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Curcumin and amaranth as potential anti-inflammatory and protective agents in bone and joint diseases

Cinthia N. Cuero[1,2], Carmen Colín-Ferreyra[1], Wael Hegazy Hassan[1], Olivier Peyruchaud[2], Patricia Cerecero[1]

[1]Faculty of Dentistry, Autonomous University of Mexico State (UAEMex), Toluca, Mexico; [2]Bone and Joint Pathophysiology: Bioactive lipids and mineral metabolism, INSERM UMR 1033, Claude Bernard University Lyon 1, Lyon, France.

***Corresponding Authors:** Olivier Peyruchaud, INSERM U1033 Pathophysiology, diagnosis and treatment of bone disease, Laënnec Faculty of Medicine, 69008 Lyon, France; Patricia Cerecero Aguirre, Autonomous University of Mexico State (UAEM), Faculty of Dentistry, 50130 Toluca de Lerdo, Estado de México, México.

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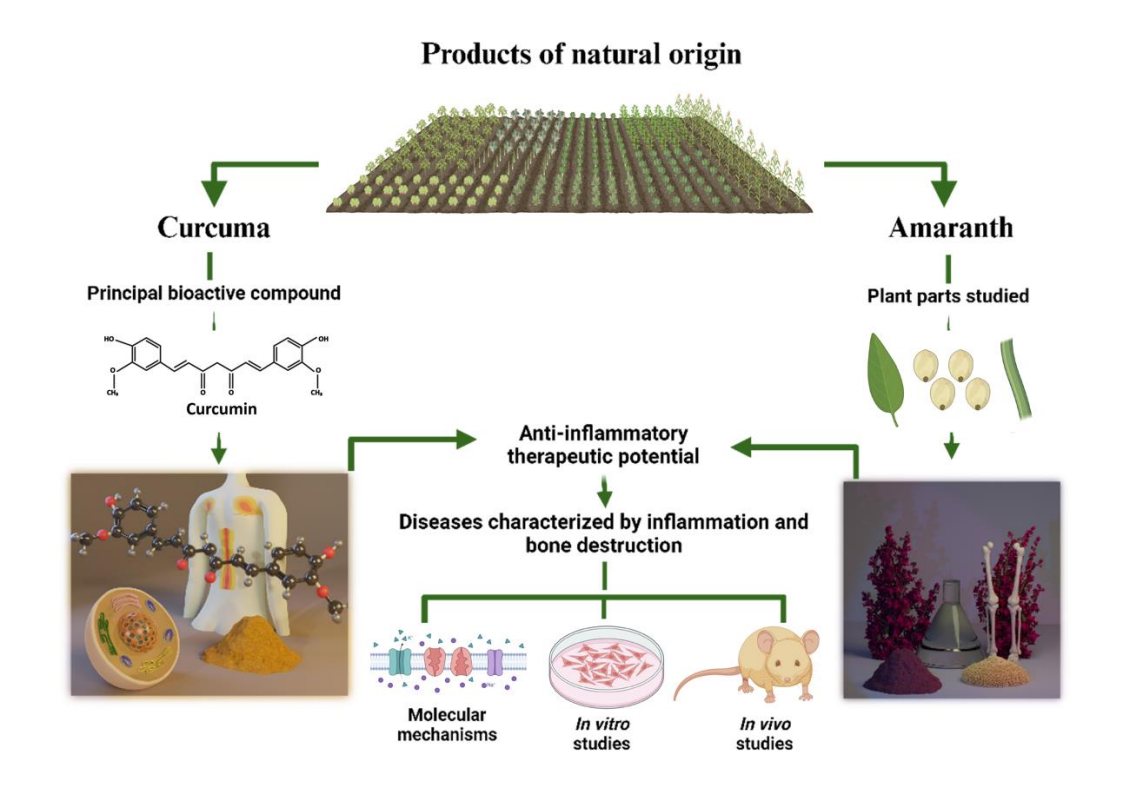
ABSTRACT

There has been growing interest in medical research focused on natural products. As a result of the ancestral knowledge passed down through generations and the demands of our current era, there has been an increased demand for new strategies and the search for new molecules with therapeutic potential. This increase is due to new technologies, the evolution of diseases, and the emergence of new ones. In this review, we focus on the work and relevance of Curcumin research, which is one of the main components of *Curcuma longa.* Additionally, we explore Amaranth in its various reported species and components (seed, leaf, stem) studied. The focus is on the anti-inflammatory therapeutic potential, not only in one, but in different diseases characterized by inflammation and bone destruction. We aim to analyze the possible molecular mechanisms by which curcumin and amaranth act as well as data currently obtained from different studies. This review aims to open a new perspective to the investigation of these compounds in the field of diseases characterized by inflammation and bone destruction.

