

Review Article

Influence of Mango (*Mangifera Indica* L.) Stem Bark Extract on Pain Intensity and Inflammation in Osteoarthritic Patients

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Introduction

Plants are endorsed as an enriched reservoir of important pharmaceutical products due to ample therapeutic facets and have been used in traditional therapeutic herbal medicines against numerous diseases and illnesses [3,4,21,35]. Osteoarthritis (OA) is one of the common form of arthritis which estimates affects 250 millions of people around the world and the highest prevalent form among these is knee osteoarthritis [11]. Osteoarthritis is a disease of joint which is represented by cartilage degeneration, inflammation, pain, impaired motility and dysfunction, mainly in elder people. Due to continuously bearing the largest part of the body weight, OA is mostly occurred in knee joints [19].

The most common rheumatic disease is osteoarthritis, which chiefly affects subchondral bone of synovial joint and also articular cartilage, which ultimately results in failure of joint. The most prominent features of OA are osteophyte formation at the end of joints, subchondral sclerosis, and reduction of joint space, chondrocalcinosis and development of subchondral cyst. It has been predicted that approximately 40% to 80% of population with radiographic changes will have symptomatic disease. About 10% to 30% population have symptomatic knee osteoarthritis worldwide, particularly in rural areas, because of their occupation that demands high physical activities [8]. Osteoarthritis severity and prevalence are increasing owing to aging of

Abstract

Osteoarthritis affects millions of people around the world, which leads to the formation of osteophytes, subchondral cyst, subchondral sclerosis and narrowing of joint space. These causes joint pain, stiffness and swelling of joints, due to which an osteoarthritic person is unable to perform their daily activities. In recent years, mango stem bark extract that contains flavonoids, polyphenols, phytoosterols, catechin and fatty acids seems as a therapeutically effective for knee osteoarthritis. It has the ability to overcome the pain and inflammation in osteoarthritis. The component Mangiferin is considered as a highly acceptable as an antiarthritic treatment. Therefore, the aim of this article is to show the dominant role of mango stem bark extract in managing osteoarthritis.

Keywords: Osteoarthritis; Osteophytes; Polyphenols; Inflammation; Mangiferin

the population, leading to locomotor dysfunction. It includes mild to severe joint pain, deprivation of function, joints stiffness and unable to perform daily activities which results in severe joint swelling and tenderness [25].

People with osteoarthritic symptoms of the knee have deep and hurting pain. At initial stage of the disease, pain is irregular and it is mostly linked with the use of joint. With various papulation, this symptomatic syndrome advances which leads to chronic pain that even occur at the night and when the body is at rest. After rest, when movement is started, the joint feels stiff which results in pain and difficulty in movement. Individuals with knee osteoarthritis experiences more difficulty while doing daily bases activities. People with progressive disease may experience a sound of 'cracking' during body movement. Indeed, osteoarthritic knee is more effective as compared to other disease for dysfunctioning in stairs climbing, walking, running and in doing household chores amongst individuals of age 50 and older [8]. There are few factors that may influence on people to osteoarthritic knee are height, genetics, age, occupational activities, weight and inadequate BMI, trauma history, occupational activities and physical actions like lifting, climbing and squatting etc [26]. Epidemiology studies have showed that both exogenous factors like joint surgery, overweight and lifestyle aspects (tobacco & alcohol) and endogenous factors like

age, sex & ethnic origin are the threats of osteoarthritis. Genetic factors are definitely playing a role in developing osteoarthritis. Spector *et al.* conducted a clinical study that involves female twins, presented heredity effect on the progression of osteoarthritis of knee and hip. An epidemiology study was performed by Grrotle *et al.* showed an important dose effect association for overweight, which is considered as a risk factor for osteoarthritic knee [16].

