Chapter 3

Alternative Therapeutic Approach for Cartilage Repair

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Additional information is available at the end of the chapter

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Abstract

The cartilage is a flexible tissue, which supports the adjacent soft tissues. The damages that cause degenerative articular diseases are marked by the increase of cytokines such as tumor necrosis factor-α (TNF-α), IL-1β, IL-6, IL-18, and IL-17, which cause intense inflammatory process and release of metalloproteinases and disintegrin enzymes that lead to cartilage degradation. The *Curcuma longa* possesses bioactive compounds designated as curcuminoids that display therapeutic potential in several pathologies. Curcumin is one of these compounds that may exhibit anti-inflammatory, antioxidant, antiviral, antibacterial, and antitumor effects. It may promote decrease of IL-1β, IL-6, IL-8, TNF-α, COX-2, and reactive oxygen species. Furthermore, curcumin inhibits the activity of several kinases related to the degradation of the cartilage, including tyrosine kinase, p21-activated kinase, mitogen-activated protein kinase, protein kinase C, the activator protein 1 pathway, and NF-κB leading to the suppression of the production of metalloproteinases and inflammatory cytokines. Curcumin has also been related to the stimulation of the production of type II collagen and glycosaminoglycan by chondrocytes. Studies have shown that this compound may alleviate joint pain and crepitation, reduce the use of other drugs for pain relief, stimulate the production of type II collagen and glycosaminoglycan resulting in a protective and anti-inflammatory action of cartilage and bones, and improve the quality of life of the patients.

Keywords: cartilage, inflammation, *Curcuma longa*, curcumin

1. Introduction

The articular cartilage is a flexible tissue, which supports the adjacent soft tissues and possesses the extracellular matrix (ECM), collagen, chondrocyte, proteoglycans, and water [1]. This tissue is alymphatic, avascular, and aneural, and for these reasons, when a severe damage occurs, the self-repair is a highly difficult process [2–4].

The damages that cause degenerative articular diseases are marked by the increase of cytokines that cause intense inflammatory process and enzymes that cause cartilage degradation [5, 6].

The osteoarthritis (OA) is an example of a progressive degenerative disease characterized by a chronic inflammatory process, joint pain, and loss of function and injury of adjacent tissue. The great destruction of the articular cartilage is the main characteristic of this disease [7–9], and therefore, it is used, in this chapter, as a prototype of cartilage destruction and regeneration.

Drugs such as nonsteroidal anti-inflammatory drugs (NSAIDS) and acetaminophen are the therapeutic approaches for the pharmacological treatment of degenerative diseases. However, this kind of medications is associated with gastrointestinal, cardiovascular, and renal adverse effects and do not effectively inhibit the disease progression and destruction of cartilage [7, 8, 10, 11]. Furthermore, corticosteroids, another therapeutic option due to their potent anti-inflammatory action and ability to reduce symptoms, should also not be used for an extended period because they can lead to a more rapid progression of OA [12].

The development of therapeutic alternatives that do not cause adverse effects and inhibit the progression of the disease is urgent and, therefore, has been widely studied. *Curcuma longa*, herbal medicine, has been shown to be one of these possible alternatives because it presents significant benefits in degenerative diseases such as OA, and this plant may play a crucial role in the reduction of the inflammatory pathways [13].

2. Physiopathology and cartilage destruction

In healthy cartilage, chondrocytes can form ECM components and enzymes that degrade cartilage in equilibrium. Although the pathophysiology of OA and its triggers have not yet been fully elucidated, it is known that inflammation, joint destruction, synovitis, and osteoclastogenesis are involved [9].

In OA, there is an increase in the enzymes involved in the cartilage degradation such as disintegrin and metalloproteinase (MMP) with a thrombospondin motif (ADAMTS). This enzymatic increase occurs due to stimulation by interleukins (IL) and inflammatory mediators such as tumor necrosis factor-α (TNF-α), IL-1β, IL-6, IL-18, and IL-17 [6, 14].

The most widely studied and related to the destruction of cartilage are ADAMTS4 and ADAMTS5 that are released after stimulation of inflammatory cytokines such as IL-1β. They are aggrecanases and aggrecan aggregation of proteoglycans and one of the components of ECM. After degradation of aggrecans by these enzymes, MMP-3 acts in synergism in the degradation of proteoglycans [8, 15–17].

