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Cover Page Footnote

I would like to thank Dr. Saleem for his help on this paper.

The Effects of Herbal Products in Cartilage Healing and Reducing the Progression of
Osteoarthritis

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I. ABSTRACT

Treatment for osteoarthritis (OA) includes symptom management with nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, and acetaminophen. However, these drugs pose health risks for long-term use, such as contraindications and gastrointestinal/cardiovascular issues. This systematic review of the literature was conducted to evaluate the impact of the herbal products, turmeric and ginger, in cartilage healing and reducing the progression of OA. It was found that turmeric and ginger can aid in symptom management for OA and promote cartilage regeneration, with turmeric extract yielding greater evidence-based results. Turmeric reduces the amount of pain and stiffness experienced from OA and can restore cartilage by subduing the master pro-inflammatory transcription factor, nuclear factor-kappa B (NF- κ B), signaling tracts in chondrocytes. Ginger decreases the number of inflammatory cytokines caused by OA through similar mechanisms, and it also significantly lowers the production of the principal mediators of inflammation, nitric oxide (NO) and prostaglandin E2 (PGE2), in cartilage tissue, stimulating cartilage recovery. The beneficial implications of these herbs, especially turmeric, could be confirmed for medical use upon the completion of more studies that assess their prime-dosage and long-term effects.

KEYWORDS: Cartilage anatomy and physiology, Herbal products, Nutrients, Osteoarthritis treatment, Over-the-counter products

II. INTRODUCTION

Osteoarthritis (OA) is a degenerative disease prevalent in geriatric populations. Noninvasive treatment includes exercise and diet modifications, whereas invasive treatment includes injections and surgery (Bennell et al., 2012). With the rise of the herbal medicine industry,

interest has been given to herbal products' restorative effects (Chatfield et al., 2018). Many patients with chronic conditions, such as OA, seek alternative treatments in conjunction with exercise modifications and prescribed medication(s) (Van Haselen, 2003). Some healthcare professionals requested more information regarding the makeup and production of these herbs to ensure that patients are not taking any product that could potentially cause more harm than good (Del Grossi Moura et al., 2017). A systematic review of the literature was conducted to examine these claims and provide insight into how patients of OA respond to incorporating turmeric and/or ginger into their treatment plans. Thirty-eight articles from search engines including ProQuest, PubMed, and Wiley were screened to ensure that they were related to the research topic. Some of the articles were excluded as they were geared more towards rheumatoid arthritis (RA), whereas the focus of this review was OA, a degenerative, mostly non-inflammatory condition (Park et al., 2018). Articles included in this review were most applicable to answering whether certain herbal products could promote cartilage healing and/or reduce the progression of OA. These articles contained information on the function of cartilage, description and statistics of OA, background and overview on popular herbal products, and details regarding the use of certain herbal products. No specific gender, race, or ethnicity was excluded in this literature review.

III. EPIDEMIOLOGY

The major type of arthritis is non-inflammatory/degenerative arthritis (Pandey et al., 2014). OA can be further divided into traumatic and familial OA: traumatic OA is more common in younger, active populations and is usually attributed to trauma-related causes; familial OA is more common in women over the age of 50 and has a basis of heredity (Muoh et al., 2014). OA is more common than any other type of arthritis as it is estimated to affect 40% of people over

the age of 70 (Valdes & Spector, 2011). Joints that are commonly affected include the hand, hip, and knee (Muoh et al., 2014). The elderly experience the greatest effect of age for hip and knee OA; women have been shown to be at higher risk of hip, knee, and hand OA possibly linked with estrogen deficiency (Prieto-Alhambra et al., 2014). The obesity epidemic in America also contributes to individuals developing symptoms of OA (Bijlsma et al., 2011). In regard to race, the prevalence of knee OA among older black people is at least as high as that reported for white people, however black patients report more severe pain than white patients do as a result of substantial disparities in reporting of knee pain, likely reflecting the racial disparities in receiving a total knee replacement (TKR) surgery among other treatments (Ibrahim, 2021).