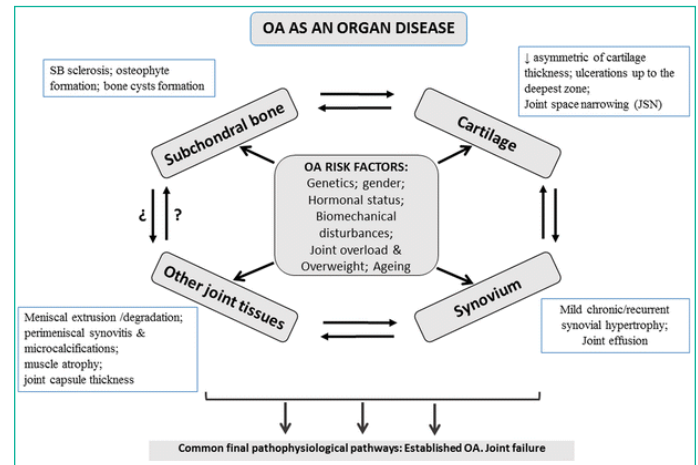
Osteoarthritis is a joint disease. When cartilage loses from the joint then the bone grows that makes effort to heal impairment. Rather the things become better, the opposite happens and the bone grows irregularly and the things becomes worse. For example, the bone can develop as misshape that makes the joint unbalance and hurting. According to the doctor's osteoarthritis basically caused by the thinning of cartilage. So, Osteoarthritis (OA) is now called as whole joint disease. Exercise is an activity that improves and strengthen muscles and keeps a person physically active. Exercise has a great impact on overall health. Now a days people exercise for many purposes, like to boost muscles, to maintain weight or either to overcome the symptoms of OA [8].

In osteoarthritis, there is chronic and low-grade inflammation that primarily involve innate immune mechanism. The common outcome of OA is synovitis which is basically infiltration of inflammatory cells into synovium, which is considered to be occur at initial stage of the disease but it is more dominant as the stages more advanced and can be led to severity. There are several inflammatory mediators in osteoarthritis which includes Prostaglandins (PGE2), plasma protein (C-reactive protein, defined as a marker for progression & development of OA), leukotrienes (LKB4), and cytokines ((TNF, IL1 β , IL6), growth factors (TGF β , nitric oxide and complement components [18].

The well-known pro-inflammatory cytokines of osteoarthritis are Tumor Necrosis Factor (TNF)- α and Interleukin -1 β . Reactive oxygen species and inflammatory mediators are produced due to disturbance of homeostatic balance of chondrocytes stimulated by IL-1 β and (TNF)- α by reducing anabolic activity and increasing catabolic activity of the articular cartilage. Inflammatory mediators that involve nitric oxide, cyclooxygenase 2, prostaglandin E2 and reactive oxygen species are produced by Interleukin 1 β and tumor necrosis factor. Inflammation-related pain can be suppressed by nonsteroidal anti-inflammatory drugs with certain unfavorable health conditions. While the nutraceutical mango has a major role in managing of OA [7]. It is believed that the main tropical fruit in the world is 'Mango' that is originated from Asia [28]. Mango is a plant widely used in traditional medicine; its aqueous extract can be obtained from the stem bark. Due to its antioxidant and anti-inflammatory effects, it has been used for the treatment of OA [27]. Mango extract is a combination of components which involves fatty acids, flavonoids, polyphenols, triterpenes and phytosterols. The bark is reported to contain mangiferin, catechin, alanine and procatechic acid. *Mangiferin* (15-20%), the chief constituent of the mango extract, is a glucosylxanthone found in large quantities in the stem bark that helps in reducing pain and inflammatory mediators and suppress inflammatory cytokines [12].

Mangiferin is considered as a most prominent antioxidant which have marvelous health related benefits. It has anti-inflammatory, antioxidant, antidiabetic, antiviral and anticancer properties.¹³ Previous studies advised that MSBE could be used to treat chronic pain inflammatory components [9]. The super-abundant type of compound in *mango* are polyphenols which includes Catechins, Gallic acid and Mangiferin [20].

Antioxidants are defined as a constituent that delay and prevents from oxidative damage by catching free radicals to targeted molecules [23]. Natural compounds like Polyphenols act as a good antioxidant. From various studies, it has been described that Reactive Oxygen Species causes several diseases and syndromes in humans. In humans, there is an antioxidative mechanism which acts against Reactive Oxygen Species and about some other oxidants by disabling free radicals before they attack targets in human body. Most of the mango parts contains polyphenols, that are eminent antioxidants [1].



Prevalence

As the age increase, the prevalence of OA also increases, which normally affects women more as compared to men. Mostly, OA is affected to knee and hip due to bearing the largest part of the body [25]. Globally, the OA knee prevalence in people of aged 15 is 16% and in people of aged 40 and over is 22.9% [6]. The prevalence of knee OA in Pakistan is about 25% in rural population and 28% in urban population. It has been shown in various studies that the prevalence of Bangladesh is 10.20% and in India it is about 5.78% [8]. The prevalence of knee OA in Japan in men and women is approximately 11% and 30% respectively [21]. In UK and US population, the prevalence is about 12.5% [5].