MMPs are enzymes implicated primarily in the destruction of type II collagen and therefore play a fundamental role in the destruction of cartilage. MMP-1, MMP-3, MMP-9, and MMP-13 are the most involved enzymes in this process, and the last one is not found in adult cartilage without OA. Fragments from cleavage of collagen type 2 by MMPs amplify the destruction of ECM and amplify the release of more MMPs [5–9].

Activated synoviocytes also produce inflammatory cytokines such as IL-1, IL-6, and TNF-α, which act by amplifying the inflammatory process and cartilaginous destruction. There is increased release of reactive oxygen species (ROS), mainly nitric oxide (NO), peroxynitrite ($ONOO^-$), and superoxide anion radicals ($O2^-$). Other inflammatory mediators such as cyclo-oxygenase-2 (COX-2), produced by synovial monocytes, and prostaglandins 2 (PGE2) are also involved in the pathophysiology of the disease [6, 15].

The nuclear factor-kappa B (NF-κβ) pathway is responsible for the production of various cytokines and induction of inflammation. When stimulated by interleukins IL-1β and TNF-α, there is activation of I kappa beta kinase (IKK), which promotes the phosphorylation of IKB-α. Thus, IKB-α is degraded by ubiquitination, and the dimers compounded by p50 and p65 reach the nucleus and can stimulate the expression of more than 400 genes, of which some are pro-inflammatory and pro-apoptotic genes [8, 18]. Therefore, there is production of various interleukins, including IL-1, IL-6, IL-8, and IL-10 [8, 15, 16].

Besides the destruction of cartilage in OA, an intense process of bone resorption occurs. This process is a result of osteoclast activation known as osteoclastogenesis [19]. The receptor activator NF-kappa ligand (RANKL) is produced by some cells as the osteoblast and has an affinity for RANK, which is present in the membrane of osteoclast precursor cells [20]. When RANKL binds to RANK, a phosphorylation process occurs, culminating in the activation of NF-kB [5, 21, 22]. The osteoprotegerin also has an affinity for RANK, thus competing with RANKL, inducing apoptosis of mature osteoclasts [5]. In the OA, the increase of RANKL and the decrease of OPG are observed [23, 24]. **Figure 1** summarizes the inflammatory process in the cartilage.

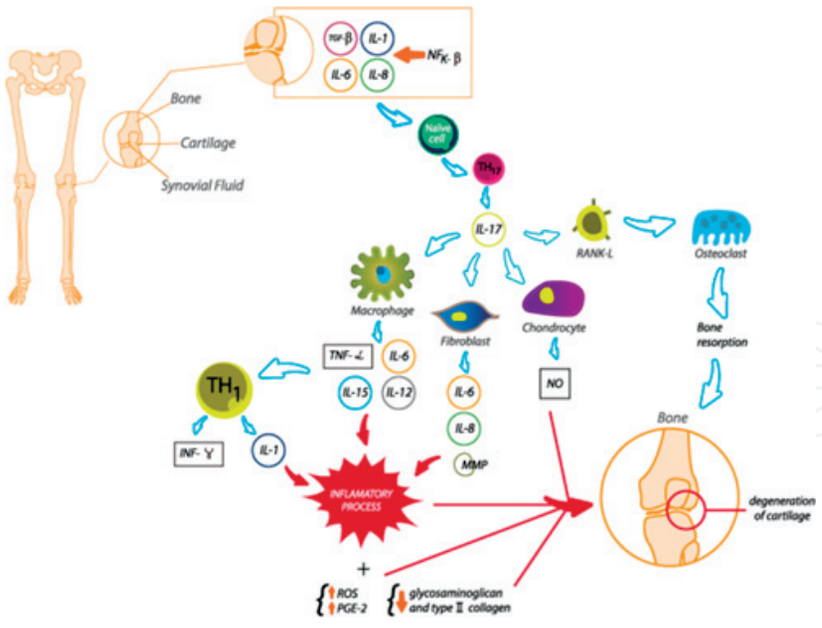

Figure 1. The activation of NF-kβ is related to the release of TGFβ, IL-1, IL-6, and IL-8 and further activation of TH17 that leads to the stimulation of several cells and expression of other inflammatory cytokines and metalloproteinases (MMP), and further development of features characteristic of inflammation and degradation of cartilage and bone. NF-kβ: nuclear factor kβ; IL: interleukin; TH17: T-helper 17; MMP: matrix metalloproteinase; RANKL: receptor activator of nuclear factor κB ligand; TH17: type 17 T-helper; TNF-α: tumor necrosis factor-α; TGF-β, transforming growth factor-β; ROS: reactive oxygen species; and NO: nitric oxide.

