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Review Article

The Pathogenesis, Diagnosis, Treatment and Future Prospectives in Pharmaceutical Research and Innovation of Osteoarthritis

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ABSTRACT

The clinical term osteoarthritis (OA) refers to a collection of degenerative illnesses characterized by subchondral bone remodeling, progressively diminishing articular cartilage, and usually moderate synovitis. It is generally accepted that OA has a complicated etiology including immunological, metabolic, and mechanical components. Many environmental risk factors can initiate many disease pathways, such as trauma, low levels of education, obesity, and occupation. Epidemiological principles can be used to explain the distribution of OA in the community as well as the impact of risk factors on the onset and progression of the illness. Alterations in one tissue could effect changes in the other and ultimately influence how osteoarthritis (OA) progresses. This illustrates the dynamic interaction between cartilage and bone. Bone cells from OA patients have the capacity to alter chondrocyte metabolism. Traditionally, a physical examination has been used to diagnose OA clinically. This examination assesses joint soreness, swelling or abnormalities, and range of motion. An increasing amount of research indicates that recreational running, which is a non-contact/collision exercise, is not associated with an increased risk of developing knee OA or having it worsen. Osteoarthritis (OA) has a complex etiology that involves elements including trauma, aging, obesity, mechanical stress, kinematics, muscle restrictions, and inflammation that deteriorates cartilage. Both surgical and noninvasive methods are used to manage or treat osteoarthritis.

INTRODUCTION

The clinical term "osteoarthritis" (OA) refers to a collection of degenerative illnesses characterized by slowly deteriorating articular cartilage, subchondral bone remodeling, and usually mild synovitis. The condition can be defined as either a sickness or a process of age-related change. It is more frequent in women than in men, and its incidence significantly increases around the age of 60.[1] Osteoarthritis (OA) is characterized by the following symptoms: mild inflammation of the synovial membrane, degeneration of the bone

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beneath the joint, damage to the joint cartilage, and swelling of the joint with newly generated bone. [2] Although ovitis is not directly connected with the severity of OA, it is believed to be linked to the onset of OA and could be an indication of chondropathy in the future.Osteoarthritis is a common ailment that affects synovial joints. Its pathological features include localized focal foci of articular cartilage destruction in load-bearing regions. These regions are connected to subchondral bone alterations, thickening of the joint capsule, moderate synovitis, and the development of new bone at the joint borders (osteophytosis). [4] While it can appear in any synovial joint in the body, the most common places it affects are the hands, knees, hips, and spine. One joint may be affected, even though multiple joints are affected most of the time. Osteoarthritis is an age-related condition; it is less common before 40 but increases in frequency as people age, to the point where most people over 70 show radiographic evidence of the disease in certain joints[5] Clinical problems associated with these pathological and radiological changes include pain during limited range of motion, stiffness in joints during brief periods of inactivity, and discomfort related to joint use. and crepitus, or joint cracking. Pain is very important, and osteoarthritisc disease is thought to be the primary cause of the high prevalence of regional joint pain in the senior population. It is characterized by concomitant morphological and functional changes, a progressive loss of articular cartilage, and degeneration of the meniscus (in the knee), synovium, periarticular ligaments, and subchondral bone of the joint. Degeneration of the articular cartilage, alterations in the subchondral bone, and restricted intra-articular inflammation are all associated with osteoarthritis. [6] It is probably the result of rapid deterioration that occurred over a period of 10 to fifteen years. However, due to alterations in the cartilage matrix's composition that result in joint degradation after growth ends, hereditary OA often manifests quite early and after growth stops.[7] According to the WHO, osteoarthritis affects 18% of women over 60 and 9.6% of males worldwide. On the other hand, 5% of Indonesians over 61 suffer from osteoarthritis. Meanwhile, it is estimated that 255 million people in Indonesia suffer from osteoarthritis in their knees, with 15.5% of males and 12.7% of women affected (Koentjoro, 2010).[8]

