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Review: Novel Drug Delivery for the Treatment of Osteoarthritis (OA)

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Abstract:- As people live longer, the prevalence of osteoarthritis has increased, making it the most frequent kind of arthritis. During osteoarthritis, tissue of cartilage on articular joints corrodes, causing pain and sometimes debilitating loss of function in patients. The most significant risk factor for osteoarthritis is getting older. Osteoarthritis, is the most common chronic joint illness, and becomes common nowadays as people become older. It disturbs the majority of people over 65 and is a main musculoskeletal reason of reduced mobility in the elderly. Because the particular molecular mechanisms behind the degradation of cartilage matrix and the development of OA are unknown, there are presently no viable therapies to slow the advancement of OA or prevent irreversible cartilage degradation other than total joint replacement surgery. The major molecular pathways involved in OA pathogenesis will be discussed in this study, as well as new insights into prospective molecular targets. Various Novel carrier are used to enhancement of drug delivery to the site of action.

Keywords:- *Osteoarthritis(OA),Aging, Cartilage,Distruction,Nanocarrier.*

I. INTRODUCTION

The most common category of disease arthritis is (OA) osteoarthritis(1)**.** OA mainly disturbs the joints of the hip, knee and hand and is induced by articular cartilage deterioration and subsequent synovitis.(2)**.** Obesity, genetic susceptibility, and joint injury are all responsible for the development of osteoarthritis(3).Osteoarthritis is most common causes of chronic impairment in older people(4). In many patients, functional impairment and discomfort can lead to depression and significant sadness (3)**.** The disease's prevalence is expected to rise as the world population's lifespan lengthens**.**(5)**.** It's a cartilage condition, which affects the smooth rubbery cushion that surrounds the joint's bones. (6)**.**Osteoarthritis causes cartilage breakdown, which is linked to damage to the menisci and other joint components, as well as bone remodeling.

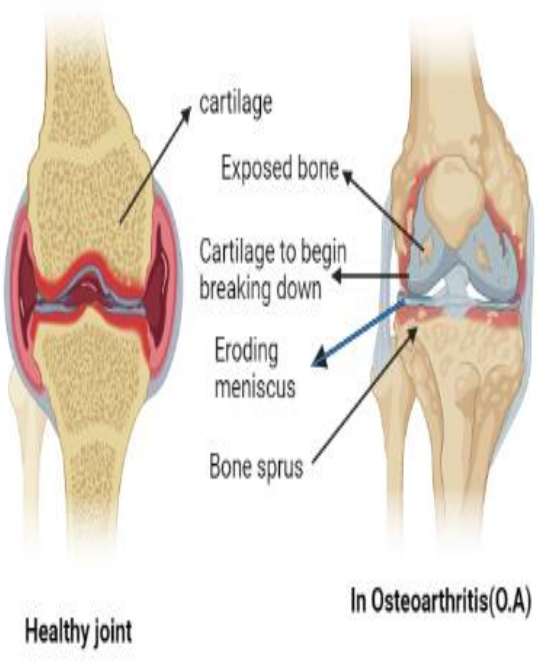

Fig. 1: Shows a normal/healthy joint and a joint affected with Osteoarthritis

According to the 3rd Nutrition Examination and National Health Survey, approximately 37.4 percent of persons aged 60 and up in the United States had radiographic evidence of OA(7).OA is a primary musculoskeletal reason of reduced mobility in the old aged people, affecting joints such as knees, wrists, hips, and spine(8). While various risk factors for osteoarthritis have been proposed, such as genetic susceptibility, ageing, joint misalignment and obesity, the pathophysiology of osteoarthritis is still not clear(9). Stiffness, joint deformities, stiffness, chronic pain, radiographic joint space constriction and joint instability are the most common clinical complaints(10).

The risk factors of osteoarthritis have been identified as: Genetic, Susceptibility, Age, Obesity, Joint misalignment, and among others(11).

Clinical symptoms: Stiffness, joint deformities, stiffness, chronic pain, radiographic joint space narrowing, Redness(12).