IV. PATHOPHYSIOLOGY

Cartilage damage is a prominent aspect of osteoarthritis where chondrocytes express a subset of factors, such as cytokines, that begin a dangerous cycle of cartilage breakdown and trigger an inflammatory process by producing synovial macrophages and fibroblasts in the synovial fluid (Jang et al., 2021). The hyaline cartilage initially degrades from the surface with the loss of two main components of its extracellular matrix, the type II collagen fibrillar network and the proteoglycan aggregates, both of which are responsible for absorbing high compressive loads (Grenier, et al., 2014). Factors that contribute to the initial destruction of cartilage include excessive mechanical load and/or tissue-degrading enzymes (Brandt, 2010). In OA of the knee, which is the most prevalent form of OA, OA targets the synovial joint from which the cartilage degrades, and osteophytes (bone spurs) begin to form (Chen et al., 2017). OA is usually classified as a noninflammatory disorder as the leukocyte count in OA synovial fluid typically falls below the threshold of the definition of an inflammatory disorder (Sellam & Berenbaum, 2010).

V. GINGER

Background Information

Zingiber officinale, more commonly known as ginger, is a member of the Zingiberaceae family that has been used for centuries in Ayurvedic and Chinese medicine for its healing properties; patients suffering from chronic inflammatory and degenerative diseases have adopted ginger into their diets/wellness routines in hopes of improving their symptoms as studies have shown that ginger contains anti-inflammatory and analgesic qualities that can reduce pain generated from these diseases (Antoniewicz et al., 2021).

Mechanism of Action

In a rat model with induced arthritis, ginger essential oil was found to block cyclooxygenase-2 (COX-2), an enzyme whose products increase the symptoms of inflammation, preventing the onset of chronic inflammation (Antoniewicz et al., 2021). Ginger was also shown to decrease the concentration of the inflammatory factors, tumor necrosis factor-alpha (TNF- α) and Interleukin-1 beta (IL- β), along with the serum concentrations of NO and high-sensitivity C-reactive protein (hs-CRP) in patients with osteoarthritis after they consumed 1 gram of ginger supplementation daily for 3 months (Mohd & Makpol, 2019). Massaging affected joints with ginger oil was shown to provide relief for patients as led to increase in serotonin and dopamine levels which closed the pain gate linked to sensory neurons; massage is believed to facilitate more blood flow which can increase the clearance of local pain mediators (Yip & Tam, 2008).

An orthopedic study reported that ginger is believed to block the development of the inflammatory chemicals, cyclooxygenase (COX), lysyl oxidase (LOX), and leukotriene (LT) (Sorbie, 2002). Vitro studies of human synoviocytes have demonstrated that ginger extract can

stop TNF- α activation and COX-2 expression, supporting ginger's anti-inflammatory properties (White, 2007).

Clinical Trials

Ginger has been found to reduce stiffness, pain, and difficulty in patients suffering from knee osteoarthritis based on the Visual Analog Scale (VAS) (Mohd & Makpol, 2019). In a 10-year randomized control where oral and topical ginger were used as pain relievers for chronic inflammatory and degenerative diseases (including OA of the knee), 9 of the randomized controlled trials claimed that ginger was effective in reducing pain from their condition, while 1 claimed that ginger did not provide significant relief for their symptoms; it should be noted that ginger was taken orally solely, primarily, and in combination with other botanicals, and the combination trial was most productive in alleviating knee pain (Rondanelli et al., 2020). In a clinical trial that explored the effectiveness of aromatic ginger and orange essential oil through massage for knee OA, aromatic ginger and orange essential oil (1% ginger oil and 0.5% orange oil in olive oil as the base lubricant) were helpful in decreasing symptoms of moderate-to-severe knee joint pain as well as stiffness and daily function in short-term use, but not for quality of life based on the (WOMAC) scale after massaging the knee joint in approximately 30-minute sessions six times over a span of two-three weeks (Yip & Tam, 2008).

Risks

Ginger has been shown to cause fibrinolytic activity and mild gastrointestinal effects, so patients taking certain medications such as anticoagulants should be cautious; the safety of using ginger for long-term use is somewhat cautioned against as in a great percent of individual studies of ginger, patients reported various gastrointestinal issues such as heartburn, diarrhea, and

irritation of the mouth (White, 2007). Although no adverse effects were cited in the study on ginger oil, the study used a lower amount of ginger oil, 1%, so perhaps trying a 2% or 3% would yield different results; possible errors in the methodology of this study included the sample size being too small and the nurse massage therapist being aware of the different treatments being administered to patients (Yip & Tam, 2008).