ETIOLOGY OF OSTEOARTHRITIS

Modern imaging methods recognize osteoarthritis (OA) as a multitissue joint disease that can impact multiple tissues, each of which carries a distinct phenotype. Specifically, subchondral bone is important for the development and genesis of osteoarthritis. Particularly, compared to healthy individuals, OA knees have a greater subchondral bone area at the femorotibial articulation. This is associated with osteophytes and narrowing of the knee joint space.[9] While there is significant evidence relating obesity to osteoarthritis (OA) of the knee, there is contradictory information regarding the relationship between body weight and the development of OA of the hip. Saville and Dickson. [10] It is well accepted that OA has a complicated etiology including immunological, metabolic, and mechanical components. Many environmental risk factors can initiate many disease pathways, such as trauma, low levels of education, obesity, and occupation.[11] The exact cause of osteoarthritis is unknown. Numerous interrelated factors, including weight, trauma, and genetics, contribute to this disorder. Any event that alters the environment of the chondrocyte can lead to osteoarthritis.[12]

EPIDEMIOLOGY OSTEOARTHRITIS

The epidemiology of osteoarthritis varies among joints; specific problems and concerns are related to OA in the knee, hip, hand, foot, and ankle in addition to spinal OA. While it is not as common

as weight-bearing joints like the hip and knee, osteoarthritis (OA) can also develop in the shoulder.[13] Epidemiological principles can be used to explain the distribution of OA in the community as well as the impact of risk factors on the onset and progression of the illness.[14] It is a chronic degenerative joint disease that typically leaves a person disabled. In a clinical setting, it manifests as joint deformity, discomfort, and limited movement.[15] KOA is the 11th major cause of disability worldwide and ranks 38th among disability variables that affect life expectancy because to the aging of the population and the rise in the percentage of obese persons.[16] The most used method for radiological definition of OA is the Kellgren-Lawrence (K-L) grading system for radiological assessment of OA.[17] The lack of a single, accepted definition for OA is the reason for the significant differences in prevalence and incidence found in the numerous research conducted for each joint. There were 528 million OA individuals globally as of 2019, a 113% rise from 1990.[18] Recent meta-analyses have brought attention to the gender gap in prevalence and shown that women are more likely to develop both prevalent and incident knee OA. [19] Osteoarthritis (OA) is the most common cause of musculoskeletal pain, impairment, and handicap in Western industrialized countries.[20] The modern search for the causes of OA began with the work of British scientists Kellgren and Lawrence, who carried out epidemiologic studies encompassing several ethnic groups in various geographic areas, including western European and specifically British Caucasians, African and Jamaican blacks, and Native Americans.[21] Osteoarthritis usually develops over a number of years, though symptoms may not change for long periods of time during this time. Based on clinical and radiological features (panels), the disease is diagnosed.22]

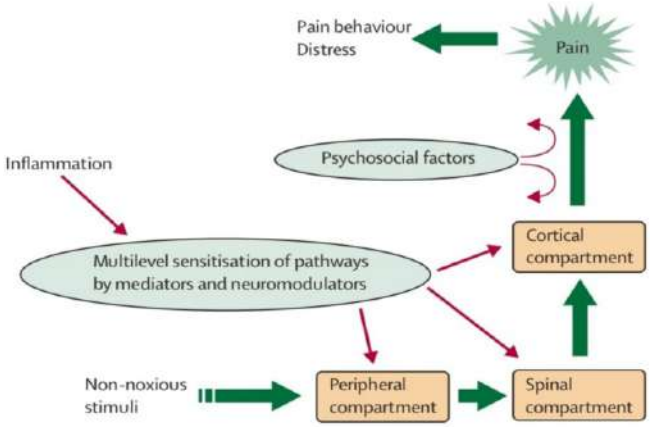


Fig No 01 Epidemiology Osteoarthritis

Bone :- Bone The alterations in the bones could potentially be the result of systemic changes. The results of Dequeker and colleagues. [23] has produced evidence of altered bone metabolism at sites like as the iliac crest, suggesting changes that may be systemic in nature. Basic changes in bone metabolism have been detected by the molecular composition of OA bone studies.[24] Alterations in one tissue could effect changes in the other and ultimately influence how osteoarthritis (OA) progresses. This illustrates the dynamic interaction between cartilage and bone. Bone cells from OA patients have the capacity to alter chondrocyte metabolism.[25] Because of bone resorption, urine contains more deoxypyridinoline cross-links.[26]