Nutritional Composition of Mango

Due to essential and significant substances, *Mango* has a high nutritive value and also have a lot of health benefits. Mango components are categorized as; *micronutrients* which include vitamins & minerals and *macronutrients* which includes proteins, amino acids, carbohydrates, fatty acids, lipids & organic acids and phytochemicals which includes pigment, polyphenol & phenolic. There are also structural carbohydrates in mango that are cellulose and pectin [15].

A ripe mango is a best source of sugars like glucose, sucrose & fructose, while an unripe mango is a rich source of pectin and starch. The protein amount in mango is low (0.5% -5.5%), as compared to carbohydrates. In terms of micronutrients, the best way to prevent from vitamin A deficiency is to consume mango in accurate amount. In macronutrients, the pulp of mango comprises of proteins, lipids, amino acids, organic acids, dietary fiber and also carbohydrates (16-18%) [13].

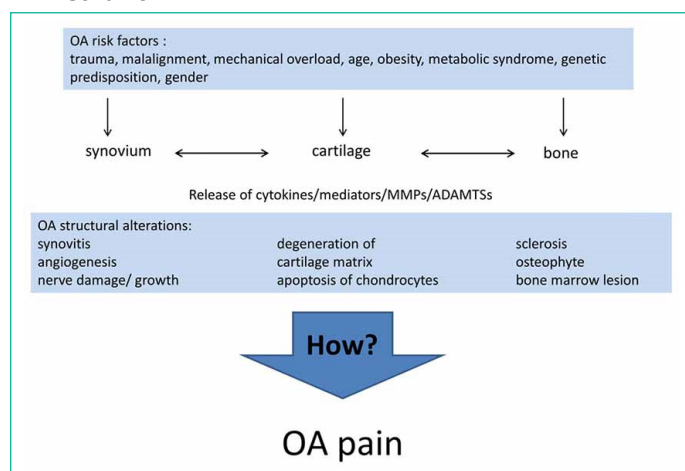
According to various studies, the mango contains phenolic which are catechin, quercitrin, epicatechin, quercetin and leucocyanidin. Shivashankara *et al.* stated that the chief flavonoids in mango are catechin & quercetin (Kabir *et al.*, 2017). The most ironic phenolic compound in mango is Gallic acid [24]. It is reported that mango bark contains catechin, mangiferin, kinic acid, γ -amino-butyric acid, alanine, glycine and others. The leaves and bark of mango encompasses high level of phenolic

compounds, especially *mangiferin* which plays major role in pharmaceutical activities [33]. The best source of carotenoids is mango, basically carotenoids gives flesh color: red, yellow or orange [17].

Health Benefits

Fruits like mango, are a noble source of several health stimulating bioactive components. Universally, all fruits and vegetables contain polyphenols and it delivers antioxidant and gives shielding effects to human body. A study was conducted by Gonzalez *et al.* that reported plant cell has advanced mechanism containing various metabolic compounds (catalase, flavonoids, peroxidase, lignans, glutathione reductase and ascorbate peroxidase etc.) which transform Reactive Oxygen Species (ROS) into less toxic products in order to prevent injuries. For the production of antioxidant molecules in signaling pathway reactive oxygen species are involved (Kabir *et al.*, 2017).

Mechanism

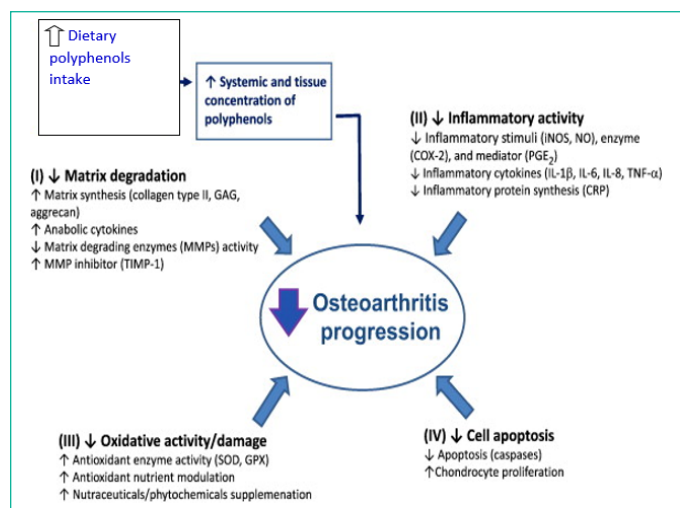


Articular cartilage loss is a signature pathologic feature of Osteoarthritis (OA) which is typically determined on plain radiographs in joint space. Joint disturbance and loss of cartilage is associated with efforts at repair with new bone development take place and the formation of osteophytes and subchondral sclerosis. Due to more advanced and comprehensive technology of studying imaging, chiefly Magnetic Resonance Imaging (MRI), osteoarthritis is now known a disease which involve synovium (synovitis), ligament, joint capsule, and menisci. The evidence of abnormal bone structure at the subchondral boundary with cysts and Bone Marrow Lesions (BMLs) also shown by MRI studies [22].

