Non-Surgical Management of Knee Osteoarthritis: Are Complementary Oral Medications Effective?

Manejo no quirúrgico de la artrosis de rodilla: ¿Son efectivos los medicamentos orales complementarios?

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Abstract

Osteoarthritis (OA) is a progressive disease of the synovial joints that causes pain, functional impairment, disability, and progressive degeneration of the joint. Regarding its treatments, especially in early stages, there are different interventions to avoid its development and progression and also to achieve an adequate management of symptoms, and there are unconventional oral medical treatments with controversial evidence. The objective of the present paper is to provide an update, to specialists in Orthopedics and Traumatology, regarding the current evidence on complementary oral therapies in the treatment of knee osteoarthritis. References are made to the most widely used and studied complementary pharmacological methods, mentioning the method of action and the consequences studied on knee osteoarthritis. The article ends with a table of recommendations based on current evidence.

Keywords
- osteoarthritis
- pain
- knee
- chondroitin
- diacerein
- hyaluronic acid

Resumen

La artrosis es una enfermedad progresiva de las articulaciones sinoviales que causa dolor, impotencia funcional, discapacidad, y degeneración progresiva de la articulación. En sus tratamientos, sobre todo en etapas tempranas, existen distintas intervenciones para evitar tanto su desarrollo y progresión como también para lograr un adecuado manejo de los síntomas, y hay tratamientos médicos orales no convencionales con evidencia controvertida. El objetivo de este trabajo es proporcionar una actualización, dirigida a especialistas en Ortopedia y Traumatología, respecto a la evidencia actual sobre las terapias complementarias orales en el tratamiento de la artrosis de rodilla. Se hace referencia a los métodos fármacológicos complementarios más usados y estudiados, mencionando el método de acción y las consecuencias estudiadas sobre la artrosis de rodilla. Se finaliza con una tabla de recomendaciones basada en evidencia actual.

Palabras Clave
- artrosis
- dolor
- rodilla
- condroitina
- diacereína
- ácido hialurónico
- colágeno

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Introduction

Osteoarthritis is a progressive disease of the synovial joints that causes pain, functional impairment, disability, and progressive degeneration of the articular cartilage.[1] This pathology occurs more frequently in patients older than 50 years of age, with an increasing incidence, and is one of the leading causes of disability worldwide.[1,2]

Currently, there are no disease-modifying therapies for osteoarthritis; the only treatment option is a combination of pharmacological and non-pharmacological therapies used for the management of symptoms, mainly pain and loss of functionality.[3]

Most patients with osteoarthritis do not receive the appropriate treatment, as this is a complex, chronic pathology that is frequently aggravated by the presence of other comorbidities, which also limits the use of certain therapeutic strategies. The typical management is characterized by reactive and palliative care, instead of focusing on shared decision-making, coordinated actions, and prevention, with the goal of providing individualized treatment for each patient, with pain being the dominant symptom and the greatest problem to be treated.

In the current narrative review, we present an update on the efficacy of the oral pharmacological management of osteoarthritis with the following drugs:

1. chondroitin;
2. glucosamine;
3. oral medicinal herbs;
4. diacerein;
5. hyaluronic acid; and
6. hydrolyzed collagen.

Chondroitin and Glucosamines

Glucosamine is an amino sugar that was initially isolated from shellfish chitin, and it is an important component of glycosaminoglycans, which bind to form proteoglycans, an essential component of cartilage.[4]

Glucosamine has been reported to participate as a substrate in the synthesis of glycosaminoglycans, proteoglycans, and hyaluronate in articular cartilage. It also acts on chondrocytes by stimulating the synthesis of proteoglycans and inhibiting the synthesis of metalloproteinases. The use of glucosamine is based on studies[5,6] carried out in animal and in vitro models, which showed that its use normalized joint metabolism, in addition to having a mild anti-inflammatory property. Reginster et al.[7] concluded that glucosamine is more efficient than placebo in improvement symptoms, and that it could also have the potential to slow the progression of joint narrowing in osteoarthritis.

Chondroitin is a glycosaminoglycan found in many types of tissues, including hyaline cartilage. It is found as an over-the-counter nutritional supplement made primarily from chondroitin sulfate. The method of action of chondroitin has not been well elucidated, but it has been proposed that it has anti-inflammatory and antioxidant properties, increases the synthesis of proteoglycans, and alters the function of chondrocytes.[8] Within its structure, there are amino acids that contain sulfur, one of the essential building blocks for cartilage molecules in the body. Recent studies[9] have concluded that chondroitin stimulates cartilage synthesis and also acts by inhibiting the synthesis of interleukin-1 (IL-1) and metalloproteinases.

