# Therapeutic effects of statins on osteoarthritis: a review

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**Abstract**

Osteoarthritis (OA) is a progressive joint disease. The etiology of OA is considered to be multifactorial. Currently, there is no definitive treatment for osteoarthritis, and the existing treatments are not very effective. Hypercholesterolemia is considered a novel risk factor for the development of osteoarthritis. Statins act as a competitive inhibitor of the β-Hydroxy β-methylglutaryl-CoA (HMG-CoA) reductase and are widely used to manage hypercholesterolemia. Inhibition of HMG-CoA reductase results in reduced synthesis of a metabolite named mevalonate, thereby reducing cholesterol biosynthesis in subsequent steps. By this mechanism, statins such as atorvastatin and simvastatin could potentially have a preventive impact on joint cartilage experiencing osteoarthritic deterioration by reducing serum cholesterol levels. Atorvastatin can protect cartilage degradation following IL-1β-stimulation. Atorvastatin stimulates the STAT1-caspase-3 signaling pathway that was shown to be responsible for its anti-inflammatory effects on the knee joint. Simvastatin had chondroprotective effects on osteoarthritis in vitro by reducing matrix metalloproteinases (MMP) expression patterns. In this study, we tried to review the therapeutic effects of statins on osteoarthritis.

**Keywords:** Statins; Osteoarthritis; Therapy

## Introduction

OA is a progressive joint disease that can affect several joints, including but not limited to the knees, hips and spine (Michael, Schlüter-Brust, & Eysel, 2010; Suri, Morgenroth, & Hunter, 2012). It is also known as degenerative joint disease, affecting many elderly individuals (Okma-Keulen & Hopman-Rock, 2001). Joint pain, joint swelling and limited range of movement are among the common symptoms of OA. The rise in the old age population has turned OA into a public health problem (Michael et al., 2010). The development of OA is multifactorial in origin (Suri et al., 2012). The two main pathophysiological mechanisms are the local mechanical factor(Hardingham, 2008) and the systemic factors(Sowers, 2001). The systematic causes of OA development are congregated in a wide range of metabolic disorders such as hypertension, diabetes, abdominal obesity and dyslipidemia(Le Clanche, Bonnefont-Rousselot, Sari-Ali, Rannou, & Borderie, 2016). In addition, depression(Lin, 2008), stress(Jurmain, 1977), and diet(Morales-Ivorra, Romera-Baures, Roman-Viñas, & Serra-Majem, 2018) have also been associated with both the onset and progression of OA (Cooper et al., 1996; Okma-Keulen & Hopman-Rock, 2001).

The systematic factors are mainly due to the release of proinflammatory mediators such as cytokines. These mediators are secreted from different body tissues and adipose tissue (Felson et al., 2000; Kapur & Musunuru, 2008; Suri et al., 2012). It has been shown that types of inflammatory mediators may differ in different OA phenotypes (Berenbaum, 2013). The mechanism underlying the development of OA is the regression of the articular cartilage, which leads to the narrowing of joint space and eventually roughens the joints. Tissues that are relevant to OA are also involved in the process, and thus the condition is associated with bone hypertrophy and capsule thickening (Baker, Walsh, & Mulhall, 2011; "The burden of musculoskeletal conditions at the start of the new millennium," 2003; Kapoor, Martel-Pelletier, Lajeunesse, Pelletier, & Fahmi, 2011; Michael et al., 2010). Among the numerous risk factors listed for OA, obesity and joint injury have shown to be the most significant modifiable risk factors (Suri et al., 2012). Unfortunately, no treatment has yet been introduced to halt the disease progression. The goals of the current OA remedy are focused on the control of pain and improvement of joint function. NSAIDs, analgesics and locally administered corticosteroids are among the frequently prescribed medications(Sellam et al., 2020). Unfortunately, the lack of drugs that could modify OA leads to the progression of cartilage damage which may ultimately demand surgical interventions (Kapoor et al., 2011).