3. *Curcuma longa*

C. longa, or turmeric or saffron, is native to Asia and India and belongs to the Zingiberaceae family, and its rhizome has been used as a seasoning and in the traditional medicine since ancient times [18, 25].

The bioactive compounds derived from turmeric are called curcuminoids and have shown therapeutic potential in various pathologies. The three most important compounds originated from this rhizome are curcumin (diferuloylmethane), bisdemethoxycurcumin, and demethoxycurcumin, which are present, respectively, in concentrations of 77, 17, and 3%. Curcumin gives the typical yellowish coloration of the rhizome, and this part of the plant is the most widely studied [18, 26, 27].

Several studies have been conducted in order to show their actions *in vitro* and *in vivo*. Curcumin acts with different mechanisms and in different cell types and pathways. It shows anti-inflammatory, antioxidant, antiviral, antibacterial, and antitumor effects. Its therapeutic potential covers diseases such as cancer, Alzheimer's disease, osteoporosis, inflammatory bowel disease, depression, arthritis, diabetes, vitiligo, endometriosis, and several others. **Figure 2** shows some effects of curcumin [5, 28–30].

Studies on the action of curcumin and its analogs show that it can act directly or indirectly in the decrease of the formation of inflammatory molecules and pro-inflammatory transcription factors. Under its action, there is a reduction of IL-1β, IL-6, IL-8, TNF-α, NF-kB, COX-2, and reactive oxygen species (ROS). Apart from that, curcumin has been shown to inhibit the activity of several kinases related to the degradation of the cartilage, including a tyrosine

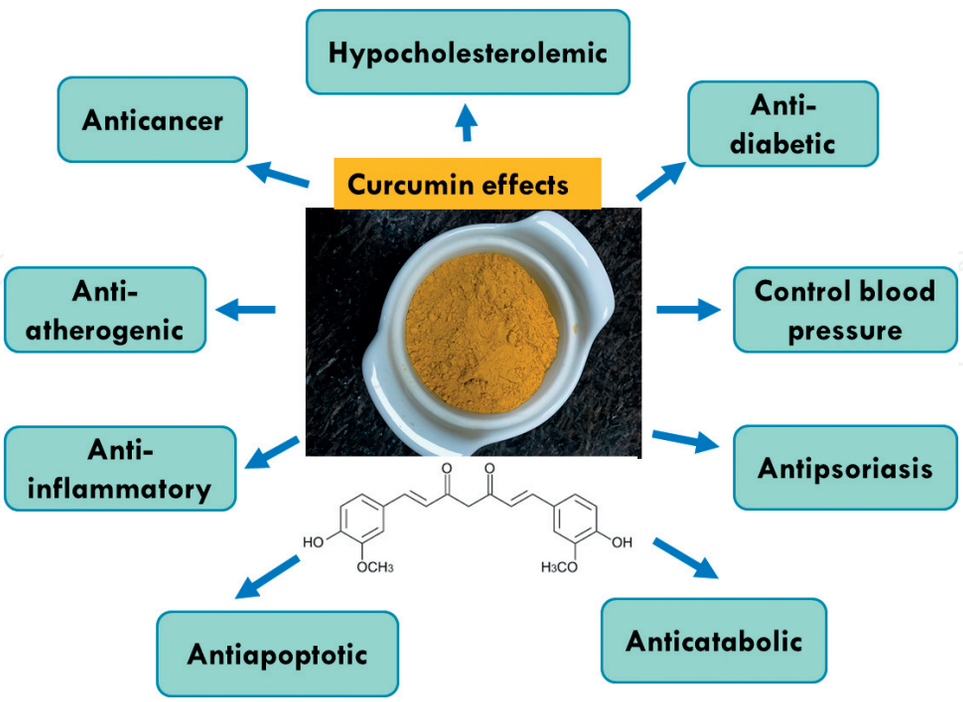

Figure 2. Some benefits of curcumin on human health.

kinase, p21-activated kinase 1 (PAK1), mitogen-activated protein kinase (MAPK), and protein kinase C (PKC). **Figure 3** shows the process of cartilage inflammation and the effects of curcumin in the healing process [29, 31, 32].