The synergistic use of chondroitin and glucosamine is still under study. A systematic review and meta-analysis[10] published in 2018 found that oral supplementation with glucosamine or chondroitin sulfate reduces pain in knees with osteoarthritis; however, there is no additional effect in their combined use for the symptomatic management of osteoarthritis.

Regarding the efficacy of glucosamine, there are numerous studies with the goal of determining its effect on the symptoms of osteoarthritis. A Cochrane review[11] of 25 randomized controlled trials of all glucosamine formulations in 4,963 patients with osteoarthritis failed to demonstrate the benefits of glucosamine in pain relief; however, when trials using the proprietary crystalline glucosamine sulfate (pCGS) formulation were analyzed separately, the latter alone was found to be superior to placebo regarding pain management, although with high heterogeneity between the trials.[11] In contrast, the analysis of these trials for all other preparations of glucosamine failed to show a benefit in terms of pain over placebo. This information is also corroborated by another meta-analysis,[12] in which the authors found that pCGS products yield better results regarding osteoarthritis pain compared to other glucosamine sulfate and glucosamine hydrochloride preparations.[12] Towheed et al.[11] point out that 56% of the studies have some relationship with the pharmaceutical industry, and emphasize that if the evaluation only includes studies without conflict of interests, there is no relevant clinical benefit in the use of glucosamine for the treatment of osteoarthritis, which includes pCGS and its related studies with the pharmaceutical company Rotta.

McAlindon et al.[13] evaluated fifteen randomized controlled trials analyzing the benefit of using glucosamine and chondroitin for the treatment of osteoarthritis of the knee and hip. They concluded that both produce at least moderate effects, but that the quality of the published studies is insufficient, and that the quantification of the reported effects was generally overstated. Another point of interest in the study by McAlindon et al.[13] is that most of the studies were conducted with funding from the pharmaceutical industry, highlighting that the effect of the medication was inferior when only large, well-designed trials were considered.[5,6]

Reichenbach et al.[14] evaluated the use of isolated chondroitin sulfate in 20 studies with a total of 3,846 patients. They concluded that the use of chondroitin alone is not

associated with a reduction in pain and improvement in functionality, highlighting the large number of studies with methodological defects.

In a Cochrane systematic review[15] on the use of chondroitin in osteoarthritis, the authors point out that it can improve pain slightly in the short term, but in studies with more than six months of evaluation, it is not possible to say that the pain decreases more with chondroitin than with placebo. The authors stated that it probably improves the quality of life measured by the Lequesne index (a combination of pain, functionality and disability measures). In the same review,[15] it was demonstrated that chondroitin has few or no differences in terms of adverse effects against other agents, and that it slightly reduces the narrowing of the joint space in the x-rays of the affected joint after 2 years of follow-up, with 0.18 mm less of reduction in joint space compared to people taking placebo. In the same work,[15] the authors point out that there are many studies with unsound methods that evaluate the effect of chondroitin, that for some results there are insufficient data, and that, in some of the studies with better methodological quality, no improvement in relation to pain and physical function is shown.

Vlad et al.[16] showed that most of the studies on this topic have conflict of interests and are too heterogeneous among themselves to be able to be compared, with the positive results being mostly found in studies funded by the pharmaceutical industry.

Oral medicinal herbs

Oral medicinal herbs are defined as properly finished and labeled pharmaceutical products that contain active ingredients from parts of herbs or some other component extracted from them, and this extract can be found either raw or as preparations (extracts, oils, tinctures). Although the mechanism of action of oral medicinal herbs has not been fully elucidated, experimental studies[17] indicate that there is an interaction of these herbs with inflammatory mediators and cartilage destruction, providing a rationale for the efficacy of these products in the relief of osteoarthritis symptoms. In the present review, we will mainly analyze avocado/soybean unsaponifiables (ASUs) and *Boswellia serrata*, two of the most used herbs and those with more studies.

There are in vitro studies that describe the possible mechanism of action of ASUs as therapeutic agents in osteoarthritis. Henrotin et al.[18] determined that ASUs have an inhibitory effect on IL-1 beta and that, through this effect, it probably reduces the spontaneous production of metalloproteinases, IL-6, IL-8, and prostaglandin E2 in human chondrocytes.

In a Cochrane review[19] in which 45 studies with 33 different medicinal herb products that could improve the discomfort related to osteoarthritis were analyzed, multiple studies showed moderate to high evidence only available for proprietary ASU products, better known as Piascledine (Laboratories Expanscience, Courbevoie, France) and *B. serrata*. As for the rest of the products, the quantity and quality of the studies[19] are insufficient to be able to obtain solid conclusions about their effectiveness in the treatment of osteoarthritis.