Cartilage:- The typical localized process of OA-related articular cartilage degradation can occur, as in the case of early experimentally induced OA in rabbits following partial medial meniscectomy and/or anterior cruciate ligament sectioning. Focal lesions can alter articulating surfaces and subsequently spread to harm specific joint components by creating variations in stresses. Days or weeks after a joint injury, such as damage to the meniscus or anterior cruciate ligament, alterations in the turnover of the cartilage matrix can be observed, and degenerative changes in post-traumatic OA can impact the entire articular cartilage. [27] Further cracks pierce the cartilage that has been wounded more superficially. Cell

cloning is restricted to areas that are more apparent, despite being observed early on. After then, the cartilage gradually starts to wear down. Apoptosis is elevated in OA, particularly at and around the articular surface.[28]

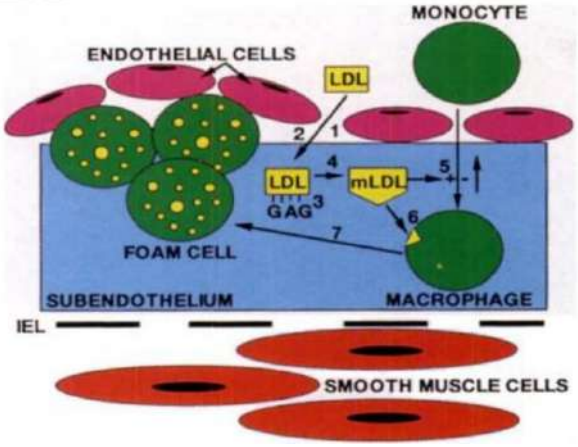


Figure:1

a schematic illustrating the steps needed to produce a fatty stripe. Beneath a damaged endotheilum are the foam cells of monocyte/macrophage origin that comprise fatty streak. Injury-induced increase in endothelial cell permeability set off a chain of events that eventually led to the formation of foam cells derived from macrophages. [29] After navigating permeable endothelium and entering subendothelium, low-density lipoprotein (LDL) can transform into modified low-density lipoprotein (mLDL) [30], where it binds to glycosaminoglycans (GAG). The presence of mLDL draws macrophages to the area, where they swallow it via scavenger receptors, leading to the development of foam cells. IEL, or Internal Elastic Lamina, [31]

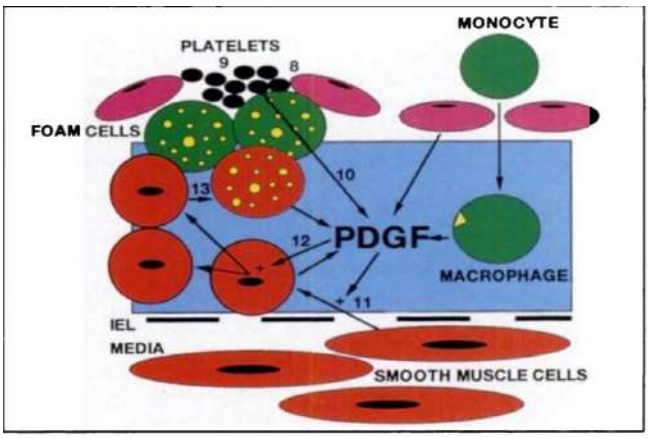


Figure:2

Lesion with atherosclerosis Fig. 2 shows the recruitment of smooth muscle cells. The atherosclerotic lesion draws smooth muscle cells from the media and subendothelium. Where there is localized endothelial cell denudation, platelets adhere and release platelet-derived growth factor (PDGF). Because PDGF is a chemoattractant, smooth muscle cells migrate from the media to the intima, where the mitogenic effects of PDGF promote cell proliferation. Some smooth muscle cells may absorb fat to become foam cells.[32]

