



AN OVERVIEW ON PATHOPHYSIOLOGY OF OLD AGE DISEASE- OSTEOARTHRITIS AND ITS HERBAL TREATMENT

Nasreen Sulthana^{*1}, K.Vijaya²

¹Research Scholar, Faculty of Pharmacy, Pacific Academy of Higher Education and Research,
Udaipur, Rajasthan-313003.

²Principal and Professor, TKR College of Pharmacy, Meerpet, Hyderabad- 500097

***Corresponding author E-mail: nasrpharma31@gmail.com**

ARTICLE INFO

Key Words

*Osteoarthritis,
Angiogenesis,
Inflammation,
Circadian rhythm,
Herbs*



ABSTRACT

Osteoarthritis is a degenerative disorder characterized by regression of cartilage and formation of osteophytes. The symptoms of osteoarthritis include soreness and stiffness in joints, swollen and tender joints, nodes formation with restricted movements. The hyaluronic acid present in the articular cartilage contributes to the viscoelastic properties by acting as a lubricant. Osteoarthritis is mainly caused due to the imbalance between matrix synthesis and degeneration in articular cartilage. The hyaluronic acid levels decreases thereby resulting in reduction or narrowing of joint space. Recent investigations reveal the involvement of DDR-2 receptors in the pathogenesis of Osteoarthritis. Angiogenesis in osteoarthritis is induced by various factors like Vegetative endothelial growth factor, Tumor Necrosis factor- α , MIF, Leukotrienes, Matrix metalloproteinases. Disrupted circadian rhythms are also considered as a novel risk factor for Osteoarthritis with the involvement of SIRT 1 gene. Disrupted SIRT 1 decreases the number of chondrocytes and cartilage leading to Osteoarthritis serving as a new therapeutic strategy in Osteoarthritis. The present review focuses on the symptoms, risk factors, pathogenesis and herbal treatment of Osteoarthritis which can be incorporated for research as the future therapeutic targets in effective treatment of osteoarthritis.

INTRODUCTION:

Osteoarthritis also known as degenerative arthritis is a pro-inflammatory degenerative disorder characterized by the degeneration of cartilage and formation of osteophytes. It is common in weight bearing joints such as spine and hips. It occurs when the cushion i.e articular cartilage breaks down leading to pain, swelling and stiffness in joints.^[1] Osteoarthritis occurs more frequently with increase in age. Before 45 years of age osteoarthritis is common in males than in

females whereas after the age of 55 years it occurs more frequently in females than in males.^{[2], [3]} Geographically it is frequent in Japanese population whereas it is less frequent in South African blacks, East Indians and Southern Chinese^[4]. Signs and Symptoms of osteoarthritis vary from patient to patient. The primary symptoms include soreness and stiffness, swelling, creaking, pain, heberden nodes in joints^{[5],[6]}. The joints often affected are knees, lower back, groin, hip joint etc.

The Risk factors contributing to OA include:

Family history or heredity contributes to the risk of OA. The gene responsible for the heredity is not yet known.

Age: OA prevalence increases in old age especially after the age of 65yrs.

Sex: Before the age of 55, men are more prevalent to get OA. After the age of 55, women are more prone to get OA due to the hormonal changes in women during menopause.

Diet: Diet is also a considerable risk factor for OA. The important nutritional factor for OA is Vitamin D. Deficiency of Vitamin D makes the bone thin, brittle and misshapen which in turn increases the risk of OA^[7].

Disease conditions: Conditions like congenital subluxation, Legg-Calvé-Perthes disease, and slipped capital femoral epiphysis increases the risk of hip OA in later life^[8]. Other risk factors include obesity, damage to a bone or ligament, occupation in which there is excess of mechanical stress also contributes to Osteoarthritis.

Types of Osteoarthritis:

Primary Osteoarthritis:

It is considered as degenerative or “wear and tear” arthritis which is caused due to unknown predisposing factor. It is age related arthritis and is commonly diagnosed after the age of 55yrs.

It is again classified as:

Localized Osteoarthritis: It involves one or two sites.

Generalized Osteoarthritis: It involves three or more sites.

Secondary OA:

It is considered as a degenerative arthritis that is caused due to a predisposing condition like trauma, obesity, etc that has adversely affected the articular cartilage of the joints. It often occurs in relatively young individuals.

Stages of osteoarthritis:

Acute Osteoarthritis:

Occasional joint pain is the main characteristic feature of acute osteoarthritis. Minor stiffness in joints and painful mobility is seen for short period of time.