The authors[19] concluded that the evidence for ASUs (Piascledine) in the treatment of osteoarthritis symptoms is moderate to high with its short-term use, although long-term studies with comparisons with an apparently active control have less convincing results. Several different medicinal plant-based products, including *B. serrata* extracts, show a trend towards benefits that would warrant additional and in-depth research, furthermore considering that the risk of adverse events appears to be low.

In a meta-analysis, Christensen et al.[20] concluded that ASUs (Piascledine) demonstrated a significant benefit in the treatment of osteoarthritis, both in terms of pain and reduction in the Lequesne index, with a more pronounced effect in knee than in hip osteoarthritis. However, this meta-analysis has the important limitation that all the included studies were sponsored by the pharmaceutical industry.

Furthermore, there is no evidence that Piascledine significantly improves joint structure, and there is limited evidence that it prevents narrowing of the joint space. Structural changes were not tested with another herbal intervention. Additional research is required to determine the optimal daily doses that produce clinical benefits without adverse events.[19]

Diacerein

Diacerein is a slow-acting drug, administered orally in the form of pills, which can slow cartilage breakdown and relieve joint pain and inflammation. The main mechanism of action of diacerein is the inhibition of IL-1 and its subsequent signaling.[21] Diacerein has been shown: to impact IL-1 function by reducing the production of the converting enzyme;[22] to affect the sensitivity to IL-1 by decreasing its receptors on the cell surface of chondrocytes;[23] and to indirectly increase the production of IL-1 receptor antagonists.[24,25]

In animal models,[26] diacerein has shown a tendency to reduce cartilage loss compared to untreated controls, but these changes were not statistically significant. Kitadai et al.[27] found that diacerein improves cartilage lesions in experimental chondrolysis of the hip in immature beagles, while Ghosh et al.[28] found that its use induced an increase in bone mineral density, as well as a decrease in the thickness of the subchondral bone plate.

In a Cochrane review, Fidelix et al.[29] concluded that diacerein has small but significant effects on pain management after 3 to 36 months of treatment. In addition, the

results of a subgroup analysis that demonstrated a residual effect of diacerein compared to placebo or nonsteroidal anti-inflammatory drugs (NSAIDs) on pain and physical function were presented.

In a meta-analysis of 19 publications, Rintelen et al.[30] demonstrated that there is a statistically significant superiority over placebo in relation to pain management and improvement in physical function. However, they showed that, compared to standard treatments, mostly NSAIDs, there were no significant differences in relation to pain and physical function.

Diacerein is a compound that has a long history, but its mode of action is still not well understood. Its efficacy is currently studied only in knee and hip osteoarthritis, and it has not been confirmed for other locations or subtypes of osteoarthritis.[31] More high-quality studies with good methodological design are also required to explore the potential of diacerein in the progression of the disease.

Regarding the safety of diacerein, the most reported adverse effects are loose stools and diarrhea. This laxative effect is well known, and is a result of its anthraquinone chemical structure. Fidelix et al.[29] obtained a relative risk of 3.52 (95% confidence interval [95%CI]: 2.42–5.11) for diacerein versus placebo, with an increase of 24% in the absolute risk (95%CI: 12–35) for patients presenting with diarrhea. Along the same lines, Rintelen et al.[30] summarized that 39% of patients treated with diacerein versus 12% of patients who received placebo experienced at least 1 episode of loose stools or diarrhea. From the point of view of the liver, in a review for the evaluation of risks in drug surveillance, the European Medicines Agency[32] analyzed seven clinical trials in which abnormalities in liver tests were found. Most of these alterations were characterized by a slight to moderate increase in liver enzymes (alanino aminotransferase [ALT], aspartate aminotrasferase [AST], < upper limits of normal [ULN]), without an increase in bilirubin.[32] From a cardiovascular point of view, with more than 20 years of use, there have been no reports of acute coronary syndrome or acute myocardial infarction.