Keywords: curcumin, amaranth, treatment, inflammation, bone.



INTRODUCTION

Currently, several inflammatory diseases affect the bones, such as rheumatoid arthritis, osteosarcoma, osteoarthritis, osteoporosis, and bone metastasis caused by cancer. Today several molecules and drugs with anti-inflammatory potential, such as anti-TNF (tumor necrosis factor), have been investigated [1]. Within inflammatory diseases, some interest has been generated by immune-mediated inflammatory diseases (IMIDs), such as rheumatoid arthritis (RA) disease [2]. This has increased the search for molecules with anti-inflammatory potential. However, while current treatments and drugs offer advantages such as symptom reduction, they do not offer a cure and demonstrate gastrointestinal and cardiovascular adverse effects [3]. Consequently, and based on the attributes given to certain plants, there has been an increase in the research of extracts of certain plants. It should be noted that the application of phytotherapy is not recent as it has origins since ancient times. Phytotherapy is understood as the application and/or use of herbs as medicinal tools to treat different diseases. Over time, immigration made the exchange and transfer of medicinal herbs more and more feasible as cultures and knowledge were exchanged. Nowadays, as a consequence of diseases, antibiotic resistance, drug problems, and more, researchers have focused their attention on investigating the biomolecular effects of medicinal herbs [4]. This has led to the development of functional food science, which is focused on the discovery and development of bioactive food compounds. Bioactive compounds are found in food and have a bioactive impact on human health [5]. Functional foods of plant origin have been reported to exhibit activities such as anti-proliferative, antioxidant and anti-cancer effects. These activities are often attributed to natural substances produced by plant metabolic

pathways, such as phenolic compounds (phytochemicals) [6]. Some plants, such as curcumin and amaranth, have garnered attention for their anti-inflammatory potential.

Curcumin is a phenolic bioactive compound with pharmacological activities, such as anti-inflammatory, antioxidant, anticancer, and antiangiogenic [7]. On the other hand, amaranth has been used since ancient civilizations such as the Inca, Mayan, and Aztec. These cultures used amaranth to prepare tortillas and drinks, utilizing both the seeds and leaves. They also consumed amaranth as a vegetable. While amaranth was one of the primary food crops during the pre-Columbian era due to its nutritional properties, its significance resides in the religious aspect, mainly in ceremonies. Similarly, amaranth held religious importance in India and Nepal. However, it is currently cultivated in Asia, Africa and Europe due to its content of proteins, fats, macro, and micro elements [8-9]. Amaranth is a staple food and is also consumed for its medicinal properties [10]. It is important to note that in some cases some people do not use the word "herbal", as previously mentioned, but rather, they use the word "phytotherapy." This entails the significance of studying plants with therapeutic potential, which lies mainly in the need to find new molecules with therapeutic potential. Secondly, it involves the discovery of various plants that demonstrate therapeutic potential. This applies to curcumin as well as amaranth and remembering that the use of phytotherapy has been one of the oldest ways of treating ailments. Modern phytotherapy is currently based on scientific and profound knowledge, encompassing pharmacodynamic and pharmacokinetic aspects as well as preclinical and clinical studies. However, it is essential not to overlook the origins of the plants and the culture that possess fundamental knowledge in order to determine which have or show a pattern with biomedical interest. Another aspect to consider is that while bioactive compounds originate from food, they must be dosed according to bioavailability, metabolic processes, and among other considerations in order to guarantee efficacy in promoting health in disease prevention or treatment and avoiding toxic and ineffective amounts [11]. Furthermore, it is critical to recognize that a every part of a plant does not need to exhibit the same potential or qualities. For instance, curcumin, derived from the rhizomes of the plant, and amaranth, where both leaves and grains are being studied, exemplify this variability. This review is oriented to the work, evidence, and potential of curcumin and amaranth as anti-inflammatory agents in various inflammatory diseases.

The information in this review article was obtained from a rigorous search in reputable databases including PubMed, Redalyc, Scopus, Web of Science, and Food Science Publisher for insuring data reliability.