The molecular mechanisms of dietary polyphenols' effects on cartilage chondrocytes. Dietary Polyphenols (DP) mitigate inflammation and degeneration of joint by modulating STAT, MAPK, AP-1 and NF- κ B signaling pathways. Dietary polyphenols also inhibit apoptosis of chondrocytes. The activation of STAT, MAPK, AP-1 and NF- κ B signaling leads to the generation of iNOS, COX-2 and MMP-13 that causes the degradation of cartilage matrix. With the activation of these critical pathways by Inflammatory stimuli (IL-1 β), many relevant events were blocked by the supplementation of dietary polyphenols [29].

Experimental Studies

Wang *et al.*, A was investigated the benefits and shielding effects of Mangiferin and shows us the mechanism of these functions on the joints of arthritic rats. The rat model of Adjuvant-induced Arthritis (AA) was developed and clinically assessed by plasma, arthritis index, synovium homogenate parameters and paw edema. The joint destruction severity was evaluated by radiologically and histopathological. Real-time PCR, transwell assay, flow cytometry and CCK8 were used to evaluate the vitro



effects of Mangiferin on production of inflammatory mediators in RA-FLSs, migration, apoptosis and proliferation respectively.

The results revealed that pannus formation, synovial inflammation & bone erosion ($p < 0.05$) were inhibited by Mangiferin. Additionally, Mangiferin effectually reduced the damaging behavior of RA-LFSs by preventing secretion of inflammatory mediators, proliferation, promoting apoptosis and migration. The advance mechanistic results showed that Mangiferin have an antiarthritic effects through barring the pathway of NF κ B and MAPKs (ERK2 and p38) [34].

A study was investigated by Arif *et al.*, that *Spondias Mangifera* (*S. mangifera*) have traditionally been used in India for managing rheumatism. The current research discovers the antiarthritic and anti-inflammatory effects of extract of *Spondias Mangifera*. In both vitro and vivo, the experimental study was accomplished. In vitro, the parameters free radical-reducing potential, 1, 1-Diphenyl-2-Picrylhydrazyl (DPPH), protease inhibitory activity and albumin denaturation were used. Thus, in vivo the action was calculated by the following factors: IL-6 inhibition assay, COX, arthritis score in Freund Adjuvant (CFA) models at a dose of 400 mg/kg per day of different fractions and TNF- α . The vitro activities showed results of decrease in protease inhibitors, albumin denaturation and scavenging activity at 500 μ g/ml. Intake of the above stated dose of *Spondias Mangifera* alcoholic fraction shows noteworthy dropping ($p < 0.01$) of paw diameters, IL-6, arthritis score, TNF- α then diseased animals. The present study showed that *S. Mangifera* alcoholic fraction extract has anti-inflammatory properties and holds tremendous properties on arthritis and further can also be used for managing arthritis [2].

Original Studies Regarding Effect of Mango on Reducing Pain in Osteoarthritis

Sr.no	Study subjects	Dietary intervention	Duration of the treatment	Treatment effect	References
1	50 patients with knee pain	600 mg extract supplement	3 months	↓ Synovial thickness ↓ Joint pain	14
2	18 male guinea pigs	20 μ mol Intra-articular injection	18 weeks	Smooth and continuous articular surface	31
3	20 patients with OA	900 mg extract supplement + methotrexate	3 months	↓ Swollen joints ↓ Tenderness of joint	32
4	30 Arthritic rats	20 μ mol Intra-articular injection	12 weeks	↓ Synovial inflammation ↓ Bone erosion	33
5	24 female rats	40 μ mol Intra-articular injection	9 weeks	↓ Cartilage degradation Normal cartilage surface	29

Conclusion

OA is a joint disease, which causes pain and inflammation. Besides of pharmacological and nonpharmacological treatment, nutraceutical mango plays an important role in reducing joint pain, due to its antiviral, anti-oxidant and anti-inflammatory properties. Mangiferin, the main component of mango stem bark extract has a promising function in the management of OA and show a prominent effect on suppressing inflammatory cytokines.

Author Statements

Conflict of Interest

The authors declared that present study was performed in absence of any conflict of interest.

Author Contributions

Zarwa Iqbal designed and also wrote the manuscript. Moina Shahis showed statical expertise and assembled data. All authors read and approved the final version.

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