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REVIEW ARTICLE

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.[1,2] 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.[1,3,4] 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 hypocholesterolemic, anti-apoptotic, neuroprotective, anti-inflammatory, and anti-proliferative effects[6,9,11-16] and some authors have shown that *C. longa* components may exhibit benefic effects in the treatment of degenerative diseases as OA.[2-5]

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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.[7,18,19] 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].[8-10,21,23-30]

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-κβ) and declining the synthesis of reactive oxygen species.[13,18,22]

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 has a low oral bioavailability.[19] Therefore, to improve this property of curcumin and bisdemethoxycurcumin, researchers have used delivery systems, including nanoparticles, micelles, liposomes, and phospholipid complexes.[22,31] Szymusiak *et al.*[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.[32]

OA occurs due to multiple factors, which include genetic and environmental factors.[33,34] 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.[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-kβ 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-kB is activated. Then, these precursor cells differentiate into osteoclasts, which are activated by starting the osteoclastogenesis.[11,35,36,38,39]

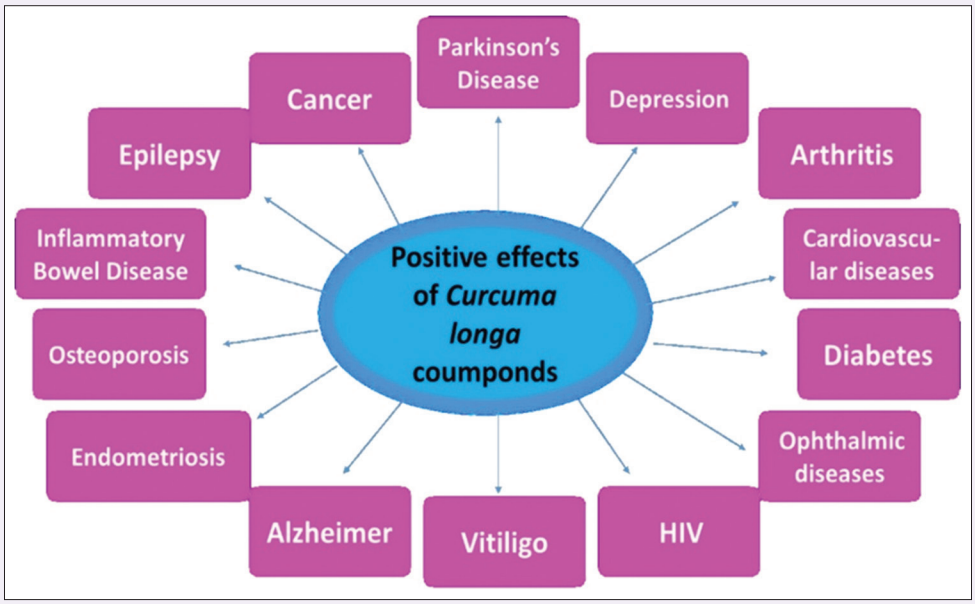

Figure 1: *Curcuma longa* compounds may positively influence several pathologies

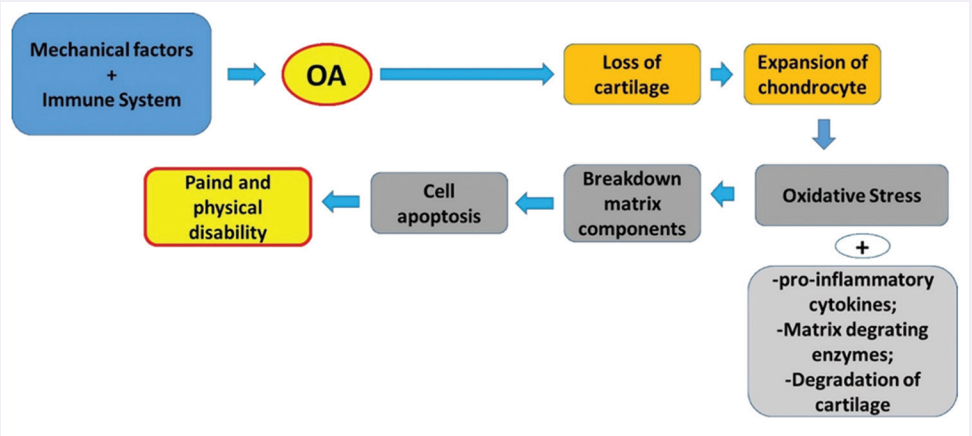

Figure 2: In the Osteoarthritis it is possible to observe a disruption in the matrix homeostasis and consequent loss of cartilage, expansion of chondrocytes leading to increase in the release of pro-inflammatory cytokines and increase in the production of reactive oxygen species. This scenario is related to the breakdown of matrix components and cell apoptosis resulting in pain and physical disability. Modified from Lee *et al.*[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.[11,40-42] 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.[11,43,44] Portions of collagen cleaved by this protease can be labeled in OA as demonstrated by the study of Mort *et al.*[43] Kozawa *et al.*[45] showed that people who do not have the disease have a lower activation 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.[15,46] Among the metalloproteinase, MMP-13 is more 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[11,40,46,47] IL-6 also acts on chondrocyte decreasing the production of type II collagen.[33,48] 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.[15,33]