Several studies have hypothesized that the disorders of lipid metabolism may play a role in the pathogenesis of osteoarthritis (Aspden, Scheven, & Hutchison, 2001; Kadam, Blagojevic, & Belcher, 2013). This can be explained by in vitro studies showing that excessive lipid levels in the synovial fluid bring about arthritic vicissitudes. It is also shown that higher levels of leptin found in obese individuals were associated with joint cartilage destruction (Kadam et al., 2013). It is thus possible that lipid-lowering agents may have a role in changing the course of OA's progression and its symptoms (Riddle, Moxley, & Dumenci, 2013; Valdes et al., 2014; Veronese et al., 2019). β-Hydroxy β-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, also identified as statins, are among the most effective lipid-lowering agents (Kapur & Musunuru, 2008). HMG-CoA is recognized as a key enzyme in the mevalonate pathway. Its inhibition reduces the bioavailability of farnesyl pyrophosphate, geranylgeranyl pyrophosphate, heme A, coenzyme Q10 and other metabolites that have a vital role in cellular physiology. Furthermore, cholesterol is a final product of this pathway, but it is a substrate for other compounds, such as corticosteroids and vitamin D (Golomb & Evans, 2008; Mollazadeh et al., 2021; Stancu & Sima, 2001). The pharmacodynamic characteristics of statins explain why they employ a wide range of pleiotropic effects (Calabrò & Yeh, 2005). In addition to the various beneficial effects of statins in endothelial health and reduction of cardiovascular disease risk (Davignon, 2004; Mohammadzadeh et al., 2020), a wide range of therapeutic effects have been discussed for statins, from the treatment of brain tumors and reducing plasma levels of von Willebrand factor to protection against neurodegenerative disease (Afshari, Mollazadeh, Henney, Jamialahmad, & Sahebkar, 2021; Bagheri et al., 2020; Parizadeh et al., 2011; Sahebkar et al., 2016). Pleiotropic effects of statins include improvement of endothelial dysfunction, increased nitric oxide bioavailability, antioxidant properties, inhibition of inflammatory responses, and stabilization of atherosclerotic plaques (Davignon, 2004). However, it has been indicated in different studies that not all of the pleiotropic effects of statins are related to their cholesterol-lowering properties. Many of its effects may even be completely dissociated from inhibition of HMG-CoA reductase, and some even occur at very low drug concentrations (Davignon, 2004).

Various studies have shown the effect of statins by preventing inflammation in the recovery of patients with osteoarthritis(Dancevic & McCulloch, 2014). Baker et al. have reviewed the potential of statins in the treatment of OA. They discussed the effects of statins regarding different molecular and clinical aspects. There were only in vitro cell studies and studies applied in animal OA models (Baker et al., 2011). In recent years, the results of a number of

cohort studies and clinical trials (Clockaerts et al., 2012) have been reported, considering the effect of statins in both the incidence reduction and treatment of OA. This review focuses on the therapeutic effects of statins on OA.

## Osteoarthritis

A joint illness, osteoarthritis, is defined by the gradual degradation of the articular cartilage and accompanying alterations throughout the joints' subchondral bone, synovial fluid, and other supporting structures (Lories & Luyten, 2011). There has been a good understanding of the consequences of osteoarthritis on the extracellular matrix (ECM) of cartilage(Heinegård & Saxne, 2011; Rilla et al., 2019). Most of the other features and effects associated with osteoarthritis are evident and potentially started already in the pericellular matrix (PCM), even though the ECM of cartilage has been widely researched regarding this disease. The freshly produced matrix elements, enzymes, and growth factors first travel across PCM as the main link between the chondrocyte and the articular ECM (Guilak, Nims, Dicks, Wu, & Meulenbelt, 2018). At the moment, there is no treatment for osteoarthritis, and the existing treatments are not very effective and are frequently associated with a variety of debilitating complications (Zhang, Ouyang, Dass, & Xu, 2016). Available therapies primarily aim to alleviate pain and to improve the articular functional ability (Zhang et al., 2016).

## Prevention and control of osteoarthritis

Most recommendations advocate non-pharmacologic therapies, such as endurance training, weight reduction, and awareness, as the cornerstone of early interventions (Nelson, Allen, Golightly, Goode, & Jordan, 2014). Suitable activities enhance muscular stability to improve articular flexibility. Weight reduction is encouraged for individuals who are overweight. The emphasis of conventional pharmaceutical treatments is on symptom control (Bálint & Szebenyi, 1997). The most frequently utilised medications are oral and topical non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen, and opioids (Smith, Deshpande, Collins, Katz, & Losina, 2016). It is essential to note that acetaminophen is not consistently suggested in the recommendations because of various undesirable consequences. Additionally, despite their widespread usage, opioids have several adverse effects that exceed their advantages, as well as a variety of other problems, such as overdoses and fatalities (Wegman, van der WINDT, van TULDER, Stalman, & de VRIES, 2004).

## Cholesterol is a novel risk factor for osteoarthritis

The body's total cholesterol comes from two sources: the cellular cholesterol synthesis mechanism and food consumption (Farnaghi, Crawford, Xiao, & Prasadam, 2017). In the biosynthetic route, the majority of cell types, especially hepatocytes, can manufacture cholesterol (Q. Wang et al., 2022). Ras, Hedgehog, and Rho are signaling molecules controlled by cholesterol, a critical cellular membrane constituent (Lv, 2019). Cholesterol, in combination with its biosynthetic precursors, regulates the activity of these signaling factors. The human synovial fluid has been found to have low amounts of cholesterol compared to plasma (Loike et al., 2004).