Curcumin: One of the most studied varieties is *Curcuma longa* L., and its derivatives, consisting of approximately 235 compounds have been identified, which are mainly phenolics and terpenoids. However, curcuminoids and essential oils, which have bioactive potential, are predominantly found in the rhizomes. The main and most active curcuminoid among them is known as curcumin [4, 12-14]. Curcumin is a yellow polyphenolic substance widely used in different ways including to give flavor and color to food, in tea, and for beauty and health. It has been used to treat gas, colic, toothache, during the menstrual period, stomach problems, wounds and scars, digestive problems, as an antibacterial agent, for vision, dental problems, and as an anti-inflammatory agent, among other applications [12, 14]. The use of curcumin has not only been of empirical use, but several studies have described its anti-inflammatory, antimicrobial,

antioxidant and bone resorption prevention properties in certain diseases such as periodontal diseases [15]. Commercial curcumin is poorly soluble in water; however, it can be dissolved in ethanol, methanol, dimethyl sulfoxide (DMSO), or ethyl acetate, which is of relevance when performing experiments both *in vitro* and *in vivo* [16]. Given curcumin's low absorption rate, it is important to consider the most suitable medium for its dissolution in order to improve its bio-dissolution [17-18].

Curcumin is also known as diferuloylmethane, and its IUPAC name is (1E,6E)-1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione. Its chemical formula is $C_{21}H_{20}O_6$ (Fig 1) and has a molecular weight of 368. 38. The absorption spectrum of curcumin shows two intense bands, one in the visible region ranging between 410 and 430 nm, and the other in the UV light region with a maximum of 265 nm. For the application of curcumin, it should also be considered that degradation occurs in aqueous organic solutions and increases with rising pH levels. However, degradation decreases if curcumin binds to lipids, liposomes, albumins, and other macromolecular systems. Thus, it is possible to prepare stable solutions of curcumin in culture medium containing 10% Fetal Bovine Serum (FBS) [19].

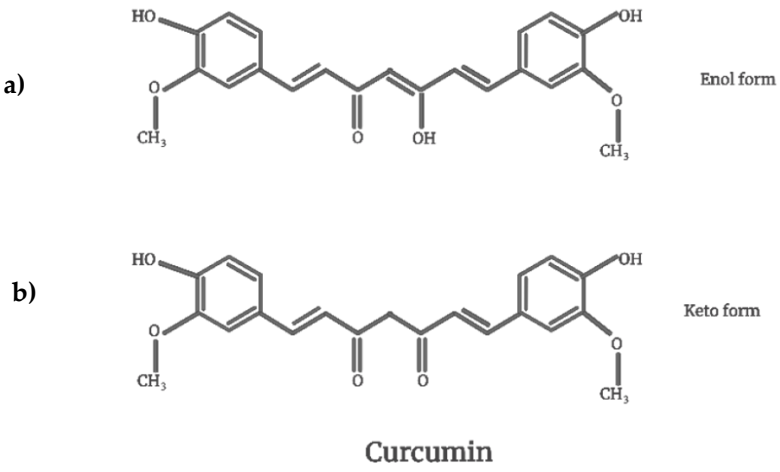


Figure 1. Chemical structure of curcumin. (a) The enol and (b) keto forms of curcumin are common structures of the drug. Created using BioRender.com.

Curcumin attenuates inflammatory response: Several studies have evaluated and affirmed that curcumin has certain antioxidant and anti-inflammatory activity.

Rheumatoid arthritis: Rheumatoid arthritis (RA) is an inflammatory autoimmune disease, which has been reported to affect between 0.5 and 1% of the world's elderly population [20]. RA has different hallmarks such as fibroblast hyperplasia and is therefore a focus of research. Currently, the effect of curcumin on the proliferation of synovial fibroblasts has been tested, demonstrating inhibition of their growth and induction of apoptosis through the cyclooxygenase COX-2 pathway [21]. Additionally, a metabolomic profile of primary fibroblasts (FLS) stimulated with TNF-α and treated with curcumin reaffirms the effect of curcumin on COX-2 (Fig 2) and the inhibition of Il-6, IL-8, MMP-1 and MMP-3 [22]. Bone erosion is another hallmark of RA, making it important to evaluate the effect of curcumin on osteoclastogenesis. It is reported that curcumin inhibits osteoclast gene potential by suppressing MAPK/ RANK/c-Fos/NFATC1 signaling pathways [23].