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.[11,13,39] 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 IkBα, 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.[1,11,15] 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).[1,15,51] Another effect is the inhibition of expression of ADAMT-5. Aggrecanase-mediated aggrecan degradation is a relevant situation that occurs in early-stage OA. Aggrecanases

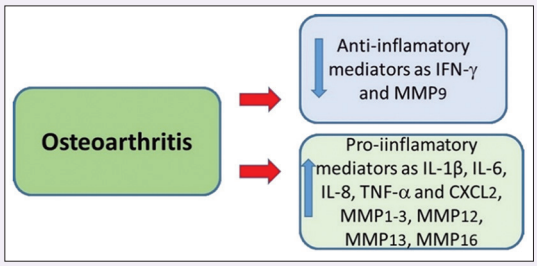

Figure 3: Osteoarthritis is related to the decrease of anti-inflammatory (as IFN-γ and MMP9) and increase in pro-inflammatory mediators (as MMP1-3, MMP 12, MMP 13, MMP 16; TNF-α, IL-1β, IL 6, IL-8 and CXCL2). MMP = Matrix metalloproteinase, IL = Interleukin, TNF-α = Tumor necrosis factor, CXCL = Chemokine (C-X-C motif) ligand, INF-γ = Interferon gamma. Modified from Wang *et al.*[37]

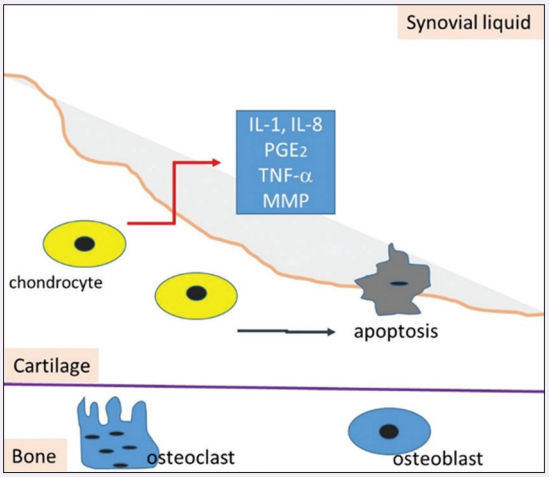

Figure 4: Scheme showing the production of pro-inflammatory cytokines as IL-1, IL-8, PGE-2, TNF-α and MMP by aberrantly activated chondrocytes in synovial liquid. In osteoarthritic state, the production of these mediators and catabolic growth factors as PGE-2 induces the catabolic effects. Apoptosis also occur resulting in cartilage loss. IL = Interleukin, PGE-2 = Prostaglandin 2, TNF-α = Tumor necrosis factor, MMP = Matrix metalloproteinases (Modified from Lee *et al.*, 2013)[32]

Table 1: Biological effects of *Curcuma* sp.

Compound	Effects	Other comments
Curcuma coumpounds[53]	Improvement in OA-related endpoints	Similar results to NSAIDs and glucosamine
Phenolic compounds of *C. aromatica*[54]	Antioxidant activity in cell based model (RAW264.7 cell)	Avoids evolution of articular destruction by anti-inflammatory effect
Curcuminoids (HM)[55]	Increase of SOD, decrease of GSH and MDA concentrations	Reduction of oxidative stress in patients with OA
C. domestica extracts HM[52]	Improvement in WOMAC pain and WOMAC function scores	Similar effects ibuprofen treatment with less abdominal adverse effects
Curcuma extract (flexofylol®) (HM)[56]	Pain reliever, stiffness and quality of life	Conflict of interest involved
C. longa extracts (HM)[57]	Improvement in pain, walking distance, joint line tenderness and crepitus	Improvement in symptoms scoring and clinical examination, with no adverse effects (more successful than celecoxib)
Polysaccharide rich *C. longa* extract (HM)[57,58]	Decrease pain and improve function of the affected knee	Reduce in the utilization of rescue medications
RA-11, Ayurvedic drug composed by plants and *C. longa* (HM)[59]	Decrease in pain and improvement in WOMAC scores	There is presence of mild adverse effects
Curcuminoid from *C. domestica* (HM)[60]	Decrease the secretion of COX-2 by synovial monocytes	Effective as diclofenac sodium in reducing COX-2