Many studies have shown that curcumin has potent effects on the induction of apoptosis and decreased tumor cell proliferation and may promote the inhibition of important angiogenesis regulators, signal transducers and activators of transcription 3 (STAT3), and vascular endothelial growth factor (VEGF). Besides, it downregulates the expression of differentiated embryochondrocyte expressed gene 1 (DEC1) and hypoxia-inducible factor-1-α (HIF-1α) [33–36].

Furthermore, several authors have shown that the supplementation with curcumin may bring a plethora of benefits in the treatment and prevention of the osteopenia [37]. This compound has been demonstrated to be able to avert the suppression of osteoblasts proliferation and to enhance the index of osteoprotegerin and RANKL, which indicates osteoblastogenesis [38].

As mentioned earlier, the actions of curcumin vary from potent anti-inflammatory and anti-apoptotic to antioxidant [39]. The wide variety of sites of actions and consequently decrease in the inflammation markers make this compound and its analogs extremely promising in chronic inflammatory diseases such as OA [5, 28]. Also, this herbal medicine inhibits the phosphorylation of IKB-α and thereby reduces cartilage degradation, as shown in **Figure 4**.

Conventional OA therapies are restricted to the reduction of symptoms in patients, but they do not decrease the degradation of cartilage and, consequently, do not alter the progression of the disease. For these reasons, the need for new therapies is striking, and curcumin and its analogs have become extremely promising in this context [13, 28].

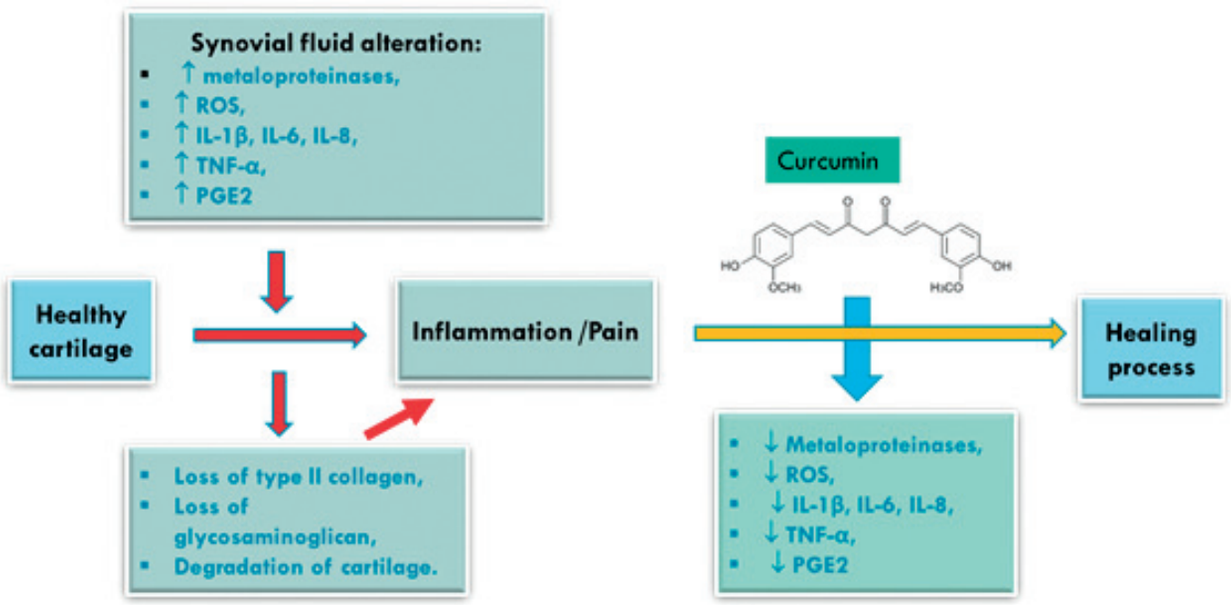

Figure 3. The inflammation of the cartilage may occur due to several processes such as an increase in the expression of enzymes, increase in the formation of ROS, and release of cytokines. The consequence is the loss of type II collagen and glycosaminoglycan resulting in the degradation of the cartilage. Curcumin interferes in this scenario and may help in the healing process. ROS: reactive oxygen species; IL: interleukin; TNF-α: tumor necrosis factor-α; PGE2: prostaglandin E2.