There are several models of rheumatoid arthritis; however, one of the most widely used is the murine model of collagen-induced arthritis (CIA). In the CIA model, the effect of curcumin on the expression of proinflammatory cytokines, such as TNF-α, IL-1β, INFγ and IL-6 (Fig 2) has been studied, revealing a reduced expression of TNF-α, IL-1β and suppression in the production of INFγ, IL-6 and IL-17 These findings suggest that curcumin exerts an anti-inflammatory effect by inhibiting proinflammatory mediators and intervening in the humoral and cellular immune responses [24-26]. Curcumin is also known to inhibit the mTOR pathway (Fig 2) in a murine CIA model, in addition to inhibiting the levels of IL-1β, TNF-α, MMP-1 and MMP-3, which are proinflammatory cytokines [27]. Curcumin has been shown to induce improvement in paw swelling, arthritis index score, inflammation, and subsequent joint development [28-29]. Given the efforts to investigate and elucidate the mechanisms and effects of curcumin in rheumatoid arthritis, this compound has also been studied in patients with mild to moderate disease severity. It is reported that curcumin has fewer adverse effects than diclofenac sodium and acts similarly to anti-TNFs [30]. Concerning clinical symptoms, such as visual analog scale (VAS), disease activity, and rheumatoid factor (RF), curcumin has been shown to improve response and act as an analgesic and anti-inflammatory agent in RA [31]. However, it is necessary to emphasize that further research and studies are needed to conduct a long-term study of curcumin in patients with rheumatoid arthritis.

Osteosarcoma: Osteosarcoma is a malignant bone tumor whose hallmark is metastasis. Knowing this, the potential of curcumin has been investigated not only as inflammatory properties but also its antiproliferative effects. Several studies have evaluated curcumin's impact on different osteosarcoma cell lines such as SAOS-2 (HTB-85), U2OS (HTB-96), HOS, 143B, LM5, Hu09, MG-63. These studies show that curcumin can inhibit cell growth through apoptotic processes, such as inducing a decrease in the expression of the anti-apoptotic protein BCL-2 [32-35], specifically in the case of MG-63 cells. It has been shown that curcumin can decrease the proliferation of these cells without affecting healthy osteoblasts. Additionally, curcumin inhibits genes such as Smad4, NFκB p65, and cyclin D3 [36-37].

In order to further clarify the mechanisms by which curcumin acts in osteosarcoma, several studies have been conducted using cell lines to investigate its effect on signaling pathways, genes, and processes. These studies have reported that curcumin is able to inhibit the Wnt/β-catenin pathway (Fig 2), which promotes tumorigenesis and metastasis of osteosarcoma [38-39]. Additionally, curcumin reduces estrogen-related receptor alpha expression (ERRα), triggering inhibition of cell proliferation. It also suppresses growth under hypoxic conditions by inhibiting the Notch1 signaling pathway [40-41]. Furthermore, it has been suggested that curcumin acts by regulating the ITPR1 gene, which encodes the intracellular calcium release channel type 1 InsP3R, and thereby binds to sensitized cells and cytochrome c to apoptotic stimuli [42]. On the other hand, curcumin induces cell G0/G1 phase arrest via the p-JAK2/p-STAT3 pathway, suggesting that the suppression of cell growth by curcumin occurs through this pathway [43].

It can be summarized that the potential of curcumin as a treatment for osteosarcoma is promising. Researchers have begun to develop and analyze the mechanisms of various curcumin analogs such as EF24,

DK1, and GO-Y078, which have demonstrated favorable results in apoptosis and antigenic activity [44-47].

Osteoarthritis: Osteoarthritis is one of the most common diseases belonging to the group of joint diseases and as well as in arthritis. The effect of curcumin in osteoarthritis (OA) has also been evaluated in different models, such as in a mouse model of medial meniscus destabilization (MMD). It has been reported that curcumin suppresses the expression of proinflammatory mediators such as IL-1β and TNF-α, as well as reducing the progression of OA disease, cartilage erosion, and synovitis [48-49]. This coincides with other studies reporting that curcumin is able to decrease the expression of MM-3, MyD88, p-IκBα, NF-κB, TNF-α, IL-1β, and IL-6 (Fig 2), upon induction of OA by monosodium iodoacetate (MIA), and thereby reducing the inflammation [50-51].

In order to elucidate the mechanism of action of curcumin in OA, studies have focused on different targets. It has been reported that curcumin inhibits MMP3 expression in OA synovial cells. This inhibition promotes the inhibition of cell proliferation, reduction of cell viability, increased apoptosis and alleviation of inflammation [52]. Additionally, curcumin reduces gene expression and/or proteins involved in pain, such as PGE2 and NGF [53]. Curcumin also inhibits oxidative stress-induced chondrocyte apoptosis through the expression of SIRT, which inhibits the PERK-eIF2α-CHOP pathway [54]. Moreover, the chondroprotective role of curcumin is also through the AMPK/PINK1/Parkin pathway [55]. Another reproted pathway through which curcumin acts to ameliorate inflammation is Sox9/NF-kB, as it suppresses NF-kB activation by promoting Sox9 expression [56].