Nevertheless, in patients with inflammatory joint disorders, the synovial fluid is found to have greater cholesterol crystals than in healthy persons(Farnaghi et al., 2017). Generally, overweight or obese individuals can develop hypercholesterolemia due to alterations in their lipid metabolic pathways. There is emerging evidence on the effects of excess cholesterol on the prevalence of OA (Ni et al., 2015). Various epidemiological studies have drawn findings on the connection between OA and excessive levels of blood cholesterol. In a study by Hart and et al in 1995 showed that hypertension, hypercholesterolemia, and blood glucose are related with both unilateral and bilateral knee OA(Hart, Doyle, & Spector, 1995).In another study by Munter and et al in 2016 showed that increased cholesterol levels intensely raise synovial activation and ectopic bone formation in early-stage collagenase-induced OA(de Munter et al., 2016). Numerous investigations have shown that hypercholesterolemia and OA have a significant positive association (van Gemert et al., 2021).

**Statins**

When it came to hydroxymethylglutaryl-CoA reductase (HMG-CoA) blockers, there was a significant number of evidence published the year before 1976, describing substances ranging from oleic acid to cyclic AMP that was reported to be inhibitors of the enzyme. Statins are composed of a pharmacophore and a component composed of a circular system with various substituents. All statins have the same pharmacophores as dihydroxyheptanoic acid fragments identical to the HMGCoA substrates. The circular framework comprises an intricate hydrophobic architecture covalently bonded to the pharmacophore to interact with the HMG-CoA reductase. Statins act as a competitive inhibitor of the HMG-CoA reductase by imitating the natural substrates (Istvan & Deisenhofer, 2001). Due to the slowdown in generating a metabolite (mevalonate), cholesterol biosynthesis is reduced in the following steps. Because hepatocytes are responsible for the vast bulk of cholesterol production throughout the body,

HMG-CoA reductase inhibitors are concentrated inside the liver. Instead of just competing with the usual substrates at the active site, statins change the conformation of the enzyme itself when attached, hindering HMGCoA reductase from achieving an active arrangement (Thelen et al., 2006). Table 1 shows members of statins, such as atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin.

## Pharmacokinetic properties of statins

Lovastatin and simvastatin are lactone pro-drugs that are enzymatically hydrolyzed in the body to their active, hydroxy-acid form(Sugimoto et al., 2001). The active hydroxy acid form of the other statins is used. All statins are quickly absorbed following treatment, reaching maximal plasma levels within 4 hours. The rate and amount of atorvastatin absorption are altered by time of day dosing, whereas rosuvastatin pharmacokinetic parameters are unchanged. The elimination half-life of atorvastatin is approximately 14 hours; active metabolites of the atorvastatin parent component prolong the inhibitory impact on HMG-CoA reductase to 20–30 hours. Rosuvastatin has a half-life of 19 hours, whereas pitavastatin has a half-life of 11 hours. The statins now on the market have low systemic bioavailability, implying substantial first-pass extraction. Cerivastatin has a greater systemic bioavailability of 60%, while pitavastatin has an even higher systemic bioavailability of roughly 80%. Given that statins' target organ is the liver, effective first-pass absorption may be more crucial for statin action than high bioavailability. Meals have a varying influence on statin absorption; lovastatin is better absorbed when taken with food, but atorvastatin, fluvastatin, and pravastatin bioavailability is reduced(Schachter, 2005). The cytochrome P450 (CYP450) family of enzymes, which includes over 30 isoenzymes, is primarily responsible for the metabolism of statins. In humans, the CYP3A4 isoenzyme metabolizes most medications, including lovastatin, simvastatin, and atorvastatin. Active metabolites account for a fraction of the circulating inhibitory activity of these three drugs for HMG-CoA reductase. The principal active metabolites of atorvastatin are 2-hydroxy- and 4-hydroxy-atorvastatin acid, whereas the major active metabolites of simvastatin are -hydroxy acid and its 6′-hydroxy, 6′-hydroxymethyl, and 6′-exomethylene derivatives. Fluvastatin is metabolized mostly by the CYP2C9 isoenzyme, whereas pravastatin, pitavastatin, and rosuvastatin do not undergo significant CYP450 metabolism. After metabolism by the liver, the bulk of statins is eliminated mainly through the bile. As a result, hepatic dysfunction is a risk factor for statin-induced myopathy, and all manufacturers advise care when giving statins to those who have had the liver illness in the past(Bellosta, Paoletti, & Corsini, 2004).

## Anti-inflammatory effects of statins

The relative importance of statins' direct anti-inflammatory actions in vitro and animal models. Other anti-inflammatory medicines, such as glucocorticoids and nonsteroidal anti-inflammatory drugs, do not clarify the significance of the statin activities outlined above since their mode of action and anti-inflammatory profile differ from statins and are associated with detrimental effects on lipid metabolism, glucose metabolism, and blood pressure(Montecucco & Mach, 2009). In OA, interleukin-1 (IL-1) may be the most important pro-inflammatory cytokine. This, along with TNF, is important for activating a variety of degrading agents, including as nitric oxide (NO) and matrix metalloproteinases (MMPs)(Shakibaei, John, Schulze-Tanzil, Lehmann, & Mobasheri, 2007). In fact, IL-1 can induce the development of most of the proteinases that cause cartilage breakdown. Local matrix synthesis is reduced by IL-1, and other inflammatory mediators such as IL-6 and -8 are stimulated(Akasaki, Matsuda, & Iwamoto, 2009). When the circumstances are right, IL-6 can work in tandem with IL-1 to induce collagenases. IL-1, IL-17, IL-18, and TNF have all been linked to articular cartilage catabolism, whereas IL-4, IL-10, and IL-13 have been shown to have an anti-catabolic impact(Akasaki et al., 2009). According to the evidence statins are able to diminish inflammatory processes and may have a role to show in the treatment of OA.