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II. RISK FACTORS

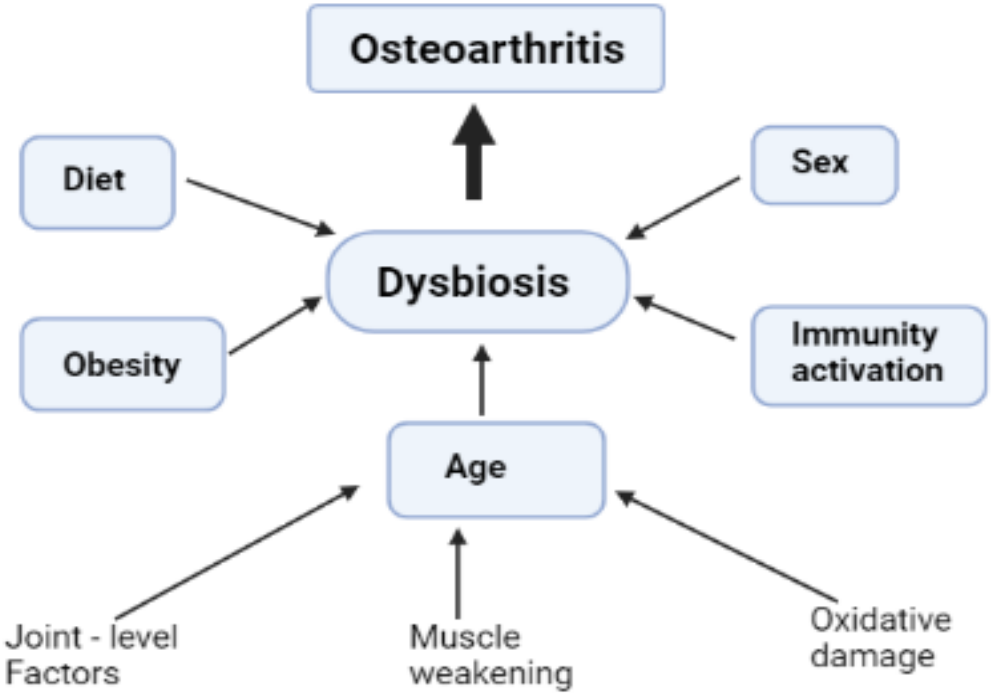

Fig. 2: Various risk factors of osteoarthritis

III. TYPES OF OSTEOARTHRITIS

- **Primary Osteoarthritis:** Its pathogenesis is unidentified; though, a complex etiology involving the contact of local and systemic components is most likely(13).
- **Secondary Osteoarthritis:** It is caused by degenerative variations in the joints as a consequence of identifiable factors such as chronic or acute joint trauma, inflammatory arthropathies (rheumatoid arthritis), muscle dysfunction, repetitive use and obesity(14). Gout and calcium deposits in the joints .Many chronic comorbidities, like metabolic syndrome, diabetes, and cardiovascular disease are now being linked to OA(15). Factors linked to these comorbidities, such as abdominal insulin resistance, dyslipidemias, increased blood pressure, obesity and are thought to play a main role in the onset and development of osteoarthritis (16).Furthermore, there is mounting evidence that patients with comorbidities experience clinical indications of osteoarthritis early with more intensity(17).
- **PATHOPHYSIOLOGY:** Members of the metalloproteinase and disinterring with MMPs and thrombospondin motif' (ADAMTS) family, which breakdown collagen (MMPs) and aggrecan (ADAMTS), respectively, are responsible for the degradation of articular cartilage(18)**.** OA chondrocytes secrete greater quantities of Tumor Necrosis Factor alpha (TNF)and cytokines such IL-1, which can activate and induce these catabolic enzymes(19).It's not clear how important joint inflammation is in tissue degradation. Human OA is related with mononuclear cell infiltration into the synovial membrane OA(20).There is a lot of evidence that the innate immune system is activated in illness(21). When inflammation is present, it accelerates tissue disintegration and contributes to unpleasant illness episodes(22).