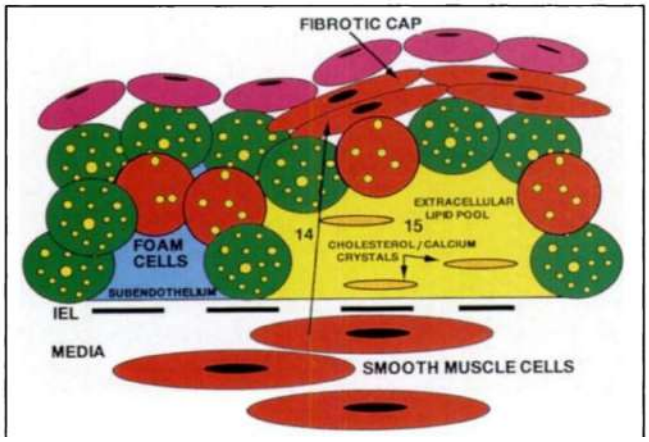


Figure:3

Figure 3 shows a diagram of a fibrotic atherosclerotic lesion and the circumstances that led to its formation. Fibrotic lesions are distinguished from fatty streaks by the presence of a fibrotic cap composed of smooth muscle cells that have migrated to the lesion's surface. Fibrotic lesions have been shown to have extracellular material pools including calcium and cholesterol

crystals. IEL stands for Internal Elastic Lamina. [33]

PREVALENCE & INCIDENCE

The prevalence of primary hip OA is higher in older persons (30–32 years old). According to the length and incidence of the disease, prevalence is the proportion of patients in the community; incidence, on the other hand, is the ratio of newly diagnosed cases to the total number of susceptible individuals within a population over a specific time period. The prevalence of hip OA varies amongst studies based on the criteria of hip OA and the characteristics of the examined group.[34] Hip OA with radiological diagnosis was less prevalent than radiographic hand or knee OA. For example, the Study of Osteoporotic Fractures Research Group discovered that radiographic hip OA affected about 7% of women over 65 [33]. Having said that, radiographic hip OA is common.[35] Depending on the definition of OA, the joint or joints under investigation, and the characteristics of the study population, the frequency of OA in the population at any one time, or the prevalence of the illness, varies. Recently, Lawrence and colleagues.[36] According to the Framingham Osteoarthritis Study. The Johnston County Osteoarthritis Project estimated that 28% of women over 45 had hip osteoarthritis.[37] The estimated prevalence of knee discomfort linked to osteoarthritis (OA) in the general adult population of Spain (n = 10 291) who were over 20 years old was 10.2% (95% confidence interval [CI], 7.9–12.5). . This was largely brought on by women over 55 having a high prevalence of knee discomfort.[38] The definition of OA, the joint or joints under investigation, and the characteristics of the study group all affect how common OA is in the population at any given time, or how prevalent the sickness is. Recently, Lawrence and others.[39] The specific joints most commonly affected by osteoarthritis (OA) include the knee, hip, hand, spine, and foot; Less often affected areas include the wrists, shoulders, and ankles.[40] According to the third National Health and Nutrition Examination Survey (NHANES III), radiographic knee OA was present in about 37% of adults 60 years of age or older.[41] The well-known female prevalence of hand OA is a frequent condition that is particularly obvious in patients who present to secondary care with significant symptoms.[42]

DIAGNOSIS OF OSTEOARTHRITIS

Traditionally, a physical examination has been used to diagnose OA clinically. This examination assesses joint soreness, swelling or abnormalities, and range of motion.[43] Hip osteoarthritis is diagnosed by the patient's medical history, clinical presentation, physical examination, and additional and basic diagnostic imaging modalities. The most generally used clinical criteria for the diagnosis of hip osteoarthritis are those set forth by the American College of Rheumatology.[44] Diagnostic techniques for KOA mostly involve clinical symptoms, signs, imaging studies, and laboratory testing. [45] We believe that an early diagnosis is necessary in order to initiate appropriate therapies, including medication, lifestyle modifications, and rehabilitation. Because most OA characteristics can still be addressed with a better prognosis at an earlier stage of the disease, early detection of OA should therefore be the primary focus of therapists. Tools include the homeostasis Model Assessment (HOMA) indices.[46] A visual analogue scale (VAS) with a range of 0 to 10 mm can be used in clinical settings to measure subjective pain.[47]

The joints most commonly affected in the illness process include the knees, hips, ankles, foot, distal and proximal interphalangeal joints, low back, and first carpometacarpal joints. Elbows, wrists, or shoulders are rarely involved in a pathogenic process.[48] The most common indication of osteoarthritis is joint pain. Movement usually makes the discomfort worse, especially after a

period of inactivity. This is referred to as the "gelling phenomenon." Osteoarthritis frequently results in morning stiffness that lasts less than 30 minutes, in contrast to rheumatoid arthritis, which can induce stiffness that lasts up to 45 minutes.[49] A physical examination is required to confirm and describe joint involvement, rule out functional syndromes with other causes, such as inflammatory arthritis, and rule out discomfort.[50] Moreover, optical coherence tomography (OCT) could be used as a prognostic biomarker for osteoarthritis in the future that requires little invasiveness.[51]