## In vivo and in vitro models for the study of osteoarthritis

The in-vitro osteoarthritis model is critical for expanding research into the etiology of the disease and designing and trialling possible pharmacological agents (Kraus et al., 2011). Researchers have employed a variety of in-vitro models, but there is no agreement on which model is the best one (Fatehullah, Tan, & Barker, 2016). Models try to imitate the factors and conditions that cause OA or to analyze the active pathways of the disease. The underlying uncertainties about the etiology of OA and the various properties of isolated cells and tissues utilized mean that comparable models may generate different outcomes and may vary from the naturally existing disease (Shah, 2012). The monolayer culture model enables the expansion of cellular resources from a single sample and the examination of signaling pathways in isolation. However, the phenotype of isolated cells is altered owing to tissue isolation and the lack of a normal extracellular matrix. In the co-culture model used in cross-talk between cell types, the altered phenotype of isolated cells separates cell types needs various conditions for culture or a compromise when cultured together, which is a drawback of this approach (Johnson, Argyle, & Clements, 2016). The monolayer culture model enables the production of cellular resources

from a single sample as well as the examination of signaling methods in isolation. However, the phenotypic of isolated cells is altered owing to isolation from tissue and the lack of a normal extracellular matrix (Astashkina & Grainger, 2014). Considerable cross-talk occurs between cell types in the co-culture model. Separate cell types need various growth conditions or a compromise when cultured together, which is a drawback of this approach. Following the advancement of cell culture and 3D culture methods, the 3D cultural model was created (Singh, Moses, Bhardwaj, & Mandal, 2021). This model gives sensitive cells the structure and force, but it also has limitations (Singh et al., 2021). The magnitude of the force depends on the scaffold and may not represent that of typical tissue isolation and cell type expansion first (Singh et al., 2021). This latest model is economical and relatively easy to manufacture. In this model, cells are kept in the so-called explant model's normal extracellular matrix, with several advantages. This model has cell death at tissue cut edge, few available replicates from the same sources, more than one tissue type might be needed to keep viability, and physical characteristics may vary in culture(Pathak, Lingaraju, et al., 2015).

The majority of available human tissues for the studies were collected during the joint replacement, once OA lesions are at the end stage and nothing can be inferred about the elements that contributed to disease progression (Borthakur et al., 2006). To address this restriction, various induced and natural animal models have been used over the last 50 years to investigate disease attacks and progression and evaluate potential treatment approaches. Over the last 50 years, animal models of OA have expanded our knowledge of the disease pathophysiology and will remain a helpful tool in the foreseeable future (Johnson et al., 2016). It is not unexpected that none of the animal models of the disease can completely recapitulate all characteristics of the human OA condition. Still, the vast diversity of models available makes it probable that one or more of these animal models may successfully address the most important concerns (Piscaer, Van Osch, Verhaar, & Weinans, 2008). Although smaller animal models may be preferred for basic pathophysiology studies and early screening of treatments, bigger animal models will be necessary to validate results before proceeding to human clinical trials. The natural disease model is thought to be a superior model of human original idiopathic OA, whereas surgical models of disease may more accurately recapitulate posttraumatic OA in individuals; both play a significant role in OA research (Johnson et al., 2016).

**Effect of atorvastatin on osteoarthritis**

A reliable OA model is needed to monitor the effectiveness of new treatments, examine variables that improve their effectiveness, and forecast the destiny of such treatments inside an OA context (Hunter et al., 2018). Simulations for imitating pathophysiological research and assessment of new treatments, including the tissue engineering techniques on cartilage, are significant in experimental tests of human osteoarthritis (Makarczyk et al., 2021). Using rat articular pattern of explant culture of osteoarthritis induced by interleukin-1β (IL-1β), Pathak et al., evaluated the chondroprotective capability for atorvastatin (Pathak, Balaganur, et al., 2015). research indicates that atorvastatin provides the capacity to support cartilage from deterioration after IL-1β treatment during an in vitro OA type, suggesting that atorvastatin may be used therapeutically throughout OA (Assirelli et al., 2014).

The HMG-COA reductase inhibitor, employed in managing hypercholesterolemia and the prophylaxis of coronary heart disease, is investigated in an additional study conducted by the same investigation team on atorvastatin to examine its influence on hyperalgesic and articular destruction among osteoarthritic rats treated by monosodium iodoacetate (MIA)(Pathak, Balaganur, et al., 2015). According to their findings, atorvastatin may reduce MIA-induced osteoarthritic symptoms while protecting articular destruction by inhibiting oxidative stress, indicating that it can potentially be used in treating OA (Kumar, Kumar, Sharma, & Tandan, 2014).