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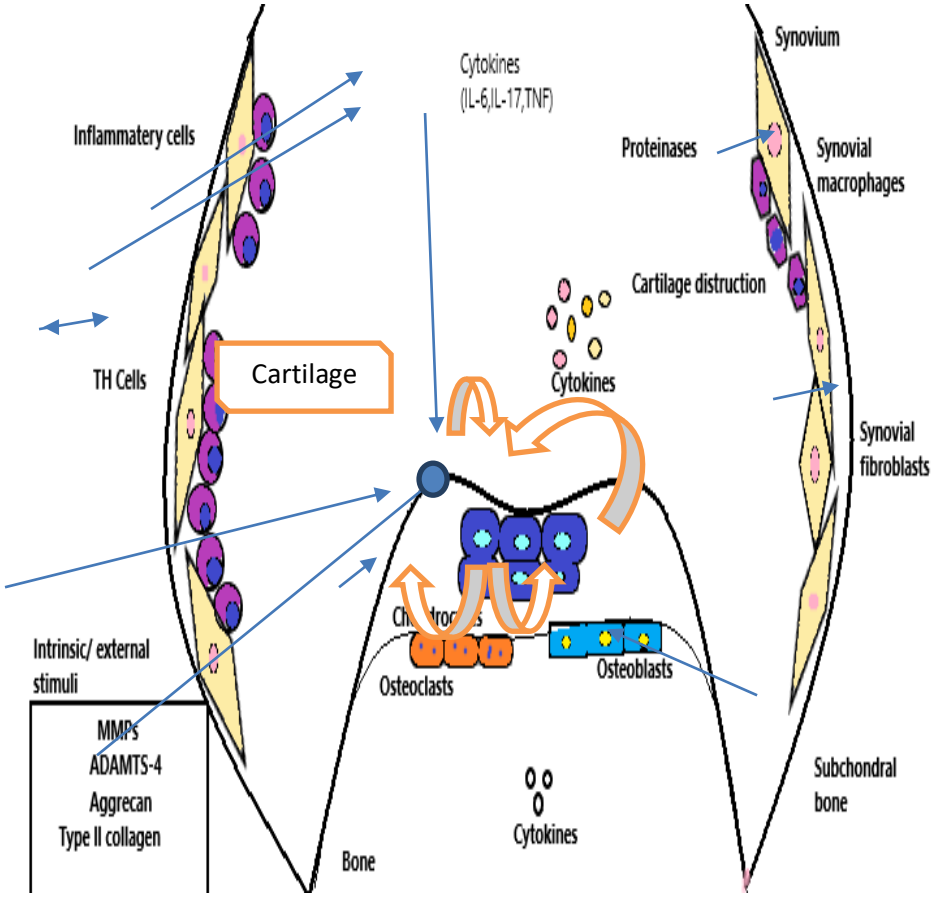

Fig. 3: Mechanisms underpinning the pathophysiology of OA. Multiple components are involved in the cellular and molecular pathways that cause OA to die. Generally, cells in osteoarthritis joints emits higher levels of pro-inflammatory cytokines, causing chondrocytes to secrete proteases that breakdown cartilage(23).