Sub acute osteoarthritis:

Localized joint pain is the main characteristic feature with excessive pain and stiffness in the fingers.

Chronic osteoarthritis:

In this type, the movement of joints is limited. It is characterized by severe pain in joints.

Degenerative osteoarthritis:

In this type the cartilage is completely lost with terrible pain. It is characterized by complete loss of cartilage surrounding the joint and terrible pain of rubbing on bone.

PATHOPHYSIOLOGY:

Osteoarthritis can occur in four components of joints namely meniscus, articular cartilage, subchondral bone and synovial membrane^[9]. Meniscus is the piece of cartilage which is found where two bones meet. It protects and forms cushion at the joint surface. It is made up of fibro cartilage where its ECM is constituted by proteoglycans, Collagen and water. Articular cartilage provides surface for the movement of synovial joints. It is made up of hyaline cartilage and its ECM is composed of proteoglycans (aggrecan) and Type II Collagen. Subchondral bone is the region similar to epiphyseal plate present just below the covering of articular cartilage. It is composed of type I Collagen and it gives support to the joint. Synovial membrane is the inner layer of synovial capsule which produces synovial fluid. It consists of two types of cells-fibroblasts and macrophages. Fibroblast produces synovial fluid whereas macrophages are activated during inflammation. Even though all these components play a role in osteoarthritis, articular cartilage plays a central role in initiation and progression of Osteoarthritis due to its mechanical properties^[10]. Cartilage is composed of specialized cells called chondrocytes that produces elastic fibres, extra cellular matrix and matrix degrading enzymes. The ECM is rich in proteoglycans (aggrecans) and collagenous proteins (Type II Collagen). Aggrecan provides negative charge to the matrix and collagen imparts viscoelastic compressive properties to the cartilage. In healthy individuals, the joint space is filled with synovial fluid that is composed of hyaluronic acid which acts as a lubricant. In OA patients, the hyaluronan concentration is less providing less lubrication which in turn reduces or narrows the joint space. This may lead to rubbing of bones against each other leading to inflammation. This inflammation contributes to the swelling and pain in the joints. Various

inflammatory mediators like cytokines, Interleukins, TNF- alpha are released which in turn produces proteolytic or degradative enzymes ^[11]. In healthy adult bones, articular cartilage is not static but it undergoes regeneration process in which the worn out matrix is degraded and replaced. In normal conditions, the matrix synthesis (anabolism) and matrix degeneration (catabolism) will be balanced and the volume of cartilage will be maintained thereby maintaining homeostasis. The catabolism is promoted by Bone morphogenetic protein-2, Insulin like growth factor-1, Transforming growth factor. Proteolysis of cartilage is stimulated by Matrix metalloproteinases namely collagenases (MMP-1, MMP-8, MMP-13), stromelysins (MMP-3), gelatinases, Tumor necrosis factor. Tissue inhibitors of metalloproteinases restrain the catabolic actions of MMPs and thereby contribute in maintaining the balance. In Osteoarthritis, this balance is disturbed due to many factors. The important factors are age, mechanical stress and heredity which lead to significant changes in the composition and mechanical properties of cartilage. In early stages of the disease the cartilage contains more water content and less proteoglycan content. There will be decreased synthesis of type II Collagen and increased break down of pre existing collagen. Due to the increase in the levels of certain molecular messengers like IL-1, TNF, NO in OA, chondrocyte apoptosis and prostaglandin synthesis also increases. In response to all these changes the chondrocytes present in the deeper layers proliferates and synthesizes new collagen and proteoglycans. Although this compensatory mechanism initially compensates for the loss of cartilage, degradation of cartilage predominates in the later stages. As the disease progresses the cartilage dehydrates, becomes brittle cracking the cartilage called as fissuring. As the number of cracks increases, cartilage flakes away. The bone will be left uncovered and the bones move against each other. Recent investigations reveal that DDR-2 (Discoidin domain receptor-2), a cell membrane tyrosine kinase receptors for type II collagen are involved in the pathogenesis of OA. DDR-2 is located on the cell surface of chondrocytes. In healthy cartilage, these receptors are inactive and are masked by aggrecans preventing their contact with collagen. As damage to the cartilage triggers the aggrecans, DDR-2 is exposed to

collagen and is activated. Active DDR-2 increases the activity of MMP-13 which in turn damages the collagen ^{[12], [13]}.