It should be noted that curcumin has also been evaluated in patients with OA, highlighting that its efficacy is similar to diclofenac, which could be an alternative in the treatment option for patients who cannot tolerate the side effects of non-steroidal anti-inflammatory drugs [57]. In addition, daily administration of curcumin in OA patients has been shown to decrease pain and inflammation, which may be due to the upregulation of microRNAs [58].

Osteoporosis: Several factors can play an important role in bone loss, such as menopause or due to diseases such as Alzheimer's or diabetes. Curcumin has been reported to provide an improvement in the adverse changes in the mechanical properties of the femur following the loss of endogenous estrogens [59] Additionally the effect of curcumin on bone microarchitecture and bone mineral density in APP/PS1 transgenic mice susceptible to osteoporosis (OP) has been reported. It showed that mice treated with curcumin presented a constant increase in trabecular bone mass, preventing a deterioration in bone structure [60]. Curcumin also prevents bone loss through coupling osteogenesis and angiogenesis of BMSC bone marrow stromal cells in hyperglycemia by blocking the NF-κB signaling pathway [61]. In addition, curcumin improves bone biomechanical properties, thereby preserving bone architecture, which may be due to the influence of curcumin on the activation of the TGF-β/Smad3/3 pathway (Fig 2) [62].

Additionally, it has been reported that curcumin can attenuate bone resorption induced by dexamethasone, a

glucocorticoid known to induce osteoporosis with prolonged exposure. This can be explained by the demonstration that curcumin can reactivate the Wnt signaling pathway, which is inhibited by dexamethasone. It also stimulates bone remodeling by balancing the RANKL/OPG ratio and increases bone mechanical strength. It protects osteoblasts from apoptosis, which could be due to the activation of the ERK pathway [63-65]. Furthermore, it has also been suggested that curcumin may act by regulating the EZH2/Wnt/β-Catenin pathway to protect and improve bone microstructure in the face of OP [66].

To clarify the role of curcumin in the processes leading to bone resorption, the effect on osteoclastogenesis has been evaluated. It has been shown that curcumin can reduce the production of CCL3 in osteoclast precursors, reducing their migration, and thus the formation of mature osteoclasts [67].

Cancer-derived bone metastasis: Bone metastasis is caused by some types of cancer, such as prostate and breast cancer, which is why, just as the role of curcumin has been studied in other bone diseases, its mechanism and effect on bone metastasis has also been explored. Regarding bone metastasis generated by prostate cancer, so far, it is known that curcumin has an inhibitory activity of mRNA expression and levels of the CCL2 protein, which is involved in the development of bone metastasis. Thus, curcumin is able to block adhesion and invasion of prostate cancer cells (PC-3) [68]. Additionally, it has been shown that curcumin also can modulate TGF-β signaling (Fig 2) [69]. TGF- β promotes the progression of cancer cells, allowing bone metastasis, so this signaling pathway is a focus of study. For this reason, we have evaluated the effect of curcumin, reaffirming what other studies have already mentioned that it is able to inhibit the TGF- β signaling pathway [70]; this is of relevance since this pathway acts in both prostate and breast cancer.

Regarding bone metastasis generated by breast cancer, it is clear that there is the participation of osteolytic factors such as PTHrP induced by growth factors such as TGF-β. In this sense, it has been reported that curcumin is able to inhibit the phosphorylation of Smad2/3, which is mediated by TGF-β, and also blocks the secretion of PTHrP, providing bone protection [71]. Given the potential that curcumin represents in bone metastasis, analogs have been generated, as in the case of UBS109, demonstrating that this analog has antitumor potential. Based on studies, this analog is feasible to prevent bone metastasis induced by MDA-MB-231 cells. It also stimulates osteoblastic mineralization and suppresses osteoclastogenesis [72]. Additionally, it has restorative effects on bone marrow cell differentiation, which has been deregulated by metastatic cells [73].

Another mechanism of action by which curcumin acts is that it inhibits the osteogenesis of human adipose-derived mesenchymal stem cells (hADSCs) by modulating the expression of miRNAs such as miR-126a-3p [74].