In addition, the capacity to genetically alter or reproduce certain pedigrees of animals that are especially sensitive to OA is a significant benefit of using animal patterns throughout OA research (Holloway, 2005). Consequently, genetically modified animals were widely employed as transgenic animals to investigate OA (Holloway, 2005). During their research on rats with atorvastatin-induced osteoarthritis, Seweidy et al. propose inflammatory patterns against the impact from diclofenac throughout rats with osteoarthritis (El-Seweidy, Sousou, Elswefy, & Mashhour, 2016). In a mouse model mimicking human lipoprotein metabolism, Gierman et al. have shown the impact of cholesterol and various cholesterol-lowering therapies on OA (Gierman et al., 2014). Their findings indicate ingested cholesterol and its higher plasma concentrations contribute to OA pathogenesis. The relationship between OA, cholesterol, and atherosclerosis shows that these parameters are interrelated. However, it suggests the involvement of additional mechanisms in the advancement of OA (Gierman et al., 2014). These results are confirmed by the inhibitory impact on OA caused by atorvastatin nor ezetimibe, which have a comparable efficacy on reducing cholesterol (Gierman et al., 2014). In addition, atorvastatin was shown to significantly reduce articular rigidity, induce histopathologic

alterations, elevate the matrix metalloproteinases 13 (MMP13) and IL1-β expression, and alleviate the GTH throughout OA rats in another animal research(Gaballah, Genedy, Ghayaty, Elhawwari, & Elmasry, 2020).

In a randomized placebo-controlled study, Wang et al. demonstrated that in individuals experiencing symptomatic knee arthritis, orally administered atorvastatin 40 mg once daily did not substantially decrease mass cartilage reduction during the last two years relative to placebo (Y. Wang et al., 2015). Atorvastatin was shown to be ineffective when used to relieve knee osteoarthritis, according to these results. Nevertheless, in individuals lacking bone marrow lesions (BMLS), atorvastatin treatment decreased cartilage loss, indicating that atorvastatin might cause disease modification among people with knee arthritis and BMLs-free (Bibbins-Domingo et al., 2016). Jokar et al. evaluated the results of orally administered atorvastatin and intraarticular hyaluronic acid among patients with knee osteoarthritis. They showed substantially improved pain symptoms in patients with intraarticular hyaluronic acid. The physical function similar to patients with knee OA was seen in the second month following therapy but not subsequent months (M. H. Jokar, Mirfeizi, Zarei, & Hashemzadeh, 2020). Among primary care patients using simvastatin or atorvastatin, Eggertsen et al. examined the impact of glucosamine on serum cholesterol levels, including total cholesterol, HDL, or LDL. There were no significant alterations in lipid profile in the simvastatin group, and glucosamine did not alter the lipid concentrations of simvastatin-treated individuals. However, the atorvastatin sample was too small to make conclusive findings (Eggertsen, Andreasson, & Andrén, 2012).

The therapeutic relevance of research findings indicates that atorvastatin may have a preventive impact on joint cartilage experiencing osteoarthritic deterioration(Aktas, Sener, & Gocun, 2011). In addition, the STAT1-caspase-3 signaling pathway was shown to be responsible for atorvastatin's anti-inflammatory effects on the knee joint (HUANG et al., 2018). Table 2 show a summary of the effect of atorvastatin on osteoarthritis. Figure 1 shows signaling pathways for atorvastatin in cartilage degradation.

## Effect of fluvastatin on osteoarthritis

Numerous studies have examined the therapeutic benefits of the topical application of statin in OA. Fluvastatin has been evaluated in studies with potent anabolic and anti-catabolic impacts on OA chondrocytes among patients. According to the findings of an investigation to explore the therapeutic benefits of topical application of statin in osteoarthritis, intra-articular infusion of fluvastatin-loaded poly(lactic-co-glycolic acid) (PLGA) microspheres may be a new therapeutic strategy for managing individuals with osteoarthritis (Goto et al., 2017).

## Effect of pravastatin on osteoarthritis

Pravastatin was shown to partly reduce cholesterol-induced inflammation and death of chondrocytes in animal studies. Therefore, it can be concluded that pravastatin significantly reduces inflammation and matrix breakdown and improves OA susceptibilities in articular cartilage, reducing the buildup of cholesterol throughout chondrocytes (Mao et al., 2018; Ni et al., 2021). Figure 1 shows signaling pathways for pravastatin in cartilage degradation.