Side effects were directly related to the dosage of ginger per day. Heartburn was rarely reported when the dosage is less than 500 mg/day (Eberhart, 2003; Ryan 2012). Incidence of heartburn increases between 7 to 10% once the dosage reaches 750 mg/day (Kalava, 2013; Paramdeep 2013). At 2000 mg/day, many patients experience heartburn (Citronberg, 2013). Diarrhea is seen in about 2% of patients once the dosage is increased to 750 mg/day (Kashefi, 2015). Bloating is also seen at higher dosages (Citronberg, 2013).

Dosage and Route of Administration

There have not been many studies which indicate a specific form or amount of ginger that can yield the most benefits. For example, using ginger oil in massages or inhaling its vapors from steamed water have been recommended, but there is still more research needed to be performed to confirm these beliefs. Most clinical research used approximately 0.25-1 g of ginger powder in capsule form one to four times a day to see an effect take place (White, 2007).

Evidence

Several studies have shown that ginger extract reduced cartilage inflammation and degradation and thus, promoted cartilage regeneration by repressing the appearance of pro-inflammatory cytokines (Buhrmann et al., 2020). Ginger was also shown to improve pain associated with OA, which was short-term (Antoniewicz et al., 2021).

VI. TURMERIC

Background Information

Curcuma longa, more commonly known as turmeric, is a member of the Zingiberace family found in turmeric root and rhizome that has been used in India and China for centuries for its remedial effects (Asher & Spelman., 2013).

Mechanism of Action

Curcumin is the yellow pigment isolated from turmeric that displays anti-inflammatory characteristics through its inhibition of many cell signaling pathways involving NF- κ B and COX-2 (Kunnumakkara et al., 2017). Based on current studies, it was also determined that turmeric acts as a synergist agent which indicates that it works better with other products including soy phosphatidylcholine and boswellia serrata, most likely due to raw turmeric being insoluble and lacking bioavailability (Henson, 2018). An article that analyzed the results obtained from in-vitro cartilage and osteoarthritis explained that turmeric is less soluble in its natural state, curcumin (curcuminoid compound of turmeric), (Henrotin & Mobasheri, 2013).

Turmeric's anti-catabolic effects block the activation of NF- κ β which reduces the spiked catabolism that occurs in joints in osteoarthritis, thereby impeding cartilage degeneration and instead stimulating cartilage-producing proteins like aggrecan in the extracellular matrix of the cell; turmeric might be able to aid in reducing the progression of OA as it contains properties which lessen the breakage of the cartilage that usually occurs in OA, and new integral molecules could be generated for the cell instead (Henrotin & Mobasheri, 2013). Turmeric regulates NF- κ β immune response similar to that of NSAIDs and its inhibitory effect on upregulation of matrix metalloproteinase-1 (MMP-1) and matrix metalloproteinase-1 (MMP-2) enzymes (which

advance the catabolism of articular cartilage) can slow the progression of OA (Paultre et al., 2021). Curcumin is speculated to target metabolic enzymes and transport proteins in alleviating OA symptoms (Asher & Spelman, 2013).

Clinical Trials

In a randomized, double-blind, placebo-controlled study of 201 patients (majority elderly female with deteriorating OA of the knee), Curamin, a mixture of curcumin and boswellic acid, assisted in managing OA symptoms (Henson, 2018). Boswellia, or *boswellia serrata*, belongs to the Burseraceae family, and the boswellic acids found in boswellia have also been noted for their anti-inflammatory and anti-arthritis properties, but more studies introducing bio inflammatory markers would be helpful in understanding the mechanism behind Boswellia's effects (McLean, 2020). The curcumin treatment was given as a CuraMed capsule which primarily contained dry turmeric extract and essential oil from turmeric rhizome while the curcumin and boswellic acid combination treatment was given as Curamin; Curamin provided the best results in improving the patients' abilities on all the physical performance measures (PPM) tests and conditions of the WOMAC index (Henson, 2018). To confirm the results of a 3-month study of a curcumin-phosphatidylcholine phytosome complex administered to 50 patients suffering from OA, a study was pursued where 100 patients were given the compound over an 8-month period, and significant improvements occurred in this trial, so it was recommended that the compound be considered for long-term treatment of OA (Belcaro et al., 2010). Another source reviewed the validity of the previous study and emphasized the benefits of Meriva for its combination of curcumin and soy phosphatidylcholine, which enabled more of curcumin's properties to be expressed, further highlighting turmeric's synergistic abilities (Kunnumakkara et al., 2017).