In addition to the aforementioned, it has been reported that curcumin intervenes with mitochondrial processes in cancer. It is known to affect proteins such as Bax, Bcl-2, and Bcl-xL and reactive oxygen species, It has also been reported that curcumin is able to inhibit the

mitochondrial $Na^+/Ca^{2+}/Li^+$ exchanger (NCLX), thus generating an antitumor effect, allowing this information to open new perspectives for research on the mechanisms by which curcumin acts [75].

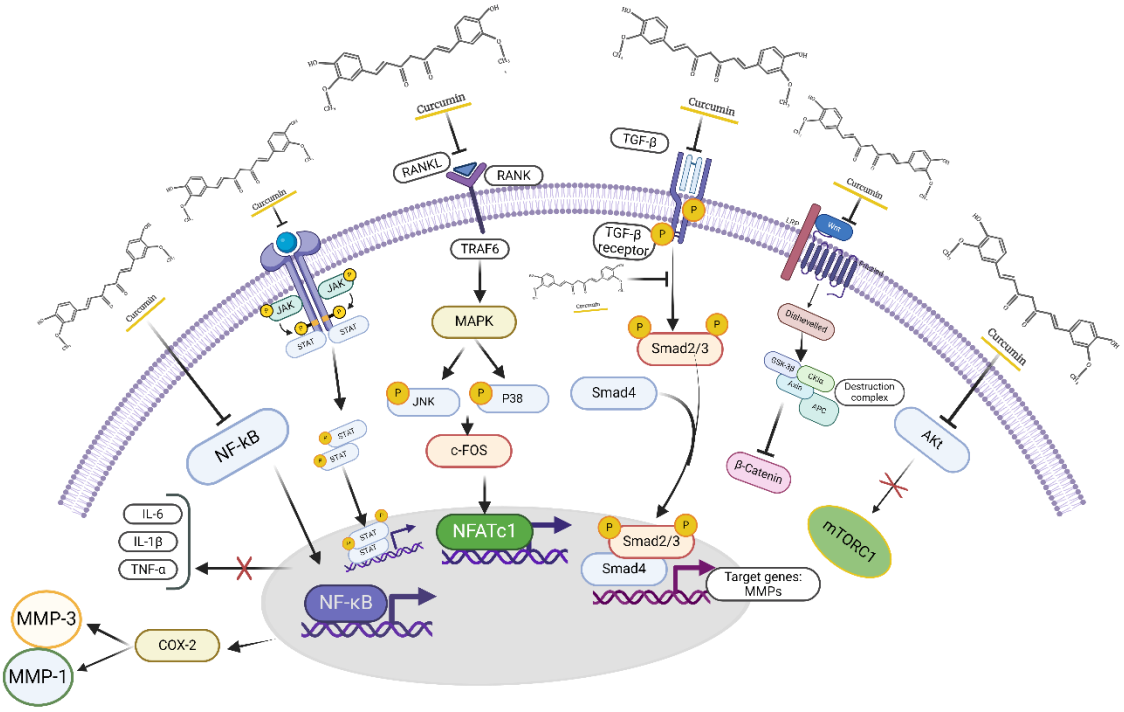


Figure 2. Illustration of the mechanisms of action of curcumin on different signaling pathways. Created using BioRender.com.

Amaranth: Amaranth is part of the so-called pseudo cereals, and it has been reported that amaranth has a dual character because it is a food that has an appropriate nutritional level to be consumed and has medicinal properties. Additionally, if we consider the factor of climate change, and that this plant has a high nutritional potential, plus its medical potential and that it presents resistance to drought, make it a focus of interest for researchers in different areas [10, 76].

Amaranth plants can reach a height of 0.8 to 1.8 m and produce seeds that are used for the production of oil or flour, while the leaves are used for salads. Historically, in Mexico, it has been used since ancient civilizations such as the Inca, Mayan, and Aztec, as it belonged to the staple foods. Besides being consumed for its medicinal properties [10], these cultures used amaranth to prepare tortillas and drinks; they used not only the seed but also the leaves, they also ingested it as a vegetable. Amaranth was one of the main food crops during the pre-Columbian era for its nutritional properties, and it is also used in religious ceremonies. Likewise, it acquired a religious importance in India and Nepal, however, it is currently cultivated in Asia, Africa and Europe, because it contains proteins, fats, macro and micro elements [8-9].

Amaranth belongs to the Amaranthaceae family and comprises approximately 70 species of plants. Each species has different uses according to its location and properties [76].