Neovascularization in OA: Growth of new blood capillaries from pre existing vasculature is called as neo vascularization or angiogenesis. It is a physiological process during embryogenesis, wound healing and menstrual cycle. It is a pathological process in conditions like chronic inflammatory diseases, growth of tumors. ^[14]. Angiogenesis in Osteoarthritis is regulated by numerous growth factors which are listed in (table 1 and table 2): ^[15] Angiogenesis in osteoarthritis is induced by VEGF, hypoxia and inflammation ^[21]. Articular cartilage is unique in being avascular. Inflammation is the major contributor of pain in Osteoarthritis. Biochemical changes and cartilage destruction in OA may lead to synovial inflammation called synovitis. Synovitis plays an important role in the pathology of OA. Synovitis leads to alterations in chondrocyte functioning, enhanced angiogenesis and changes in bone turnover. Synovitis is characterized by invasion and activation of macrophages and lymphocytes, release of pro inflammatory and procatabolic mediators and alteration in vascularity of synovial membrane. Activated macrophages produce many factors which can directly or indirectly induce angiogenesis. Indirect action is due to secretion of factors that in turn stimulate other cells to release angiogenic factors like VEGF. Macrophages themselves also release TNF- α which is an angiogenic factor. In synovitis, hypoxia is induced due to high metabolic demands of the synovial cells. In hypoxia conditions, the macrophages increases in number which in turn promotes angiogenesis as described earlier. Macrophages also express Macrophage migration Inhibitory factor (MIF) which induces the release of different angiogenic agents like TNF- α , IL-1, IL-6, IL-8 and MMPs. Hypoxic tissues also induce Hypoxia inducible factor-1 α (HIF-1 α) ^[22]. This factor in turn induces synovial cells, macrophages and other inflammatory cells to produce VEGF.

Role of leptin in Osteo arthritis:

Leptin is a cytokine like hormone secreted by adipocytes. Leptin influences food intake and energy expenditure by negative feedback mechanism in hypothalamus. It is involved in different physiological functions like lipid

metabolism, hemopoiesis, angiogenesis, ovarian function, reproduction, inflammation, immune system modulation etc [23]. It also plays a significant role in the regulation of bone mass. Leptin acts both centrally and peripherally and shows anabolic action on bone stimulating the bone formation. Role of leptin provides the missing link between obesity and osteoarthritis. Recent investigations reveal that obese patients have high levels of leptin in synovial fluid. Leptin receptors ob-R are over expressed in cartilage. Leptin also induces the production of matrix metalloproteinases, pro inflammatory mediators and Nitric oxide in chondrocytes. The cartilage of obese patients also exhibit great sensitivity to leptin highlighting its role in the pathophysiology of osteoarthritis.

Circadian rhythm and Osteoarthritis:

Disturbed circadian rhythms are considered to be the novel risk factor for osteoarthritis. Circadian rhythms play a vital role in maintaining homeostasis. Physiologically the circadian rhythm is highly organized in a 24hr cycle and is regulated by Supra chiasmatic nucleus present in hypothalamus.

They deal with the cyclic changes occurring in day and night which depends on absence and presence of light. These rhythms can be influenced by environmental factors such as sunlight, temperature, etc. Recent studies suggest the role of disrupted circadian rhythms in the pathology of osteoarthritis. Due to modern lifestyle, the circadian rhythm is disrupted due to excessive night-time exposure to light and physical activity.

Chondrocytes play a very significant role in the pathology of osteoarthritis. Age is a common risk factor for osteoarthritis. Efforts were kept in recent years to demonstrate the contribution of aging in the pathology of osteoarthritis. Recent investigations suggest that chondrocytes which play an important role in maintaining bone homeostasis are regulated by autonomous biological clock. This autonomous clock is found to be disrupted as age increases. This aging in turn is regulated by the SIRT1 gene which is under expressed during aging [24].

It is also observed that disruption of the gene SIRT1 takes place during osteoarthritis.

Various experimental data suggests that increase in SIRT1 increases the number of chondrocytes, hence cartilage. Disrupted SIRT1 decreases the chondrocytes and cartilage leading to Osteoarthritis. SIRT1 influences circadian rhythm by acting on hypothalamic nuclei (SCN). This serves a new therapeutic strategy to target SIRT1 in Osteoarthritis [25].

DIAGNOSIS

OA can be diagnosed by the following methods

Arthrocentesis: In this the synovial fluid is collected at the joint and is analyzed for the presence of crystals or any other bone deterioration.

Blood tests: Blood tests are performed to exclude other diseases that can cause secondary osteoarthritis.

