Unmet needs in Chronic Pain Management: The potential use of Curcumin

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ABSTRACT

The ultimate goal of treatment for osteoarthritis can be achieved by modifying disease progression and also symptom reduction. Non-steroidal anti-inflammatory drugs and cyclooxygenase-2 inhibitors are inflammation and pain management medications that are widely used in osteoarthritis. However, this agent has been linked to have several side effects such as cardiovascular, gastrointestinal, and kidney. These side effects represent the unmet needs in the safety of existing treatment of osteoarthritis. Such results can be caused by the overlapping functions of COX-1 and COX-2 in physiological and pathophysiological systems. The overlapping functions of COX-1 and COX-2 can be the source of these side effects. The extensive history of the use of curcuminoids and boswellia in pain relief coupled with recent findings shows that this phytochemical can play a direct role in several inflammatory processes and offers strong evidence that this product can slow down cartilage degradation and reduce pain in patients with knee osteoarthritis. Our study indicated that by reducing pain and improving function, while lowering the risk of side effects, curcuminoid formulations might become a useful addition to osteoarthritis patients for pharmacological therapeutic interventions. However, further research is needed with high-quality and large-scale RCT research probably to investigates the synergistic effects of these products with other osteoarthritis treatments.

INTRODUCTION

Osteoarthritis (OA) is one of the main causes of impairment and physical disability in the elderly (Glyn-Jones et al., 2015). An effective management for osteoarthritis remains inconclusive. Typically, osteoarthritis is managed with medication that focuses on reducing pain through palliative measures (Bijlsma et al., 2011; Zhang and Jordan, 2010). There were a significant group of patients in whom these treatments do not provide adequate pain relief (Lue et al., 2017). The previous studies of treatments that proven can stop or reversing the degenerative process are limited (Chen et al., 2017; Loeser et al., 2012).

The ultimate goal of treatment for osteoarthriti-s (OA) can be achieved by modifying disease progression and also symptom reduction. The most widely used agents for the treatment of OA are non-steroidal anti-inflammatory medicines (NSAIDs) and selective cyclooxygenase (COX) -2 inhibitors. This drug has been associated with serious side effects (Seager and Hawkey, 2001). Previous reviews have shown that NSAIDs can cause...
gastrointestinal (GI) side effects (Komers et al., 2001). A decline in GI effects is seen by the use of selective COX-2 inhibitors, but similar to NSAIDs that are correlated with kidney disorders. Concerns have also been raised regarding cardiovascular safety (Mukherjee, 2002).

The risk in multi organ limits the use of NSAIDs / Coxib for the long term. There is still unmet need for OA treatment in terms of pain reduction (Lauffer, 2004). Curcumin is a natural product that is most investigated for the treatment of inflammatory conditions (including OA). Previous review showed that the use of curcumin are promising in OA treatment (Lauffer, 2004; Wu et al., 2018).

Therefore, It is obvious that in OA treatment administration, there are unmet needs of treatment safety and clinical capability for disease management. NSAID and selective COX-2 inhibitor adverse effects can restrict their use. This restriction will adversely affect the management of pain and inflammation. This article discusses the evidence and issues surrounding the safety of NSAIDs and selective COX-2 inhibitors for GI, kidney, and cardiovascular. The future usage of curcumin to handle and resolve some of the unmet needs in OA management is also addressed in this study.

MATERIALS AND METHODS

Systematic review of current evidences about the risk of gastrointestinal, renal, and cardiovascular risk of NSAIDs and Coxib in the Pubmed. The results of systematic search are described narratively. We also performed systematic search about the evidences of the potential use of curcumin for osteoarthritis. The keywords used in the research process include: “Curcuma”, “curcumin”, and “turmeric”. Keywords “arthritis” and “pain” were also added to specify the search.

RESULTS AND DISCUSSION

The Risk of Nsaids and Coxib

The risk in gastrointestinal system

The GI possibility of NSAIDs is well known. With persistent use of NSAIDs, endoscopic proof of mucosal damage in the upper GI tract is significant, involving as many as 70% of long term users as opposed to 10% of individuals not using NSAIDs (Rao and Knaus, 2008). NSAIDs can also cause ulceration and gastrointestinal bleeding with the same process as NSAID-mediated gastrointestinal injury, except ulceration and associated bleeding are far less frequent cases. This is due to prostaglandins defensive function in inducing mucus and bicarbonate secretion, and also stimulating epithelial proliferation (Moore et al., 2007).

The risk in cardiovascular system

Compared with ibuprofen, naproxen, paracetamol and non-analgesic usage, the non-selective NSAIDs diclofenac have considerably higher cardiovascular risk (Warner and Mitchell, 2008). A study in 2005 showed etoricoxib as COX-2 selective NSAIDs were associated with a similar risk of thrombotic events compared to diclofenac (Sowers et al., 2005). All NSAIDs, however, were associated with a high risk of acute myocardial infarction as shown in another analysis (Walker et al., 2018) and highly correlated with heart failure (Nissen et al., 2016).

The risk in renal

NSAIDs also provoked renal failure involving acute kidney injury, retention of water and sodium, hyponatremia and hyperkalemia (Chiasson et al., 2019). Pathways of renal damage caused by NSAIDs-related prostaglandin synthesis inhibition (Zhang et al., 2017).

The potential role of Curcumin

Recent advances in osteoarthritis research have increased our understanding of the pathophysiology of the disease. In particular, the identification of TGF-β signaling pathways and interleukin provides hope for osteoarthritis drugs that modify the disease (Shang et al., 2017).

