41] In OA, various interleukins and cytokines such as IL-1β, IL-6, IL-11, IL-17, and TNF-α lead to increased formation of RANKL and decreased production of OPG resulting in bone lost.[38-41] In addition, cathepsin K, importantly expressed in mature osteoclasts, is the main agent in osteoclastogenesis and degrades type II collagen, thus destroying cartilage.[11,44] Portions of collagen cleaved by this protease can be labeled in OA as demonstrated by the study of Mort et al.[45] Kozawa et al.[46] showed that people who do not have the disease have lowered expression and expression of cathepsin K when compared to cartilage of patients with OA.

Furthermore, in the OA process are involved proteases degrading enzymes such as matrix metalloproteinases (MMPs) MMP-3, MMP-9, MMP-13, tartrate-resistant acid phosphatase (TRAP), a disintegrin, and metalloproteinase with thrombospondin Motifs (ADAMTS). IL-1 acts on chondrocytes β, resulting in the induction of NF-kB and activator protein 1 (AP-1) and the production of MMPs, enzymes that breakdown collagen.[13,46] Among the metalloproteinase, MMP-13 is most potent in cleavage of type II collagen. The ADAMTS acts in cleaving aggrecan molecules (another component of cartilage). In OA these proteases are increased, leading to an abnormal destruction of cartilage.[11,44,46] IL-6 also acts on chondrocyte decreasing the production of type II collagen.[38,48] Probably TNF-α acts in synergy with these interleukins in the inhibition of proteoglycan synthesis and increasing cartilage resorption.[49,50]

Authors believe that this environment full of inflammatory cytokines and proteases leads to death of chondrocytes and synoviocytes stimulation, which secrete inflammatory cytokines and recruitment of mononuclear and polymorphonuclear factors generating more cartilage destruction.[11,33]

Furthermore, various substances such as IL-1β, IL-6, IL-11, IL-17, prostaglandin-2 (PGE-2), TNF-α and the presence of reactive oxygen and nitrogen species were related to the pathogenesis of the disease.[11,37,46,47]

Figure 4 resumes the modification of osteoblasts and production of pro-inflammatory cytokines released in the synovial liquid.

**CURCUMA LONGA AND OSTEOARTHRITIS**

The curcuminoids seem to act at different locations in the pathogenesis of OA. The curcumin inhibits RANKL-induced osteoclastogenesis and TNF-α.[11,13,30] Bharti et al.[38] showed that macrophage cell line RAW 264.7 stimulated in vitro with RANKL and curcumin formed osteoclasts less than when stimulated only in the presence of RANKL. Moreover, according to studies by Yeh et al.[11] these macrophages when incubated with curcumin or bisdemethoxycurcumin loaded liposomes (Cur-Lip or BDMC-Lip) with RANKL become smaller and with a reduced number of nuclei when compared to the cells with only the presence of RANKL and LPS. These findings support the effects of curcuminoids on the osteoclastogenesis.

Authors believe that the effects of curcumin on osteoclastogenesis occurs early in the signaling because its effects are greatly reduced when added 2 days after RANKL and it is maximum if it is added 2 h before or concomitantly with RANKL. An agent that can inhibit the action of RANKL can suppress bone destruction.[38]

The curcumin inhibits the signaling that occurs through NF-kB. With the stop in the activation of IKK, there is no phosphorylation and degradation of IκB, without consequently activation of NF-kB. Furthermore, it acts by reducing the activation of NF-kB by inflammatory cytokines.[38] Moreover, as demonstrated by Yeh et al.[11] the inhibition of the expression of TRAP and cathepsin K leads to decrease of TRAP activity and consequent suppression of osteoclastogenesis. When using these curcuminoids, the OPG/RANKL rate increases, suggesting bone development. In addition to the inhibition of osteoclastogenesis, curcumin may also inhibit the pit formation.[38]

Besides decreasing bone degradation, curcumin has chondroprotective effects once it is able to inhibit the production of MMP-1, MMP-3, MMP-9, MMP-13 by inhibiting the AP-1 pathway, the NF-kB and Jun N-terminal kinase.[11,13,14] Studies conducted by Yeh et al.[11] showed that levels of MMP-1 mRNA, MMP-3, and MMP-13 in human chondrocytes receiving curcumin for 6 h were decreased compared with the control group, showing the reduction of the metalloproteinases synthesis caused by curcumin. Curcumin also restart the production of type II collagen and glycosaminoglycan and has anti-apoptotic effect on chondrocytes (inhibits caspase-3 activation).[11,33,34] Another effect is the inhibition of expression of ADAM-5. Aggrecanase-mediated aggrecan degradation is a relevant situation that occurs in early-stage OA. Aggrecanases...
There is presence of mild adverse effects. There are no conflicts of interest.

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Curcuma longa and Osteoarthritis

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