## Effect of simvastatin on osteoarthritis

According to animal research findings on the impact of simvastatin on osteoarthritis, OA starts at the molecular level in a short amount of time after knee trauma (Aktas et al., 2011). Therefore, we focused on effective ways to prevent OA because irreversible structural alterations in cartilage necessitate therapeutic procedures (Brody, 2015). Statins have been shown to have immunomodulatory and anti-inflammatory characteristics in addition to their ability to reduce blood cholesterol (Blanco-Colio, Tuñón, Martín-Ventura, & Egido, 2003). In an experimental environment, one of these commonly-used medications, simvastatin, demonstrated positive benefits on OA development and extent by decreasing cartilage degradation (Aktas et al., 2011). Provided such findings are verified in human experiments, simvastatin could be considered a disease-modifying with decreased expression of cartilage-degrading enzymes and interleukin (IL)-1β and increased expression of type II collagen and an autophagic marker, LC3, in the articular cartilage medication during the early inflammation stage of posttraumatic OA. Furthermore, animal studies show that intra-articular injection of simvastatin-conjugated gelatin hydrogel might be utilized as a novel therapeutic for OA (Tanaka et al., 2019). The effect of simvastatin on iodoacetate in rats showed that temporomandibular joint osteoarthritis (TMJOA) alleviated some osteoarthritic characteristics

and modulated the structure of some joint components to compensate for the damaged caused structures with MIA. Simvastatin had chondroprotective impacts on osteoarthritis in vitro by reducing MMP expression patterns while boosting aggrecan expression levels (Galal Abdelhameed, Mahmoud Hani, & Mohamed Mohamed Soliman, 2020). Simvastatin demonstrated no influence on chondrocyte proliferation in either in vivo or in vitro studies (Pathak, Balaganur, et al., 2015). In a study by Horecka and et al on Effect on Calcium and Silicon Plasma Levels in Postmenopausal Women with Osteoarthritis was showed that positive correlation of simvastatin concentration with silicon level in the plasma suggests that both might prompt the positive effect of osteoarthritis treatment(Horecka et al., 2016). According to the study's findings, obesity, induced by a high-fat diet, resulted in aggravating articular degeneration and abnormal metabolic pathology in subchondral bone, which might be reversed by simvastatin intervention, implying that simvastatin might be a possible candidate for the amelioration of OA development(Li et al., 2021) . Table 3 show a summary of the effect of simvastatin on osteoarthritis. Figure 1 shows signaling pathways for simvastatin in cartilage degradation.

**Effect of rosuvastatin on osteoarthritis**

Statin usage may not be linked to a reduced risk of OA onset and development, independent of joint location (van Gemert et al., 2021). In OA, atorvastatin and rosuvastatin had polar opposite effects. Because of their anti-inflammatory properties, statins may have a preventive function in OA (J. Wang, Dong, Yang, Wang, & Liu, 2020). However, a meta-analysis of 11 publications, including over 670000 people, found that statin use isn't linked to a lower risk of OA onset or progression, despite the fact that atorvastatin and rosuvastatin have opposing effects on OA (J. Wang et al., 2020). In the subgroup of intervals of statin usage and statin dosage, no link was discovered. Although there are several probable pathways through which statins may benefit OA joints, most data for statins' positive benefits has come from in vitro or animal research (J. Wang et al., 2020).

## Conclusion

OA is a multi-faceted illness affecting the whole joint, cartilage, and synovium. Currently, there are novel experimental techniques to find and develop new therapeutics or even to re-profile potential drug candidates. OA has been the subject of several clinical trials focused on structural targets, including cartilage and bone, in conjunction with reducing pain. In contrast to research on the effects of statins on osteoarthritis in lab and animal models, there is a rapidly

growing number of evidence suggesting statins can reduce inflammatory processes and, therefore, have a role in treating OA. Several studies using various kinds of statins, particularly atorvastatin and simvastatin, show that higher statin doses and statin dosage increments are related to reducing preclinically and clinically characterized OA outcomes. According to studies, statins appear to target a variety of signaling pathways to achieve their potential pharmacological effects in OA.