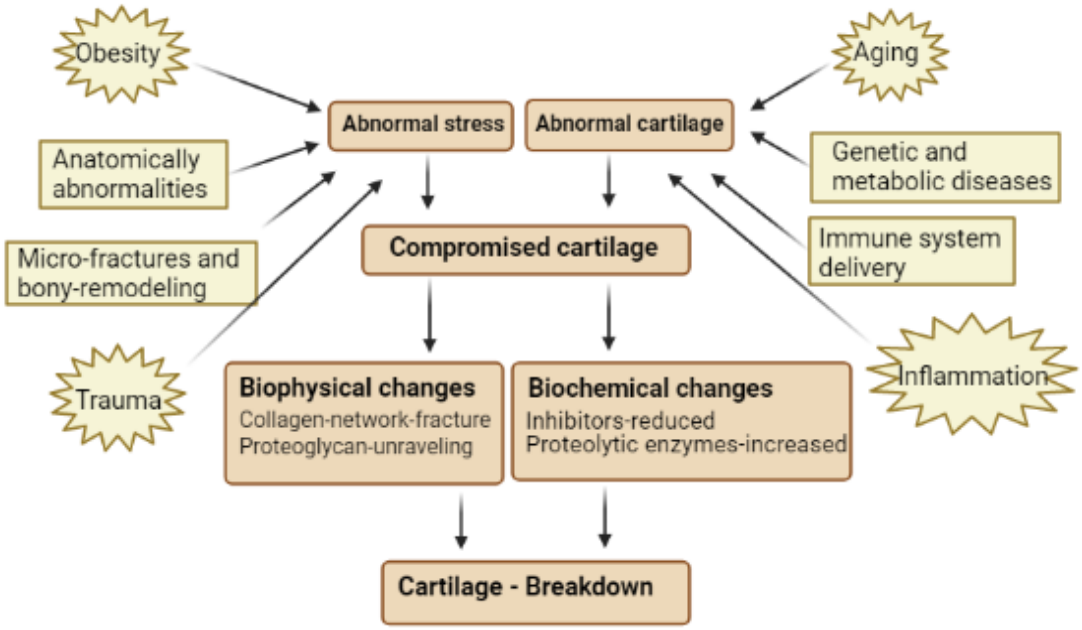

Fig. 4: Cartilage breakdown process in Osteoarthritis

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IV. DIAGNOSIS CRITERIA

OA is diagnosed using a holistic assessment method that includes a physical exam, radiographic scans, and/or detailed history(24). The quality of life, degree of function, leisure activities, occupation, social networks, relationships and mood of an individual should all be evaluated(25). QOL is frequently harmed in people with osteoarthritis, especially when the disease is advanced(26). The occurrence of bone spurs or osteophytes on X-ray, joint pain and one or more than one related indications, depending upon the affected joint, are among the diagnostic criteria mirrored by the OARSI(Osteoarthritis Research Society International)and published by the ACR(American College of Rheumatology)(27)(28).

Other related indications include point tenderness, stiffness of the affected joint lasting more than 30 minutes, deformity or enlargement of the joint, crepitus on physical exam, and a narrowing joint space and on radiography, this was detected(29). It's crucial to remember that clinical symptoms and radiographic evidence are frequently at odds, as not every person with radiographic signal of osteoarthritis has significant clinical indications, and vice-versa(30)(31).

Pain, edema, crepitus and stiffness in the afflicted joints are common presenting signs and symptoms of OA, which are often convoyed by a loss in joint function or movement limitation(32). Patients with OA of the knees frequently describe knee instability, such as buckling or locking, especially when descending steps(33). The thumb is typically affected by OA of the hand, making it difficult to remove lids, turn keys, or grip an item with any vigor(34).

V. SELECTED RISK FACTORS OF OSTEOARTHRITIS IN KNEE HIP AND HAND

	Knee	Hip	Hand	References
Occurrence	Age, sex, physical activity, BMI (including obesity), strenuous sports activities, quadriceps strength, bone density, past injury, and hormone replacement therapy are all factors to consider. Vitamin D, smoking, and (protective) (protective or deleterious), Genetics, misalignment (together with valgus and varus), and malalignment	Physical activity,age,BMI (together with obesity), past injuries, strenuous sports activities, and heredity are all factors to consider (together with congenital deformities)	Occupation, grip, strength, age, and heredity are all factors to consider.	(35)(36)
Progression	Age, BMI (together with obesity), hormone replacement therapy (protective), vitamin D, misalignment (together with valgus and varus), synovitis, chronic joint effusion, strenuous sports enterprises, and subchondral bone oedema on MRI are all factors to consider.	Age, symptomatic activity, sex, and high-intensity sports activities are all factors to consider.	Unknown	(37)(38)

Table 1

VI. SYMPTOMS

- **Pain:** When discomfort is present, it might be unilateral or symmetrical, and it can worsen with exercise, especially weight-bearing activity. It is frequently relieved by relaxation. Insidious pain with varied degrees of intensity may develop around the afflicted joint(39). Constant pain, which is linked to more severe disease, makes regular function and nighttime sleep difficult. Mention torture in the buttocks, groyne, knee or thigh is a common symptom of hip OA(40)**.**
- **Stiffness:** Stiffness is a common complaint among patients, especially when they first wake up after a period of inactivity (gelling phenomena) or in the morning(41). This indication usually goes away after 20 to 30 minutes. The stiffness is frequently relieved by moving the affected joint(42).
- **Swelling**: At first, joint swelling, or effusion, is common, but it's vital to eliminate any recent trauma or distant as a source of joint pain or swelling(43). Swelling in the joints has been linked to a number of systemic diseases, including diabetes, hypothyroidism and hyperparathyroidism (44).When the symptoms of fever or infection (redness, warmth and soreness) are present, a systemic disease or an infection should be considered, and a referral for joint aspiration to eliminate infection or crystalline arthritis should be made right away(45). Calcium pyrophosphate deposition, rheumatoid arthritis, inflammatory arthropathies(also called as pseudo gout), arthritis and Reiter's syndrome linked with inflammatory bowel illness should all be considered when swelling is evident(46).
- **Crepitus**: Finally, the crepitus is a crunching, grating sound or crackling felt on palpation and heard with passive scale of motion(47). The presence of crepitus may or may not be related with pain. It develops as the joint cartilage degenerates, causing opposing the surface of bones to grind against one another(48).