In a study exploring the potency and safety of curcumin in improving symptoms of moderate to severe OA of the knee in 107 patients, patients were randomly selected to receive either 0.4 g of ibuprofen or 0.5 g of turmeric extract (curcuminoids) twice/four times a day for six weeks, respectively; although there was no significant difference between the two active treatments, those in the curcumin group experienced less pain when climbing stairs and spent less time on a 100-m walk and going up and down a flight of stairs following completion of treatment (Henson, 2010).

Risks

In terms of adverse effects, in the study comparing curcumin and ibuprofen, approximately 20% of participants in the curcumin group and 25% of participants in the ibuprofen group complained of an upset stomach; however, participants in the curcumin group who experienced bloating and passing gas described these symptoms as beneficial gastrointestinal effects unlike patients in the ibuprofen group who reported gastrointestinal irritation symptoms (Henson, 2010). Another study that compared the effectiveness of turmeric to NSAIDs noted that turmeric appears to be safe and without serious side effects; adverse effects including non-specific gastrointestinal discomfort, dyspepsia, and diarrhea were experienced by some patients in the clinical trial(s) (Paultre et al., 2021).

Dosage and Route of Administration

Curcumin is not easily absorbed into the bloodstream, so pairing it with lipid complexes or nanoparticle samples may allow for easier/more absorption (Henrotin & Mobasheri, 2013). Different studies used a different preparation of turmeric that changed its pharmacokinetics and increased its bioavailability; the dosage varied from roughly 0.1-2 g/day (Paultre et al., 2021).

Evidence

Early clinical trials have shown that turmeric is beneficial for osteoarthritis, but longer durations of these trials are still necessary to support these notions (Asher & Spelman, 2013). According to CDC's national health and nutrition examination survey, patients are taking turmeric for at least 2-years (Goldrosen, 2004).

V. DISCUSSION

Turmeric and ginger have both been shown to contain anti-inflammatory properties that can aid in symptom management of OA. However, there was limited evidence that supported whether the benefits of ginger outweigh its risk of gastrointestinal/fibrinolytic issues and current studies do not establish an ideal dosage of turmeric extract. Nonetheless, turmeric extract has been shown to have few adverse effects and patients in various trials reported to have tolerated longer durations of walking, experienced less stiffness in the joints, and improved mobility, possibly attributed to turmeric's synergistic abilities. Even though curcumin is one of the most studied botanicals in biomedical literature, research on its long-term effects are still necessary before confirming its efficacy. It should also be noted that most participants in these studies were females and had osteoarthritis of the hip and knee, so additional studies that evaluate the effects of turmeric and ginger treatment on males and on other joints affected by OA including the fingers, hands, elbows, and back should be conducted to determine whether similar results are obtained. There seems to be no specific reason as to why some studies included more female participants as compared to male participants, but this will be a parameter to factor in when making conclusions. The strength of these herbs in comparison to drugs such as NSAIDs and COX-2 inhibitors in treating OA should be investigated as well. Implementation of turmeric in

the future could potentially result in a new treatment for OA that poses less health risks as compared to current adoptions of drugs such as NSAIDs.

VI. CONCLUSION

Turmeric and ginger have evidence suggesting that they should be classified as an alternative treatment for osteoarthritis upon the completion of more research that assess their long-term implications, ideal dosage and form, and effects when adopted in different populations. The observations or conclusions are very preliminary and needs elaborate research and statistical validation before turmeric and ginger can be safely classified as an alternative treatment for OA safe for long-term use. It seems that ginger and turmeric may play a role in alleviating the symptoms of OA and reducing its progression. When comparing turmeric to ginger, turmeric holds more promising results in alleviating pain, stiffness, and flexibility of the targeted joints. Implementation of these herbs could result in alternative treatment for OA.

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