TREATMENT OF OSTEOARTHRITIS

Controlling pain and restricted movement are the current objectives of OA treatment98. It should be noted that although medication treatment is associated with adverse events (AEs) on the cardiac, renal, and gastrointestinal (GI) systems, particularly with regard to NSAIDs, which are the most often prescribed drugs for patients with osteoarthritis (OA), there is insufficient data to support non-pharmacological and pharmaceutical therapies.[52] While non-surgical (non-pharmacological and pharmacological) or surgical treatment cannot reverse the causes of osteoarthritis (OA), it can alleviate its symptoms (pain and loss of function).[53] When secondary OA occurs, joint replacement alone may not be enough to treat the issue permanently because the condition may later resurface in the same or a different location. In these circumstances, a DMOAD would be quite helpful. [54] Therefore, maintaining and improving functional abilities in addition to lowering pain and stiffness should be the objectives of treatment. Improving quality of life and stopping the progression of joint degradation are further long-term goals. Three categories of treatment possibilities exist: non-pharmacological, pharmaceutical, and surgical. Several people receive a mix of these modalities, each tailored to their individual need and risk considerations. The European League Against Rheumatism and the Osteoarthritis Research Society International have published evidence-based guidelines for the treatment of osteoarthritis.[55] Because of the potential for liver damage, the US Food and Drug Administration (FDA) limited the amount of acetaminophen in prescription combination products to 325 mg per dosage unit.[56] It is improbable that osteoarthritis (OA), a degenerative and progressive condition, will reverse or repair damaged structures. Consequently, the aim of current treatment approaches is to lessen symptoms, unless the severity calls for joint replacement surgery.[57] Proton pump inhibitors are recommended for those who are susceptible to ulcerative conditions.[58] It has been demonstrated that topical NSAIDs are just as effective—if not safer—than oral NSAIDs. They are suggested as an additional or substitute course of treatment.[59]

PREVENTION

As mentioned earlier, a multitude of information regarding risk factors and indicators is available to help identify patients and patient profiles with early-stage knee OA who are susceptible to the illness worsening. We believe that more comprehensive patient profile is necessary in order to develop a personalized treatment approach for these people with high-risk early knee OA. Our goal is to use a specific algorithm—which will need to be developed—to identify the patient as at risk in primary care. The algorithm will resemble some evaluation techniques used to identify patients with high-risk profiles for cardiovascular events or osteoporotic fractures. [60] There is currently no conclusive evidence to suggest that preventing overweight or obesity could impede the advancement of OA illness or disease. On the other hand, obesity and excess weight increase a person's chance of getting knee OA and other chronic conditions. Additionally, when structural

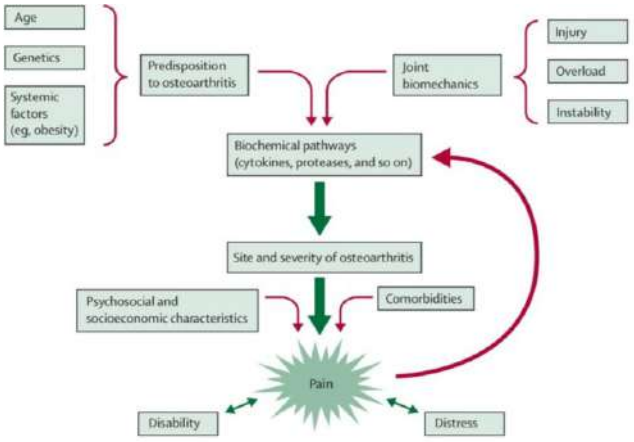
changes are prevalent, OA disease or pain reports increase.[61] However, little study has been conducted thus far to determine whether sports and exercise can also be used to postpone the onset of osteoarthritis. It is commonly known that physical activity improves cardiovascular health and is necessary for living a healthy lifestyle.[62] An increasing amount of research indicates that recreational running, which is a non-contact/collision exercise, is not associated with an increased risk of developing knee OA or having it worsen.[63] Osteoarthritis (OA) has a complex etiology that involves elements including trauma, aging, obesity, mechanical stress, kinematics, muscle restrictions, and inflammation that deteriorates cartilage.[64] However, there hasn't been sufficient research done to yet to determine whether physical activity and sports can assist postpone the onset of osteoarthritis. It is commonly known that physical activity improves cardiovascular health and is necessary for maintaining a healthy lifestyle.[65]