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VII. TREATMENT

- **Topical agents:** Capsaicin cream applied topically may give relief from local pain for patients with osteoarthritis of the hand that systemic pain relievers cannot, especially during the flare-ups(49). It's not, however, advised for hip or knee OA. Capsaicin cream is accessible in the concentrations of 0.25 percent, 0.075 percent, and 0.025 percent over-the-counter(50).To avoid the spreading of cream to the mucous membranes or eyes, the patient must be advised to apply it with the help of gloves to the affected joint(51). Local burning and skin irritation are the most common side effects of capsaicin cream(52).
- **Analgesics:** For mild to moderate pain of osteoarthritis, (Tylenol) acetaminophen is indicated as the first-line treatment, with a daily dose of 4,000 mg (maximum) divided into two doses for adults(53). Acetaminophen is tolerated in most people at the suggested doses because of its low risk of gastrointestinal damage. When used excessively, however, hepatotoxicity can occur(54).Excessive acetaminophen use is linked to taking higher-than-recommended doses, using it for an extended period of time, or using it in conjunction with other acetaminophen-containing medicines(55). As a result, liver enzymes should be constantly watched, and patients must be educated on how to take acetaminophen correctly and avoid using other acetaminophen-containing medicines at the same time. In addition, people with kidney illness should use acetaminophen with caution.(56)
- **Anti-inflammatory agents with analgesic properties**: NSAID's (oral) are indicated for managing the pain related with OA when acetaminophen does not provide adequate relief(57). The minimum active dose for the short time must be utilized to limit the hazard related to comorbidities like GI, cardiovascular, liver issues or renal, and the benefits must outweigh the dangers(58). In grown-up adults, people with major comorbidities and people who are taking other drugs that cause GI difficulties, caution is advised. While on NSAID therapy, the American Academy of Orthopedic Surgeons recommended that patient's liver and renal function testing be monitored each 6 months(59).

For individuals with a history of upper-gastrointestinal indications, a Histamine–H2 receptor blocker or a proton pump inhibitor is indicated to lower the risk of duodenal ulcers, but this has not been proved to be useful in avoiding ulcer formation in the gastric system(60).

NSAID's would be avoided during pregnancy, especially in the 1st and 3rd trimesters. (61). NSAID's usage in the 1sttrimester has been related to an increased risk of miscarriage, whereas NSAID's use in the 3rd trimester has been related to premature fetal renal impairment, ducts arteriosus closure, platelet aggregation inhibition, and labour and delivery delays(62). If the potential benefits outweigh the hazards, highly protein-bound formulations such as naproxen or ibuprofen are favored if administered during lactation(63).

- **Opioids:** It containing analgesics like oxycodone or codeine (Roxicodone, Oxecta,Oxycontin)are used to relieve moderate to severe pain for brief periods of time to cure acute exacerbations of pain and/or moderate to severe pain(64).Due to an elevated hazard of possibly catastrophic or even fatal cardiac rhythm problems, the opioid propoxyphene (Darvon), which was previously used to treat moderate to severe osteoarthritis pain, is no longer accessible in the US(65). To minimize the development of drug tolerance and drug dependency, it is advisable to take these medicines for the short duration possible at the minimum effective dose for relief from pain(66). Because of the danger of dizziness, drug-to-drug interactions, falls in older persons and constipation caution should be exercised when giving these medications(67). Tramadol (Conzip, Ultram) is a synthetic opioid agonist that works centrally to change a patient's observation and response to the pain(68).
- **Intraarticular shots**: Intraarticular shots of corticoids like as triamcinolone or methyl prednisolone have been demonstrated to be beneficial for painful flare-ups of osteoarthritis of the knee(69). Due to the uncommon chance of cartilage injury, an affected joint should not be inserted more than 3 times in a span of year(70). Patients who need injections more frequently may benefit from surgical intervention(71).