HM=Human model, OA=Osteoarthritis, SOD=Superoxide dismutase, GSH=Glutathione, MDA=Malonaldehyde, WOMAC=Western Ontario and McMaster Universities Osteoarthritis Index, COX-2=Cyclooxygenase-2 enzyme, *C. domestica*=*Curcuma domestica*, *C. longa*=*Curcuma longa*, *C. aromatica*=*Curcuma aromatic*, NSAIDs=Nonsteroidal anti-inflammatory drugs

belonging to the metalloproteinase and disintegrin with ADAMTS family of proteinases play a significant role in aggrecan depletion in osteoarthritic cartilage and increased expression of CITED2 gene (Cbp/P300 Interacting Trans-activator With Glu/Asp Rich Carboxy-Terminal Domain 2), that appears to be involved with inhibition of the activity of NF-κB.[11]

The curcumin also play anti-inflammatory role. Several studies showed its action down-regulating phospholipase A2, cyclooxygenase-2, lipoxygenases, PGEs and reducing TNFα-and interleukins such as IL-1β, IL-6, and IL-8.[11,15,51,52] It also acts as inducer of apoptosis in synoviocytes decreasing the inflammation process. This compound may reduce the synthesis of reactive oxygen species and nitrogen *in vitro*, but further studies are necessary to find out if it could help to slow the progression of the disease or in the pain.[11,15]

Other effects of this plant in OA may be found in Table 1.

Chandrasekaran *et al.*[61] and Madhu *et al.*[58] studied the effects of an aqueous based extract of *C. longa* (devoid curcuminoids, standardized to polysaccharides) and found it may act as anti-inflammatory and may modulate immune-stimulatory properties. These properties showed important effects in primary painful knee and joint pain.

CONCLUSION

C. longa is a plant with promising pharmacological properties in various diseases due to its multiple action. The study of curcumin and its derivatives in cells, animals and humans models have confirmed their benefit in the use of OA. Studies show that in addition to the improvement in the symptomatology of the patients with OA, there may be a slowing progression of the disease by reducing inflammation and cartilage and bone destruction.

For these reasons, new pharmaceutical technology and pharmacological studies should be proposed in order 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.