The role of IL-1 in osteoarthritis disease has been well explained. Analysis of the human synovial fluid and experimental model of osteoarthritis revealed a significant increase in IL-1, which associated with the severity of radiographic changes (Henrotin et al., 2010) IL-1 stimulates MMP production while reducing aggrecan and proteoglycan production in in vitro and in vivo models, ultimately results in an imbalance in the anabolic and catabolic responses of stimulated chondrocytes (Henrotin et al., 2010; Jurenka, 2009).

Molecular biology advancements have demonstrated that the ongoing cartilage degradation mechanism is guided by the release of inflammatory cytokines and accelerated by the stimulation of other inflammatory mediators, including matrix metalloproteinases (MMPs) (Shang et al., 2017). In vivo and in vitro studies have shown that the catabolic action of major inflammatory mediators in the early stages of osteoarthritis can be slowed or stopped and can continue to block the inflammatory pathway that has been associated with the development of knee osteoarthritis with curcuminoid formulations usage (Henrotin et al., 2010).
In the process to inhibit MMP secretion and activity and neutralize the decrease in glycosaminoglycans levels, which can potentially prevent further degradation of cartilage tissue. Glycosaminoglycans whose role is to accelerate or intensify cartilage damage can be disrupted by the synthesis process in certain NSAIDs (Henrotin et al., 2010). In addition, curcuminoids act as cyclooxygenase-2 (COX-2) enzymes, which are correlated with pain and inflammation, by blocking the action of tumor necrosis factor (Jurenka, 2009).

Studies from Li et al. (2017) show that Curcumin plays a role in increasing autophagy and attenuates IL-1β-mediated apoptosis at most through ERK1 / 2 autophagy that is required during activation. These findings indicate that the role of Curcumin could be a potential development strategy in osteoarthritis by increasing autophagy through increased phosphorylation of ERK1 / 2 expression (Li et al., 2017).

Previous studies have shown that curcuminoids could provide therapeutic benefits that outweigh assistance for disease modification. This result would demonstrate the strong superiority of this formulation over regular medicine with NSAIDs, especially in the fact that certain NSAIDs may concurrently have adverse effects on cartilage metabolism and well-known toxicity relative to conventional NSAIDs. (Jurenka, 2009; Aggarwal and Sung, 2009).

Figure 1: The role of inflammatory mediators in the mechanism of osteoarthritis

Inflammatory conditions in osteoarthritis, played by the important role of cytokines secreted by immune cells (as shown in Figure 1). TNF-α and IL-1β are one of the pro-inflammatory mediators and cytokines secreted in early osteoarthritis. The cell production is carried out by synoviocytes, activated chondrocytes, and mononuclear cells (Sokolove and Lepus, 2013). TNF-α and IL-1β have been used to trigger inflammatory stimulation in chondrocytes and synovial cultures. After the stimulation process, IL-1β, IL-6, IL-8, IL-10 release will occur. IL-1β is involved in cell proliferation, cell differentiation, and cell apoptosis. Thus, it can disrupt the production of important structural proteins, collagen type II and aggrecan, which affect the activity of chondrocytes in the joints (Sellam and Berenbaum, 2010).

In this figure (Figure 2), we can see that there are two pathways in the process of arachidonic acid metabolism, namely the lipogenic pathway (LOX) and cyclooxygenase (COX). Cyclooxygenase is an enzyme in the COX pathway, which plays a role in the process of converting arachidonic acid into prostaglandins and thromboxan. COX-1 is expressed in most tissues, the inhibitory process in COX-1 will produce bad side effects such as peptic ulcers or kidney disorders from renal blood flow. In contrast, COX-2 cannot be induced at the site of inflammation by intracellular signals and cytokines (Sharma, 2002).

It has been found that through intestinal and oral epithelial cells, curcumin is able to play a role in inhibiting the induction of COX-2 gene expression (Lev-Ari et al., 2006). Based on previous studies, curcumin concentrations of 20 μM, showed strong inhibition of chemically induced PGE2 production in large intestinal cells. Different curcumin concentrations will reduce the regulation of COX-2 protein levels, inhibit the synthesis of PGE2, and increase apoptosis of cells expressing COX-2 protein (Lev-Ari et al., 2006).

A recent systematic analysis reveals that curcuminoid formulations are significantly more effective than placebo administration for pain reduction and functional enhancement. There was no significant difference between curcuminoid and placebo in the safety test findings. There were no statistically significant differences in curcuminoids in the efficacy results compared with NSAIDs; significant gastrointestinal side effects are less likely to be experienced in patients receiving curcuminoids (Bannuru et al., 2018; Pinzon et al., 2019). This study also indicates that curcuminoids can be as beneficial as NSAIDs, with much lower safety risks.
The novel RCT from Pinzon et al. (2019) studied 105 subjects with osteoarthritis. This RCT shows that the combination of Curcuma longa (CL) and Boswellia serrata (BS) extracts is beneficial for improving quality of life in osteoarthritis patients with fewer side effects compared with NSAIDs (Pinzon et al., 2019). The generalization of our study may be limited by the sample size, quality, and duration of available curcumin RCT data. To create meaningful clinical practice recommendations, the body of research is currently lacking in size or quality.

There are 3 main messages from this review: (1) There are unmet needs of treatment safety in the current management of osteoarthritis; (2) The use of NSAIDs and selective COX-2 inhibitors is associated with side effects in the form of disorders of the GI, kidney, and cardiovascular; (3) Curcumin may have a tolerance advantage over current therapy.

CONCLUSIONS

The results of our review indicate that there are many concerns in the use of NSAID / Coxib, especially in long-term treatment. Our review suggests that by reducing pain and improving function, while lowering the risk of side effects, curcuminoid formulations might become a useful addition to osteoarthritis patients for pharmacological therapeutic interventions.

Conflict of Interest

The authors declare that they have no conflict of interest for this study.

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