Because they enhance the thickness of the synovial fluid in between the joint area, intraarticular shots of hyaluronic acid derivatives (Synvisc, Hyalgan), which may be effective in the treatment of pain in joints affected by osteoarthritis(72)(73)(74). Inflammation and Joint pain can be reduced within 3-5 weeks of starting weekly doses, and the effects can last up to a year(75)(76).

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VIII. TREATMENT OPTIONS FOR OSTEOARTHRITIS BASED ON THE INTERNATIONAL GUIDELINES OF THE OSTEOARTHRITIS (OA) RESEARCH SOCIETY (IF AVAILABLE)

Characteristics	Treatment	Osteoarthritis Research Society International Guidelines Recommendation	References
Modifiable risk Factor reduction	Loss of weight Exercise	Appropriate Appropriate: both in the water and on land, with a focus on strengthening	(77)(78)
Bracing and physical modalities	Crutches Cane Biomechanical interventions	Appropriate for knee-only osteoarthritis Undefined Appropriate	(79)
Alternative therapies	Tai Chi Balneo therapy/spa Acupuncture NMES Cognitive behavioral therapy Self-management and education Ultrasound TENS Electromagnetic field therapy Laser therapy	No reference Appropriate with individuals with multiple joint osteoarthritis Undefined Undefined with knee-only osteoarthritis Suitable Not suitable Uncertain in knee-only osteoarthritis, otherwise unsuitable No recommendation Uncertain in knee-only osteoarthritis, otherwise inappropriate No reference	(80)(81)
Pharmacologic (oral)	Avocado Acetaminophen Glucosamine/Chondroitin Soybean unsaponifiable Duloxetine Diacerein Opioids NSAIDs Rosehip Risedronate	Undefined Appropriate depending on comorbidities Undefined Undefined for symptom relief, not suitable for disease modification Undefined in knee-only osteoarthritis Suitable with multi joint osteoarthritis. Undefined Suitable in those without important comorbidities Undefined Not suitable	(82)(83)
Pharmacologic (topical)	NSAIDs Capsaicin Topical NSAID's Opioids	Suitable in knee-only osteoarthritis uncertain in multi joint osteoarthritis Suitable in knee-only osteoarthritis No reference Uncertain No reference	(84)

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	Tramadol		
Pharmacologic (intra articular)	Hyaluronic acid Corticosteroids	Undefined in knee-only osteoarthritis, not appropriate in multipoint osteoarthritis Suitable	(85)

Table 2

IX. NOVEL DRUG DELIVERY FOR THE TREATMENT OF OSTEOARTHRITIS

In current years, medication delivery with a regulated rate and focused distribution has gotten a lot of attention(86). The use of nanotechnology to medicament has resulted in the expansion of multifunctional nanoparticles that can be loaded with various medications and act as drug carriers(87).Nanocarriers provide a potential method to drug delivery, with qualities such as drug protection against cleavage and degradation, controlled release in the case of targeted delivery systems, drug molecule distribution to the target areas(88)(89).

- **Niosomes:**Niosomes, having double layer structure which are generated by the self-assessment of cholesterol and nonionic surface acting agents (surfactants) in an water phase, which are one of the most capable drug carriers(90). Niosomes are non-immunogenic, biocompatible and biodegradable. They have an extended shelf-life, are very stable and allow for regulated and/or continuous drug administration at the target location(91).The capability of niosomes as a medication carrier has been actively researched in current years. Various nonionic surface acting agents (surfactants) have been found to create niosomes, which allow for the trapping of a wide spectrum of medicines with varying solubility's (92).To enhance the effectiveness of niosomes for drug delivery, surface charge, number of lamellae, size and the composition of niosomes can be altered and improved(93).