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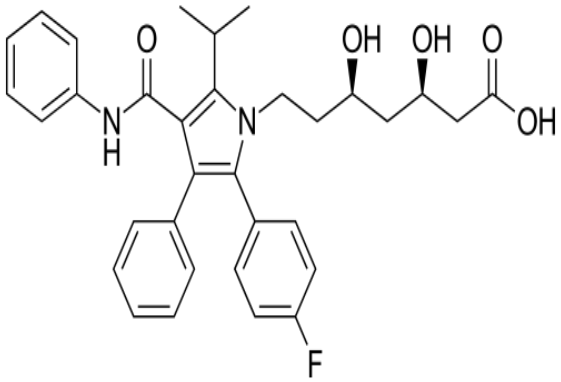
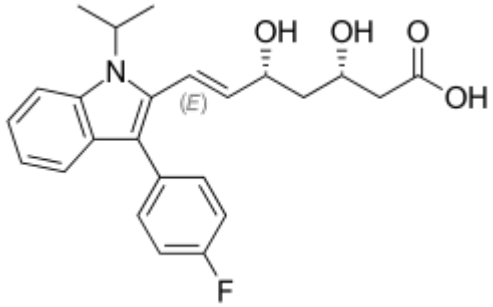
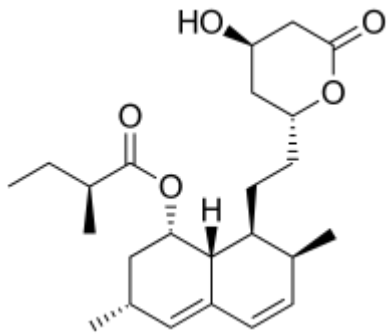
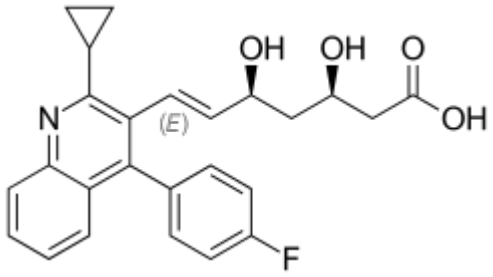
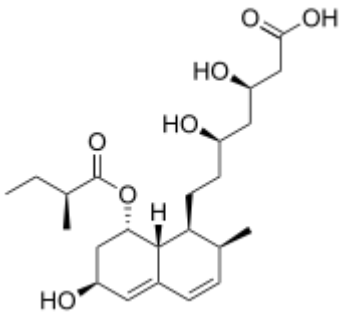
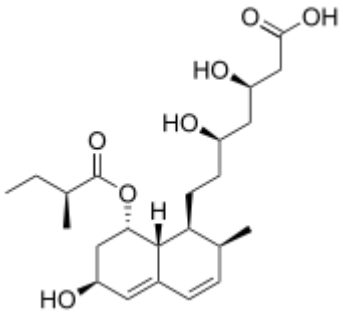
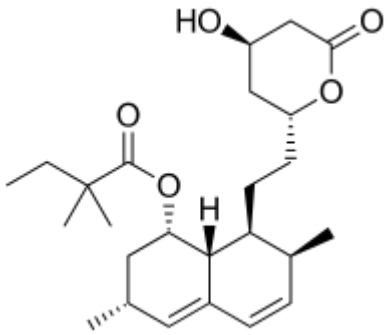
Table 1:Statins(Masadeh, Mhaidat, Alzoubi, Al-Azzam, & Alnasser, 2012)

| Scientific name | Brand name (e.g.) | Formula | Structure |
|---|---|---|---|
| Atorvastatin | Lipitor | $C_{33}H_{35}FN_2O_5$ |  |
| Fluvastatin | Lescol XL | C24H26FNO4 |  |
| lovastatin | Altoprev | C24H36O5 |  |

| | | | |
|---|---|---|---|
| pitavastatin | Livalo | $C_{25}H_{24}FNO_4$ |  |
| pravastatin | Pravachol | $C_{23}H_{36}O_7$ |  |
| Rosuvastatin | Crestor, Ezallor | $C_{23}H_{36}O_7$ |  |
| Simvastatin | Zocor, FloLipid | $C_{25}H_{38}O_5$ |  |

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816

817 Table2: Effect of atorvastatin on osteoarthritis

| **Study type** | **Statin** | **Dose** | **Results** | **References** |
|---|---|---|---|---|
| In vitro model | Atorvastatin | 1, 3, or 10 µM dissolved in DMSO | Atorvastatin can protect cartilage degradation following IL-1β-stimulated cartilage | (Pathak, Lingaraju, et al., 2015) |
| Mouse model | Atorvastatin | 3 mg/kg/day | The correlation found between OA, cholesterol and atherosclerosis | (Gierman et al., 2014) |
| Rat model | Atorvastatin | 3, 10 and 30 mg/kg | Atorvastatin attenuates MIA-induced osteoarthritic pain and protects cartilage degradation through inhibition of oxidative stress | (Pathak, Balaganur, et al., 2015) |
| Rat model | Atorvastatin | 10 mg/kg | Combination of atorvastatin and omega 3 fatty acids demonstrated marked effects than their individual use as compared to Diclofenac | (El-Seweidy et al., 2016) |
| Rat model | Atorvastatin | | Atorvastatin inhibits the inflammation of the knee joint via STAT1-caspase-3 signal axis | (HUANG et al., 2018) |
| Rats model | Atorvastatin | 10 mg/kg daily | Atorvastatin as OA disease-modifying drug worse clinical trials | (Gaballah et al., 2020) |
| Clinical trial | Atorvastatin | 40 mg once daily | Findings do not support the use of atorvastatin in the treatment of knee osteoarthritis (atorvastatin did not reduce cartilage volume | (Y. Wang et al., 2021) |

| | | | | |
|---|---|---|---|---|
| | | | loss over two years in patients with symptomatic knee osteoarthritis) | |
| Clinical trial | Atorvastatin | 40 milligrams orally daily | Intra articular Hyaluronic acid improved the pain and function of patients with knee osteoarthritis in the second months after injection. Atorvastatin did not have any effect on the knee osteoarthritis symptoms during 6 months | (M. Jokar, Mirfeizi, Hashemzadeh, & Zarei, 2017) |
| Clinical trial | Atorvastatin | 40 mg once daily | Treatment with oral atorvastatin did not reduce knee cartilage loss or knee pain over two years. | (Y. Wang et al., 2020) |