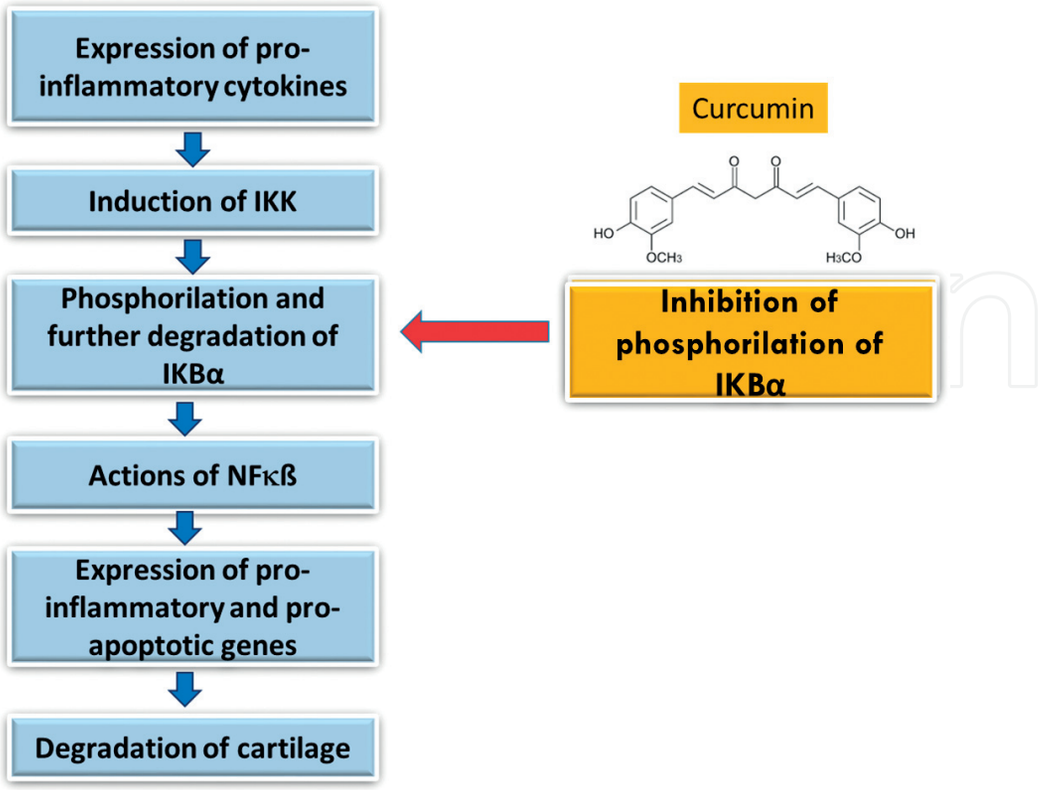

Figure 4. Effects of curcumin on the inhibition of the process involving the degradation of cartilage. IKK: I kappa B kinase; IKBα: inhibitor of kappa B; NF-κβ: nuclear factor κβ.

4. The potential effects of *Curcuma longa*

In articular cartilage, the ECM is composed of different compounds such as collagen, proteoglycans (glycosaminoglycan and proteins) mainly aggrecan and non-collagenous proteins [28, 40].

In the intra-articular space, there is the synovial fluid, which is enveloped by the synovial membrane and is also responsible for the nutrition of articular cartilage cells. The main cells in the synovial membrane are synoviocytes that have phagocytic functions and are responsible for the production of synovial fluid [41] and contribute to the inflammatory process when it releases several cytokines and proteases which contribute to joint destruction [42, 43].