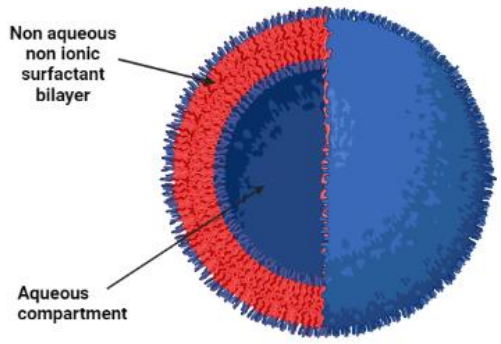

Fig. 5: Structure of Niosome

- **Liposomes:**The well-studied and most prevalent nanocarriers for the targeted medication delivery are liposomes. By stabilizing the therapeutic chemicals, overwhelming barriers to the tissue and the cellular absorption, and enhancing bio-distribution of drugs to target areas in vivo, they have enhanced therapeutics for a variety of biomedical applications(94)(95)(96)(97)**.** Liposome are closed vesicles structures composed of bilayer of phospholipids and cholesterol intended for the effective delivery of drugs and antigen having ability to encapsulate both hydrophilic as well as lipophilic molecules, allowing them to entrap wide spectrum of pharmaceuticals(98).Water loving molecules can be entrapped in the aqueous (water) core, whereas hydrophobic molecules are introduced into the double layer membrane(99).

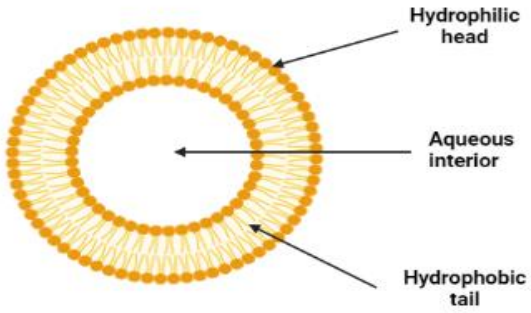

Fig. 6: Structure of Liposome

- **Transferosomes:** Transferosomes have a structure that combines hydrophobic and hydrophilic moieties; they may accept medicinal molecules with a wide series of solubility(100). Transferosomes may bend and pass through constriction up to ten times smaller than their own area without noticeable loss. This high deformability gives improved diffusion of intact vesicles(101).Transferosomes are self-assemblies with an ultra-flexible membrane that distributes the medication into or through the skin in a consistent manner(102).

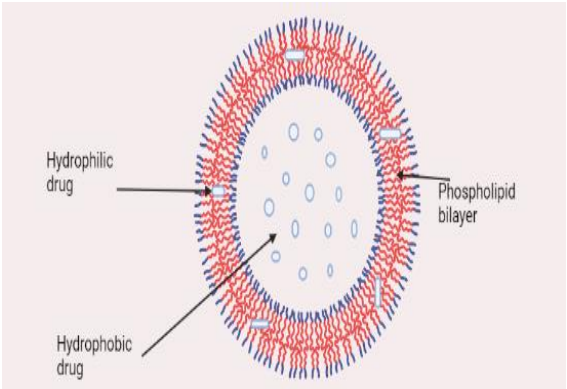

Fig. 7: Structure of Transferosomes

- **Ethosomes:**"Ethosomes are ethanol liposomes, and these are noninvasive drug delivery vehicles that allow medications to penetrate deeper into the systemic circulation and/or epidermal layers(103).Ethosomes are vesicles of lipids that contain high concentration of

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alcohol (isopropyl alcohol and ethanol), phospholipids and water. Ethosomes are soft kind of vesicles composed of ethanol (in greater amounts), phospholipids and water. Ethosomes range in size from tens of nm (nanometers) to microns, and they penetrate the layers of skin quickly and have much higher Transdermal flux(104)(105).

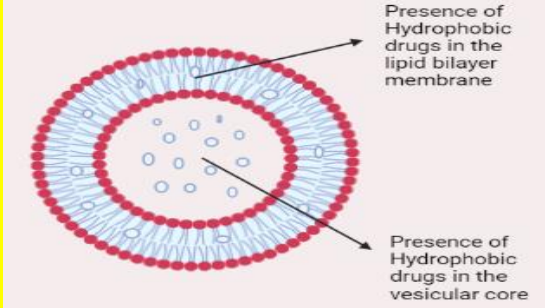

Fig. 8: Structure of Ethosomes

- **Transethosome:** The term "Transethosome" refers to a hybrid of the terms "transferosomes" and "ethosomes." Transferosomes demonstrate skin penetration as well as the ability to deform(106). Transethosome can be taken by systemic as well as topical route. This device is capable of trapping drugs with molecular weights ranging from low to high(107).Because the bioactive substance is encapsulated, its content is released in a slow and progressive way. It has a very effective trapping capability due to its biocompatible and biodegradable nature. Its development does not involve the use of any superfluous medicinal components, nor does it necessitate a lengthy process(108).