Regarding the chemical composition of amaranth, this will vary depending on the species and variety. However, it is known that the grain has high protein and lysine content. The leaves also have a high protein content. It can be said that the main biological compounds found in amaranth are proteins, fats, carbohydrates, vitamins and minerals [10, 76]. In some amaranth species, the main carbohydrate is starch, which

accounts for 60 % of dry grains [77]. In addition, amaranth seeds and leaves contain small amounts of polyphenols, saponins, hemagglutinins, phytin, nitrates and oxalates [76].

Amaranth plants have antioxidant properties, in addition to containing bioactive peptides, and influence the elimination of free radicals [78].

Amaranth and its anti-inflammatory potential: Currently, information on amaranth as a potential anti-inflammatory molecule in bone diseases is scarce; however, different studies have boosted research in this area and in general the effect in anti-inflammatory diseases.

Rheumatoid arthritis: As mentioned, the molecular mechanisms (Fig 3) by which amaranth acts are still unknown. However, some studies attribute the beneficial effects of amaranth to its secondary metabolites, such as phenolic compounds [79]. It has been reported that the phenolic compound 2-caffeoylisocitric acid (C-IA) present in the leaves of some species of amaranth has potential anti-inflammatory activity in the RAW264.7 cell line after accumulation of the compound. This suggests that the study of this compound at the *in vivo* level could provide potential results for the use of amaranth and its derivatives [80].

There are no *in vivo* studies on the compound mentioned; however, a study on the effect of dietary amaranth and its potential modulatory role in immune activation in collagen-induced arthritis has been reported using a murine model of rheumatoid arthritis. A widely used model, the CIA model, shows that amaranth has a protective immunomodulatory role (Fig 3) in the Th1/Th2 response by balancing it and also has a role in the Th17/Treg balance, so that amaranth could positively regulate the immune response in RA conditions [81].

Osteosarcoma: Osteosarcoma is related to immune and inflammatory signaling, some studies have shown that inflammatory signaling plays an important role in osteosarcoma formation, migration and invasion, and vice versa cytokine production in tumors influences inflammation [82-83]. Amaranth peptides have been studied as potential inhibitors of cell proliferation (Fig 3), with emphasis on lectin polypeptides, which could be responsible for this action [84]. However, not only grain extracts or peptides have been studied, but also amaranth leaves from some species, showing potential anticancer activity [85].

Osteoporosis: Today, the activity and effect of amaranth on bone processes and on bone diseases, such as osteoporosis, is still quite unknown. Although the scarcity of information has not limited researchers, and it has been reported that amaranth is able to suppress RANKL-mediated osteoclast differentiation (Fig 3) and the expression of specific osteoclast genes *in vitro* as well as the protection against ovariectomy-induced bone destruction *in vivo*. This shows the therapeutic potential of amaranth in osteoporosis [86].

Other diseases where amaranth has been tested for its therapeutic potential: Currently, the potential of amaranth associated with promoting health has been the focus of research, since amaranth components have begun to be evaluated in diseases associated with bone as well as with other diseases associated with inflammation or inflammation itself. In a study on the evaluation of the extrusion process in inflammatory conditions, it was found that amaranth hydrolysates inhibit LPS-induced inflammation *in vitro* by inhibiting the activation of the NF-κB signaling pathway [87]. In addition, it has been seen that they show a reduction in the expression of interleukins IL-4, IL-6, IL-22 and IL-12 p70. These interleukins are related to inflammation, demonstrating that both grains and leaves have the potential to reduce proinflammatory cytokines, and thus consider amaranth as having anti-inflammatory potential

[88]. In addition to the grain and leaf, the stem has also been analyzed, but the results of the studies have shown a higher phenolic content in the leaves, as well as greater activity and potential as an antioxidant and anti-inflammatory agent [89].