X-Rays: OA can be diagnosed by the loss of joint cartilage, narrowing of the joint space between adjacent bones and bone spur formation.

Arthroscopy: It is a surgical technique whereby a viewing tube is inserted into a joint space. Abnormalities and damage can be detected and can also be repaired.

TREATMENT OF OSTEOARTHRITIS

The goal of osteoarthritis treatment includes alleviation of pain and improvement of functional status. Therefore patients should receive a combination of non pharmacological, pharmacological and surgical therapy.

Non pharmacologic treatment:

Physical therapy:

Physiotherapy reduces pain and fatigue, improves mobility, fitness and alleviates depression.

Heat and Cold therapy:

Heat causes vasodilation and increases the blood supply, circulation thereby reducing the muscle spasm. It also alters the sensation of pain.

Cold helps in reducing the swelling, decrease pain by constricting the blood flow to the inflamed joint [26].

Weight loss:

Overweight increases the risk of Osteoarthritis by 4 times in women and by 5 times in men. Even small amount of weight loss reduces the risk of osteoarthritis.

| S. no | Stimulators of angiogenesis in Osteoarthritis | Mechanism |
|-------|---|--|
| 1 | Hypoxia | Prolonged hypoxia in cartilage leads to the expression of hypoxia induced factor α (HIF- α) which is a positive |

| | | stimulator of VEGF |
|----|--------------------------------------|---|
| 2 | Fibroblast Growth Factor | Promotes proliferation and differentiation of endothelial cells, smooth muscle cells and fibroblasts |
| 3 | Vegetative Endothelial Growth Factor | Alters permeability of blood vessels |
| 4 | Neuropilin-1 | It is a co receptor for VEGF |
| 5 | Angiopoietin-1 and Angiopoietin-2 | Important for vessel maturation, adhesion, migration and survival |
| 6 | Platelet Derived Growth Factor | PDGF secreted by ECs acts as a ligand for PDGF receptor located on the pericyte membrane, causing pericytes to produce and secrete VEGF that signals through the endothelial VEGF receptor. |
| 7 | Transforming growth factor – β | Induces VEGF expression in vascular endothelial cells |
| 8 | Chemokine c-c motif ligand-2 | Recruits monocytes, memory T cells, dendritic cells to the site of inflammation |
| 9 | Histamine | Alters vascular permeability |
| 10 | Integrins | Facilitates growth and survival of new blood vessels |

Table 1: Stimulators of Angiogenesis

| S.no | Anti angiogenic factors | Mechanism |
|------|-------------------------|--|
| 1 | Angiostatin | Inhibits endothelial cell migration, proliferation, and induction of apoptosis. ^{[16] [17]} It also targets the krebs cycle in mitochondria |
| 2 | Endostatin | Inhibits phosphorylation of kinase, interacts with cell surface receptors, inhibits wnt-signalling, blocks VEGF signaling, inhibits metalloproteinases. ^{[18] [19]} |
| 3 | Thrombospondin | Induce CD36 independent growth arrest via p53-p21 induction thereby inducing apoptosis and preventing angiogenesis. ^[20] |