Some degenerative diseases are involved with synovial inflammation and destruction of ECM of articular cartilage [44, 45]. According to the World Health Organization (WHO), musculoskeletal or rheumatic conditions consist over 150 syndromes and diseases. These ailments are liable for chronic pain, disability, and dysfunction. Among these diseases, rheumatoid arthritis, osteoarthritis, spinal disorders, and severe limb trauma deserve special mention because of the greatest impact on society such as healthcare expenditures. In developed countries, OA is one of the most disabling diseases [45].

OA is a degenerative disorder involving synovial inflammation and destruction of ECM leading to several symptoms such as pain, disability, and significant morbidity, requiring

many medications that, in most cases, do not show effective actions resulting in the damage of the synovial tissue. For these reasons, new pharmacotherapies and therapies for this illness are essential [28].

As pointed earlier, curcumin may act in many different locals of inflammation resulting, directly or indirectly, in the reduction of the production of inflammatory mediators and interleukins, resulting in less destruction of cartilage. Besides that, patients treated with curcumin have decreased C-reactive protein, a marker of inflammation [46, 47].

Moreover, curcumin has been shown to inhibit the activator protein 1 (AP-1) pathway and NF-κB leading to the suppression of the production of MMP-3, MMP-9, and MMP-13 [15, 19]. Zhang et al. [9] demonstrated in a mouse model that the production of MMP-1, MMP-3, MMP-13, IL-1β, TNF-α, and ADAMTS5 was decreased when the animals were treated with curcumin. They also showed an increase in the expression of the chondroprotective gene CITED 2 (Cbp/P300 interacting transactivator with Glu/Asp rich carboxy terminal domain 2), which seems to be involved in the suppression of NF-κB activity [9, 19]. Curcumin has also been related to the stimulation of the production of type II collagen and glycosaminoglycan by chondrocytes [5].

Curcumin inhibits the activation of I kappa B kinase (IKK) in chondrocytes, osteoblasts, and synovial cells [15, 48]. By inhibiting the phosphorylation of this kinase, curcumin prevents the activation of NF-kB. Consequently, it inhibits the expression of pro-apoptotic genes in chondrocytes (caspase-3) and the formation of inflammatory mediators [18]. Thus, it is responsible for the downregulation of lipoxygenases, COX-2, phospholipase A2, prostaglandin E2 (PGE2), IL-1β, IL-6, and IL-8 [19, 30]. Wherefore, curcumin blocks the signaling by NF-kB, leading to the inhibition of this factor resulting in the decrease of the degradation of collagen. This pathway is induced by the activation of the chondrocytes stimulated by IL-1 [15, 16].

Curcumin inhibits TNF-α, which is associated with increased cartilage reabsorption. This cytokine associated with IL-6 and IL-1 inhibits the proteoglycan synthesis [5, 49, 50].

Studies have shown that compounds from *Curcuma* sp. can alleviate joint pain and crepitation, which lead to improved scores on WOMAC (Western Ontario and McMaster Universities Osteoarthritis Index), improve function, reduce the use of other drugs for pain relief, and is as effective as the use of ibuprofen [51–59].

Therefore, curcumin acts on the NF-kB system, in addition to the stimulation of the production of type II collagen and glycosaminoglycan resulting in a protective and anti-inflammatory action of cartilage and bones, reducing pain and improving the quality of life of patients with degenerative diseases [18].

5. Disadvantages of *Curcuma longa*

The major problem of curcumin is that it is extremely hydrophobic and thus has low oral bioavailability, thus decreasing their beneficial effects. Another problem is the rapid metabolism of curcuminoids considering the extensive biotransformation and consequent reduction in the plasmatic levels [25, 60].

Some techniques, such as nanoparticles, phospholipid complexes, and liposomes, have been used as drug delivery systems to improve the bioavailability of these substances [61, 62]. Some compounds, such as folic acid, piperine, phosphatidylcholine, galactose, and the complex arginine-glycine-aspartic acid, are also used to improve this bioavailability and effects. Green tea and collagen associated with curcumin extracts may also enhance its effects [8, 30, 63, 64].

6. Conclusions

The curcumin has been used as an alternative therapy in the control of cartilage healing once it may interfere with the inflammatory pathways reducing the release of pro-inflammatory cytokines. Nevertheless, the use of curcumin and its analogs need to be more extensively studied and tested to determine the bioavailability, the therapeutic properties, adequate delivery formulations, doses, and possible risks of use.

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