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Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Yimam M, Lee YC, Jiao P, Hong M, Nam JB, Brownell L, *et al.* UP1306, a botanical composition with analgesic and anti-inflammatory effect. Pharmacognosy Res 2016;8:186-92.
2. Nakagawa Y, Mukai S, Yamada S, Matsuoka M, Tarumi E, Hashimoto T, *et al.* Short-term effects of highly-bioavailable curcumin for treating knee osteoarthritis: A randomized, double-blind, placebo-controlled prospective study. J Orthop Sci 2014;19:933-9.
3. Guo JJ, Wu K, Guan H, Zhang L, Ji C, Yang H, *et al.* Three-year follow-up of conservative treatments of shoulder osteoarthritis in older patients. Orthopedics 2016;39:e634-41.
4. Peters MJ, Ramos YF, den Hollander W, Schiphof D, Hofman A, Uitterlinden AG, *et al.* Associations between joint effusion in the knee and gene expression levels in the circulation: A meta-analysis. F1000Res 2016;5:109.
5. Scarpignato C, Lanas A, Blandizzi C, Lems WF, Hermann M, Hunt RH; International NSAID Consensus Group. Safe prescribing of non-steroidal anti-inflammatory drugs in patients with osteoarthritis – An expert consensus addressing benefits as well as gastrointestinal and cardiovascular risks. BMC Med 2015;13:55.
6. Maithilikarpagaselvi N, Sridhar MG, Swaminathan RP, Sripradha R, Badhe B. Curcumin inhibits hyperlipidemia and hepatic fat accumulation in high-fructose-fed male Wistar rats. Pharm Biol 2016;54:2857-63.
7. Yadav SK, Sah AK, Jha RK, Sah P, Shah DK. Turmeric (curcumin) remedies gastroprotective action. Pharmacogn Rev 2013;7:42-6.
8. Mirzabeigi P, Mohammadpour AH, Salarifar M, Gholami K, Mojtahedzadeh M, Javadi MR. The effect of curcumin on some of traditional and non-traditional cardiovascular risk factors: A pilot randomized, double-blind, placebo-controlled trial. Iran J Pharm Res 2015;14:479-86.
9. Devi VK, Jain N, Valli KS. Importance of novel drug delivery systems in herbal medicines. Pharmacogn Rev 2010;4:27-31.
10. Ali A, Banerjea AC. Curcumin inhibits HIV-1 by promoting Tat protein degradation. Sci Rep 2016;6:27539.
11. Yeh CC, Su YH, Lin YJ, Chen PJ, Shi CS, Chen CN, *et al.* Evaluation of the protective effects of curcuminoid (curcumin and bisdemethoxycurcumin)-loaded liposomes against bone turnover in a cell-based model of osteoarthritis. Drug Des Devel Ther 2015;9:2285-300.
12. Doshi GM, Une HD, Shanbhag PP. Rasayans and non-rasayans herbs: Future immunodrug – Targets. Pharmacogn Rev 2013;7:92-6.
13. Aggarwal BB, Gupta SC, Sung B. Curcumin: An orally bioavailable blocker of TNF and other pro-inflammatory biomarkers. Br J Pharmacol 2013;169:1672-92.
14. Shehzad A, Rehman G, Lee YS. Curcumin in inflammatory diseases. Biofactors 2013;39:69-77.