Hyaluronic acid

Hyaluronate is a ubiquitous high-weight molecule that occurs naturally in cartilage and synovial fluid. It is made up alternately by acid residues of N-acetyl-d-glucosamine and d-glucouronic, with a molecular mass of 6,500 kDa to 10,900 kDa.[33] Its rheological characteristics are involved in the main function of the synovial fluid of acting as a lubricant, of eliminating free radicals, and of regulating cellular activity such as protein binding. Its function in the joint includes lubrication, acting as a filler of the joint space to allow the joint to remain open, and regulating cellular activities such as the aforementioned protein binding.[34]

During the progression of osteoarthritis, endogenous intra-articular hyaluronic acid (HA) is depolymerized, changing from a high-weight to a low-weight molecule, which consequently decreases the mechanical and viscoelastic properties of the synovial fluid in the affected joint.[33–35] This is how HA injections are used clinically to mitigate the effect of endogenous HA depolymerization in patients with osteoarthritis, with an effect that does not restore or replace all the properties of endogenous HA, but can induce satisfactory pain relief through different mechanisms.[35] These mechanisms include the synthesis of proteoglycans and glycosaminoglycans, an anti-inflammatory effect, and the maintenance of viscoelasticity. Regarding the oral use of HA, there is clear heterogeneity in the results of the studies, with some reporting good results and others reporting only small benefits.[36] One of the conceivable potential reasons for the variable effects could be the level of hyaluronidases in the synovial fluid of patients. These are a family of enzymes that break down HA.[37]

In oral HA treatment, the body absorbs the high-molecular-weight polymer as a decomposed polysaccharide.[38] One of the methods of action proposed in the oral ingestion of HA is that it binds to the Toll-like receptor 4 and promotes the expression of IL-10 and cytokine signaling, both leading to an anti-inflammatory action in osteoarthritis.[39]

In a meta-analysis, Bannuru et al.[40] demonstrated that patients submitted to a highly-pure HA regimen reported beneficial effects on knee pain compared to placebo at week 4, with a peak at week 8 and residual effect up to 24 weeks, achieving moderate clinical significance.[40] Fakhari[41] reported that both the oral and injectable treatments can combat the symptoms of osteoarthritis, especially in patients with early osteoarthritis.[41]

Interestingly, Pannucio et al.[42] showed that if these two types of treatments are combined, oral supplementation can extend the benefits of the injectable treatment. This would enable a reduction in the number of injections over time and in the number of visits due to symptoms of osteoarthritis. However, more studies are required to determine the exact results of the combined treatment.

Hydrolyzed collagen

Hydrolyzed collagen (HC) is obtained through the hydrolysis of animal collagen tissue, and has been used both as a food and as a supplement for many years. After hydrolysis and isolation, HC has a high composition of amino acids that are important for cartilage, such as glycine, proline, hydroxylysine, and hydroxyproline.[43] The proposed mechanism of action for HC ingestion is that it increases the synthesis of proteoglycans and type-II collagen.[44] It is available in the form of gelatin or powder, mostly consumed together with water, and both are associated with minimal adverse effects, such as bloating, reflux, and bad taste.

Some studies have tried to demonstrate the efficacy of oral HC. A study by Benito-Ruiz et al.[45] evaluated the reduction in pain in patients with a diagnosis of knee osteoarthritis treated with daily oral HC. They observed a high response to placebo, but there was also a significant difference in pain reduction, with 75% representing a greater improvement compared to placebo. In another study, Bruyère et al.[46] concluded that the supplement of HC 1,200 mg per day can increase the clinical response of pain reduction (improvement of at least 20% in the visual analog scale) compared with placebo, but more studies should be performed to confirm the clinical interest of this dietary supplement.

There are few high-quality studies evaluating the improvement in symptoms in patients with osteoarthritis and undergoing treatment with HC. Although positive effects on pain and functionality have been observed, these findings were not persistent in all the populations studied, making it difficult to generate a clear recommendation.

Table of recommendations based on evidence from the main author

Treatment	Recommendation
Glucosamine	NOT recommended: Uncertain effect on pain relief for all patients
Chondroitin	NOT recommended: Pain relief not superior to that of placebo
Avocado/soybean unsaponifiables	Conditional: Failure in initial therapy, superior to placebo in pain relief
Diacerein	Conditional: Failure in initial therapy, superior to placebo in pain relief; evaluate adverse effects according to risk
Hyaluronic acid	Unclear recommendation: Its use shows partial improvement in symptoms, with current conflicting evidence
Hydrolyzed collagen	Unclear recommendation: Its use shows partial improvement in symptoms, with current conflicting evidence

Conclusions

The treatment of osteoarthritis, globally and given its high prevalence, focuses on the control of symptoms until surgical resolution of the pathology is required to maintain the adequate functionality of the patient. Multiple studies suggest benefits from the use of these complementary oral treatments, but these findings are inconsistent across trials to generate a strong recommendation for their use. Given the good safety profile that these drugs seem to have, even though it is not possible to recommend their use with the current information available, it is not possible to rule out their use and future recommendation.

Conflict of Interests
Dr. Figueroa is a paid consultant of Smith&Nephew and of Stryker;
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