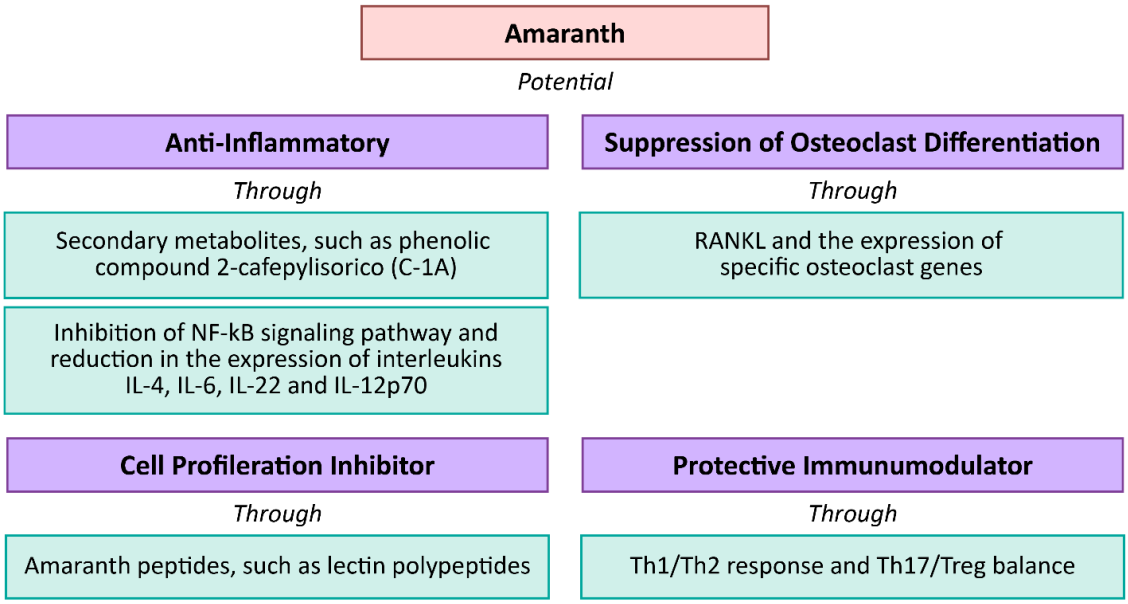


Figure 3. Summary scheme of the mechanisms of amaranth in bone diseases.

Table 1. Signaling pathways and molecular factors involved in curcumin mechanism of action

Disease	Cell Line and/or Murine Model	Signaling pathways involved	Decreasing proinflammatory cytokines	Suppressed or decreased, metalloproteinases, proteins, genes, or receptors	References
Rheumatoid arthritis	Synovial fibroblasts Collagen-induced arthritis (CIA)	COX-2 MAPK/ RANK/c-Fos/NFATC1 mTOR	Il-6, IL-8 TNF-α, IL-1β, INFγ, IL-17	MMP-1 and MMP-3	[22-25, 27, 90]
Osteosarcoma	MG-63	Wnt/β-catenin p-JAK2/p-STAT3		Smad4, NFκB p65, cyclin D3, BCL-2, ERRα	[32-34, 37-39, 43],
Osteoarthritis	Mouse model of medial meniscus destabilization (MMD)	PERK-eIF2α-CHOP AMPK/PINK1/Parkin Sox9/NF-kB	TNF-α, IL-1β and IL6	MM-3, MyD88, p-IκBα, NF-κB, PGE2 and NGF	[48-56]
Osteoporosis	APP/PS1 transgenic mice	NF-κB TGF-β/Smad3/3 ERK EZH2/Wnt/β-Catenin		CCL3	[60-61, 63-64, 66-67]
Cancer-derived bone metastasis	Prostate cancer cells (PC-3) MDA-MB-231 cells	TGF- β signaling		CCL2 Smad2/3	[69-71]

CONCLUSION

Considering the issue of inflammation in various diseases, including joint and bone diseases, it can be inferred that both curcumin and amaranth have anti-inflammatory and protective properties. This makes them research targets for therapeutic use in relation to inflammation involved in bone and joint diseases. In the case of amaranth, it is inferred that it could act through the NF-κB signaling pathway. Additionally, amaranth leaves have anti-inflammatory potential, which could be due to the phenolic and flavonoid content. However, it is notorious that it is necessary to perform more *in vitro* studies, but especially *in vivo* to further clarify the mechanisms by which they act. The present review provides the compilation of information on the signaling pathways and mechanisms by which both curcumin and amaranth act. It is of relevance to address this part because usually the research is focused on a study objective, so what is developed throughout this paper highlights the information and studies. This opens a panorama and perspectives for research and studies by the researchers of the area to continue with the investigation of the mechanisms by which both curcumin and amaranth act as the information is still scarce, with emphasis on amaranth.

List of Abbreviations: TNF: tumor necrosis factor, IMIDs: immune-mediated inflammatory diseases, RA: rheumatoid arthritis, DMSO: dimethyl sulfoxide, FBS: Fetal Bovine Serum, COX-2: cyclooxygenase 2, IL: Interleukin, MMP: metalloproteinase, CIA: collagen-induced arthritis, VAS: visual analog scale, RF: rheumatoid factor, ERRα: receptor Alpha, OA: osteoarthritis, MMD: medial meniscus destabilization, MIA: monosodium iodoacetate, OP: osteoporosis, hADSCs: human adipose-derived mesenchymal stem cells.

Conflicts of Interest: The authors declare no conflicts of interest.

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