15. Henrotin Y, Clutterbuck AL, Allaway D, Lodwig EM, Harris P, Mathy-Hartert M, *et al.* Biological actions of curcumin on articular chondrocytes. Osteoarthritis Cartilage 2010;18:141-9.
16. Mauren FM, Yanti, Lay BW. Efficacy of oral curcuminoid fraction from *Curcuma xanthorrhiza* and curcuminoid cider in high-cholesterol fed rats. Pharmacognosy Res 2016;8:153-9.
17. Lee JJ, Lee JH, Cho WK, Han JH, Ma JY. Herbal composition of *Cinnamomum cassia*, *Pinus densiflora*, *Curcuma longa* and *Glycyrrhiza glabra* prevents atherosclerosis by upregulating p27 (Kip1) expression. BMC Complement Altern Med 2016;16:253.
18. Aggarwal BB, Harikumar KB. Potential therapeutic effects of curcumin, the anti-inflammatory agent, against neurodegenerative, cardiovascular, pulmonary, metabolic, autoimmune and neoplastic diseases. Int J Biochem Cell Biol 2009;41:40-59.
19. Szymusiak M, Hu X, Leon Plata PA, Ciupinski P, Wang ZJ, Liu Y. Bioavailability of curcumin and curcumin glucuronide in the central nervous system of mice after oral delivery of nano-curcumin. Int J Pharm 2016;511:415-23.
20. Martinez-Cifuentes M, Weiss-Lopez B, Santos LS, Araya-Maturana R. Heterocyclic curcumin derivatives of pharmacological interest: Recent progress. Curr Top Med Chem 2015;15:1663-72.
21. Pescosolido N, Giannotti R, Plateroti AM, Pascarella A, Nebbioso M. Curcumin: Therapeutical potential in ophthalmology. Planta Med 2014;80:249-54.
22. Zamarioli CM, Martins RM, Carvalho EC, Freitas Luis AP. Nanoparticles containing curcuminoids (*Curcuma longa*): Development of topical delivery formulation. Rev Bras Farmacognosia 2015;25:53-60.
23. Kumar B, Singh V, Shankar R, Kumar K, Rawal RK. Synthetic and medicinal prospective of structurally modified curcumins. Curr Top Med Chem 2017;17:148-61.
24. Kaufmann FN, Gazal M, Bastos CR, Kaster MP, Ghisleni G. Curcumin in depressive disorders: An overview of potential mechanisms, preclinical and clinical findings. Eur J Pharmacol 2016;784:192-8.
25. Zhang Y, Cao H, Yu Z, Peng HY, Zhang CJ. Curcumin inhibits endometriosis endometrial cells by reducing estradiol production. Iran J Reprod Med 2013;11:415-22.
26. Kaur H, Patro I, Tikoo K, Sandhir R. Curcumin attenuates inflammatory response and cognitive deficits in experimental model of chronic epilepsy. Neurochem Int 2015;89:40-50.
27. Penagini F, Dilillo D, Borsani B, Cococcioni L, Galli E, Bedogni G, *et al.* Nutrition in pediatric inflammatory bowel disease: From etiology to treatment. A systematic review. Nutrients 2016;8. pii: E334.
28. Chen Z, Xue J, Shen T, Mu S, Fu Q. Curcumin alleviates glucocorticoid-induced osteoporosis through the regulation of the Wnt signaling pathway. Int J Mol Med 2016;37:329-38.
29. Pandareesh MD, Shrivash MK, Naveen Kumar HN, Misra K, Srinivas Bharath MM. Curcumin monoglucoside shows improved bioavailability and mitigates rotenone induced neurotoxicity in cell and drosophila models of Parkinson's disease. Neurochem Res 2016;41:3113-28.
30. Vaughn AR, Branum A, Sivamani RK. Effects of turmeric (*Curcuma longa*) on skin health: A systematic review of the clinical evidence. Phytother Res 2016;30:1243-64.
31. Mirzaei H, Naseri G, Rezaee R, Mohammadi M, Banikazemi Z, Mirzaei HR, *et al.* Curcumin: A new candidate for melanoma therapy? Int J Cancer 2016;139:1683-95.
32. Lee AS, Ellman MB, Yan D, Kroin JS, Cole BJ, van Wijnen AJ, *et al.* A current review of molecular mechanisms regarding osteoarthritis and pain. Gene 2013;527:440-7.
33. Limagne E, Lançon A, Delmas D, Cherkaoui-Malki M, Latruffe N. Resveratrol Interferes with IL1-ß-induced pro-inflammatory paracrine interaction between primary chondrocytes and macrophages. Nutrients 2016;8. pii: E280.
34. Reynard LN. Analysis of genetics and DNA methylation in osteoarthritis: What have we learnt about the disease? Semin Cell Dev Biol 2016. pii: S1084-952130121-5.
35. TenBroek EM, Yunker L, Nies MF, Bendele AM. Randomized controlled studies on the efficacy of antiarthritic agents in inhibiting cartilage degeneration and pain associated with progression of osteoarthritis in the rat. Arthritis Res Ther 2016;18:24.
36. Tamma R, Zallone A. Osteoblast and osteoclast crosstalks: From OAF to Ephrin. Inflamm Allergy Drug Targets 2012;11:196-200.
37. Wang P, Guan PP, Guo C, Zhu F, Konstantopoulos K, Wang ZY. Fluid shear stress-induced osteoarthritis: Roles of cyclooxygenase-2 and its metabolic products in inducing the expression of proinflammatory cytokines and matrix metalloproteinases. FASEB J 2013;27:4664-77.
38. Bharti AC, Takada Y, Aggarwal BB. Curcumin (diferuloylmethane) inhibits receptor activator of NF-kappa B ligand-induced NF-kappa B activation in osteoclast precursors and suppresses osteoclastogenesis. J Immunol 2004;172:5940-7.