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819 Table3: Effect of Simvastatin on osteoarthritis

| **Study type** | **Statin** | **Dose** | **Results** | **References** |
|---|---|---|---|---|
| Mice model | Simvastatin | 1-µM | Simvastatin-conjugated gelatin hydrogel could be used as a new potential therapy for OA | (Tanaka et al., 2019) |
| Rat model | Simvastatin | 2-10 mg/kg/day | Relative antiosteoarthritic effect and modulated the structure of some joint components to compensate the damaged induced structures with MIA administration | (Galal, Hani, & Soliman, 2020) |
| Rat model | Simvastatin | 20 mg/kg per day | Beneficial effects on OA progression and extent by reducing cartilage degradation | (Aktas et al., 2011) |
| Rat model | Simvastatin | Single-dose of 500µg | Simvastatin relieve some osteoarthritic features and modulate the structure of some joint components to compensate the damaged induced structures with MIA (monoiodoacetate) | (Galal Abdelhameed et al., 2020) |
| Rabbits model | Simvastatin | 10 mg/kg for 8 weeks | No significant effects on the expression of genes related to the development and prevention of osteoarthritis. | (Shiguang, Bing, & Kesen, 2008) |
| Clinical trial | Simvastatin | 20 or 40 mg/day | A positive correlation of simvastatin concentration with silicon level in the plasma suggests that both might prompt the positive effect of osteoarthritis treatment. | (Horecka et al., 2016) |
| Clinical trial | Simvastatin | 20 mg once daily | Simvastatin at the oral once-daily dosage of 20 mg is more effective than placebo in treating knee OA symptoms. | (Salman & Mohammad, 2015) |

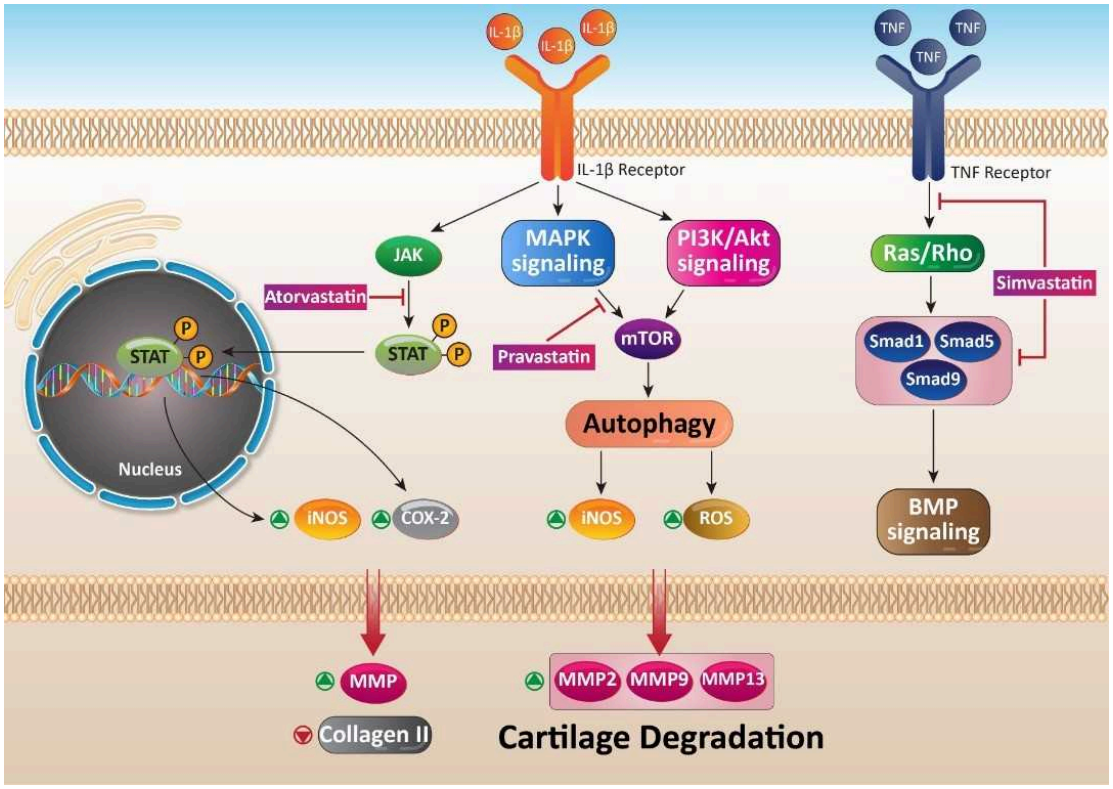


Figure 1: Signaling pathways was shown for statins in Cartilage degradation. MMP: Matrix metalloproteinases; BMP: Bone morphogenetic protein; NOS: Nitric oxide synthase; ROS: Reactive oxygen species; COX: cyclooxygenase-2.