X. COMPARISON OF VARIOUS NANOCARRIERS IS SHOWN IN TABLE

S.no	Carrier	Advantages	Disadvantages	References
1.	Niosomes	Non-ionic surface acting agents (surfactants) vesicles	Less skin penetration easy handling but will not able to reach up to deeper skin layer stable	(110)
2.	Liposome's	Biocompatible, Phospholipid vesicle	Less skin penetration	(109)
3.	Transferosomes	More stable, higher permeation owing to biodegradable and biocompatible, deformability, suited for both high and low molecular weight medications, as well as lipophilic and hydrophilic pharmaceuticals, and able to penetrate deeper into the layers of skin.	None, but for some limitations	(111)
4.	Transethosome	Transdermal medication delivery with improved drug permeability via the skin. The formulation's raw materials are non-toxic by nature. More stable The semisolid version of the transethosomal medication is used for administration. First-pass metabolism is avoided. First-pass metabolism is avoided.	Product loss occurs with the transition of products from alcoholic to non-alcoholic media. Contact dermatitis can cause skin irritation or an allergic response. Transethosomesmay Coalesce if vesicle production fails.	(112)(113)

Table 3

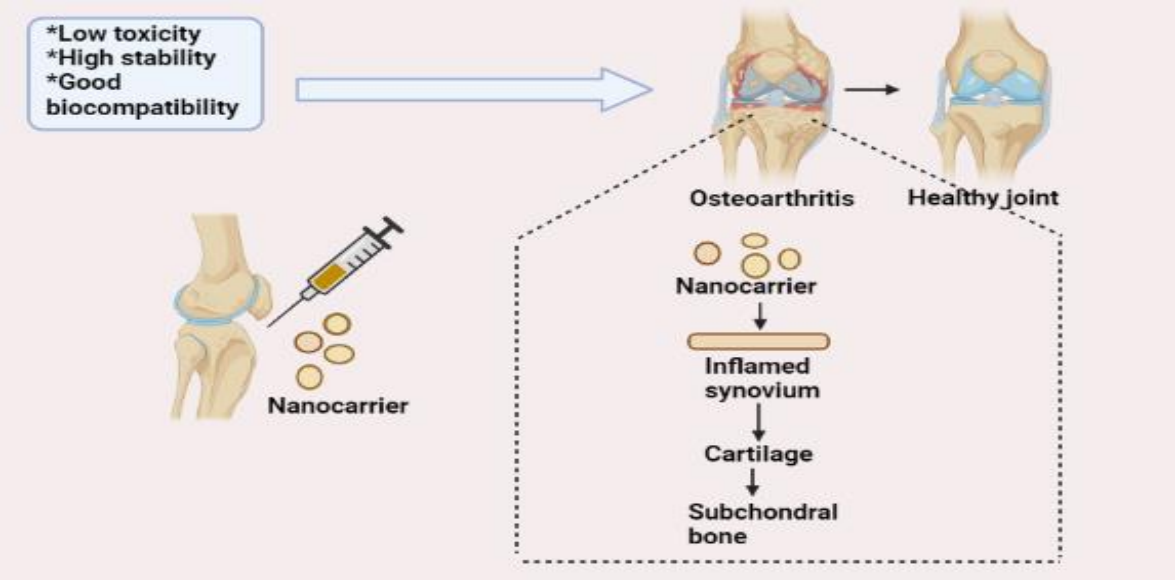

Fig. 9: Shows how the nanocarriers act on the infected joint in osteoarthritis

XI. SUMMARY AND CONCLUSION

Osteoarthritis is an autoimmune disease that affects the joints, causing excruciating pain and making movement difficult. The patient received a variety of treatments. However, in the chronic phase of OA, surgery is the sole choice for treatment. Novel carriers, such as niosomes, liposomes, ethosomes, transferosomes and Transethosome, are employed to improve medication absorption through the skin.

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