RISK FACTORS:-

Obesity :- Obesity is commonly attributed to mismatch diseases because, prior to the modern era, the majority of human bodies were rarely, if ever, exposed to prolonged high levels of positive energy balance. As a result, adaptations to deal with the effects of excess adipose tissue, particularly visceral stores, were rarely evolved.[66]

Diet:- Overweight people are far more likely to develop osteoarthritis (OA) in their knees and may also be at risk for hip and hand joint involvement. [67] Because overweight individuals do not necessarily feel a greater load across their hand joints, researchers have long wondered whether systemic factors, such as food problems or other metabolic impacts of obesity, may mediate part of this relationship. [68]

Vitamin D and OA:- Since the disease's first descriptions, pathophysiological changes in periarticular bone have been identified as a critical aspect of the osteoarthritis (OA) process.[69] as a consequence of reduced compliance and shock-absorbing capacity51, inadequate reparative response52, or maybe useful in managing the course of the illness or stabilizing an osteoarthritic j[70]



FUTURE PERSPECTIVE

We first discuss the links between joint injury and pain, with particular emphasis on the progression of joint damage and the persistence of pain, before discussing some information regarding the risk factors and pathophysiology for each of these components. We then discuss the genetic aspect of osteoarthritis and the related issue of the phenotypic expression of the disease. Finally, we provide some basic ideas on diagnosis, assessment, and care. Both surgical and noninvasive methods are used to manage or treat osteoarthritis.[71] Until recently, NSAIDs were frequently used to treat arthritis either on their own or in combination with other drugs that affect the course of the illness. NSAIDs, or COX enzyme inhibitors, lessen pain, but they don't repair cartilage or get rid of the warning signs and symptoms of a condition that is still there. In recent years, there has been evidence linking chronic NSAID usage to a number of unfavorable outcomes, including gastrointestinal (GI)

bleeding, renal and hepatic dysfunction, and other side effects. The anti-inflammatory drugs aspirin and ibuprofen (COX-I and COXII) are examples of non-specific COX enzyme inhibitors [72]. Animal and human-friendly nutraceuticals with anti-inflammatory and anti-arthritic qualities are becoming increasingly well-liked. Curcumin, shilajit, 5-loxin, avocado/soybean unsaponifiables, and type-II cartilage are a few examples of these. To ensure the quality of these innovative treatments, further safety and efficacy testing needs to be done as there is no guarantee that the condition will get better with alternative medicine. investigating the fundamental mechanisms of action that contribute to the reduction of osteoarthritis symptoms after joint injury. Cellular therapies for joints do not yet address the overall damage produced by osteoarthritis; they only cure particular cartilage abnormalities. If early disease identification continues to improve, cartilage with minimal damage may be resurfaced using cellular treatments. Even though progenitor cells from the cartilage surface zone have been found, early OA destroys the cartilage surface, which results in the loss of this layer.[73] NGF-Abs are not the only nociceptive pathway-targeting drugs being studied for the treatment of OA-related pain; other drugs include rkA inhibitors, voltage-gated sodium channel inhibitors, RBV1 antagonists, peripheral opioid receptor agonists with better safety profiles, bradykinin B2 receptor antagonists, and cannabinoid receptor antagonists.[74] These promising in vivo and in vitro results suggest that TLR4 activation levels, at any level, could be therapeutically modulated.TLR4 signaling has also been shown to be blocked by 128 tricyclic medications, 129 opioid antagonists, 130 coprohemin, 131, and thalidomide, 132; however, the underlying mechanisms are yet unknown.[75] Furthermore, given that improvements in subchondral bone integrity (microstructural and remodelling parameters) in a rabbit model of osteoarthritis (OA) impede the progression of cartilage damage, these improvements may also enhance the beneficial effects of TLR4 inhibition on the cartilage of osteoarthritis (OA) patients.[76]

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