39. Wei S, Teitelbaum SL, Wang MW, Ross FP. Receptor activator of nuclear factor-kappa b ligand activates nuclear factor-kappa b in osteoclast precursors. Endocrinology 2001;142:1290-5.
40. Liu YD, Yang HX, Liao LF, Jiao K, Zhang HY, Lu L, *et al.* Systemic administration of strontium or NBD peptide ameliorates early stage cartilage degradation of mouse mandibular condyles. Osteoarthritis Cartilage 2016;24:178-87.
41. Xu L, Guo H, Li C, Xu J, Fang W, Long X. A time-dependent degeneration manner of condyle in rat CFA-induced inflamed TMJ. Am J Transl Res 2016;8:556-67.
42. Chen S, Huang Y, Chen W, Wu G, Liao N, Li X, *et al.* Protective effects of the Tougu Xiaotong capsule on morphology and osteoprotegerin/nuclear factor-κB ligand expression in rabbits with knee osteoarthritis. Mol Med Rep 2016;13:419-25.
43. Mort JS, Beaudry F, Théroux K, Emmott AA, Richard H, Fisher WD, *et al.* Early cathepsin K degradation of type II collagen *in vitro* and *in vivo* in articular cartilage. Osteoarthritis Cartilage 2016;24:1461-9.
44. Troen BR. Molecular mechanisms underlying osteoclast formation and activation. Exp Gerontol 2003;38:605-14.
45. Kozawa E, Cheng XW, Urakawa H, Arai E, Yamada Y, Kitamura S, *et al.* Increased expression and activation of cathepsin K in human osteoarthritic cartilage and synovial tissues. J Orthop Res 2016;34:127-34.
46. Wojdasiewicz P, Poniatowski LA, Szukiewicz D. The role of inflammatory and anti-inflammatory cytokines in the pathogenesis of osteoarthritis. Mediators Inflamm 2014;2014:561459.
47. Zhang Z, Leong DJ, Xu L, He Z, Wang A, Navati M, *et al.* Curcumin slows osteoarthritis progression and relieves osteoarthritis-associated pain symptoms in a post-traumatic osteoarthritis mouse model. Arthritis Res Ther 2016;18:128.
48. Porée B, Kypriotou M, Chadjichristos C, Beauchef G, Renard E, Legendre F, *et al.* Interleukin-6 (IL-6) and/or soluble IL-6 receptor down-regulation of human type II collagen gene expression in articular chondrocytes requires a decrease of Sp1.Sp3 ratio and of the binding activity of both factors to the COL2A1 promoter. J Biol Chem 2008;283:4850-65.
49. Saklatvala J. Tumour necrosis factor alpha stimulates resorption and inhibits synthesis of proteoglycan in cartilage. Nature 1986;322:547-9.
50. Séguin CA, Bernier SM. TNFalpha suppresses link protein and type II collagen expression in chondrocytes: Role of MEK1/2 and NF-kappaB signaling pathways. J Cell Physiol 2003;197:356-69.
51. Buhrmann C, Mobasheri A, Matis U, Shakibaei M. Curcumin mediated suppression of nuclear factor-κB promotes chondrogenic differentiation of mesenchymal stem cells in a high-density co-culture microenvironment. Arthritis Res Ther 2010;12:R127.
52. Kuptniratsaikul V, Dajpratham P, Taechaarpornkul W, Buntragulpoontawee M, Lukkanapichonchut P, Chootip C, *et al.* Efficacy and safety of *Curcuma* domestica extracts compared with ibuprofen in patients with knee osteoarthritis: A multicenter study. Clin Interv Aging 2014;9:451-8.
53. Perkins K, Sahy W, Beckett RD. Efficacy of *Curcuma* for treatment of osteoarthritis. J Evid Based Complementary Altern Med 2017;22:156-65.
54. Anuthakoengkun A, Itharat A. Inhibitory effect on nitric oxide production and free radical scavenging activity of Thai medicinal plants in osteoarthritic knee treatment. J Med Assoc Thai 2014;97 Suppl 8:S116-24.
55. Panahi Y, Alishiri GH, Parvin S, Sahebkar A. Mitigation of systemic oxidative stress by curcuminoids in osteoarthritis: Results of a randomized controlled trial. J Diet Suppl 2016;13:209-20.
56. Appelboom T, Maes N, Albert A. A new *Curcuma* extract (flexofytol®) in osteoarthritis: Results from a belgian real-life experience. Open Rheumatol J 2014;8:77-81.
57. Kizhakkedath R. Clinical evaluation of a formulation containing *Curcuma longa* and *Boswellia serrata* extracts in the management of knee osteoarthritis. Mol Med Rep 2013;8:1542-8.
58. Madhu K, Chanda K, Saji MJ. Safety and efficacy of *Curcuma longa* extract in the treatment of painful knee osteoarthritis: A randomized placebo-controlled trial. Inflammopharmacology 2013;21:129-36.
59. Kertia N, Asdie AH, Rochmah W, Marsetyawan. Ability of curcuminoid compared to diclofenac sodium in reducing the secretion of cycloxygenase-2 enzyme by synovial fluid's monocytes of patients with osteoarthritis. Acta Med Indones 2012;44:105-13.
60. Chopra A, Lavin P, Patwardhan B, Chitre D. A 32-week randomized, placebo-controlled clinical evaluation of RA-11, an Ayurvedic drug, on osteoarthritis of the knees. J Clin Rheumatol 2004;10:236-45.
61. Chandrasekaran CV, Sundarajan K, Edwin JR, Gururaja GM, Mundkinajeddu D, Agarwal A. Immune-stimulatory and anti-inflammatory activities of *Curcuma longa* extract and its polysaccharide fraction. Pharmacognosy Res 2013;5:71-9.