Table 2: Inhibitors of Angiogenesis



Fig 1: Risk factors of Osteoarthritis

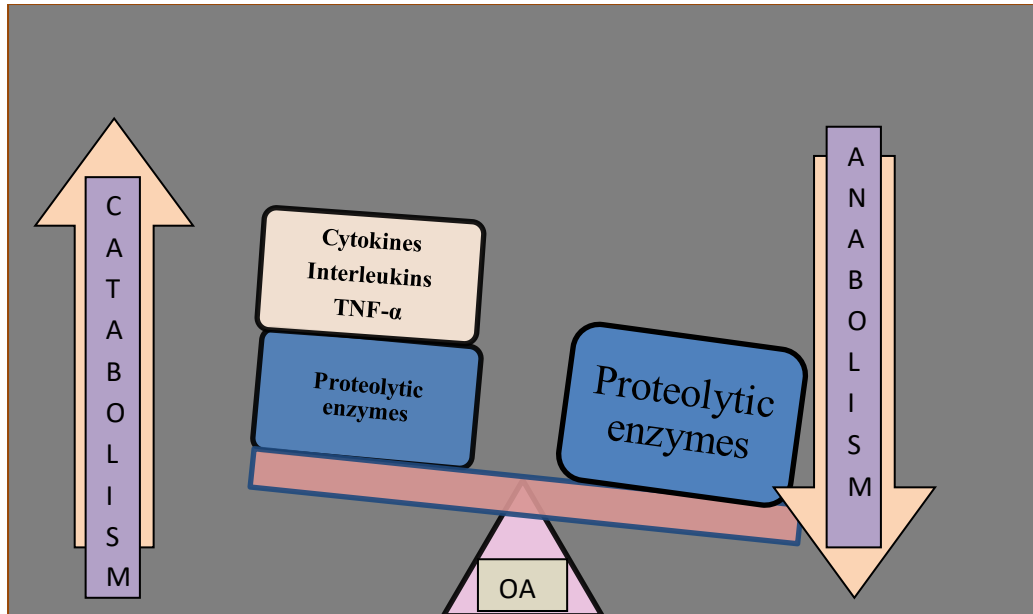


Fig 2: Pathogenesis of Osteoarthritis

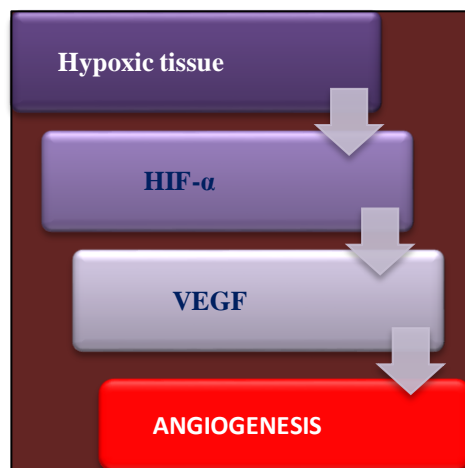


Fig 3: Angiogenesis in hypoxic tissue

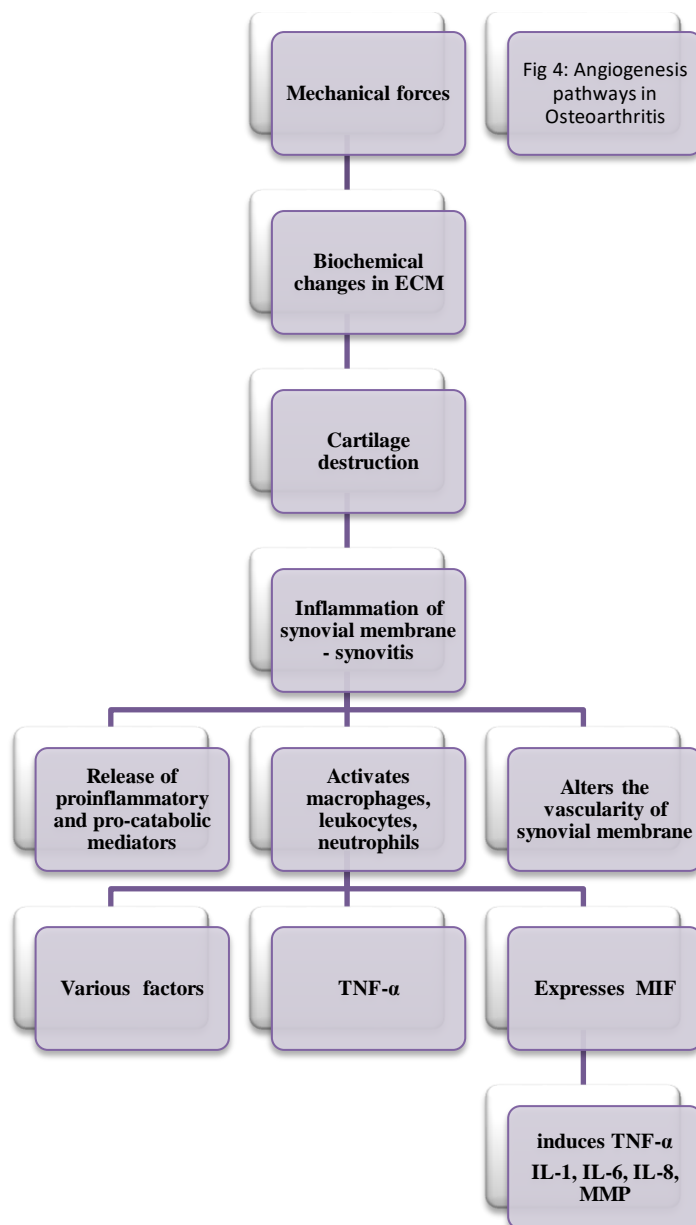


Fig 4: Angiogenesis pathways in Osteoarthritis

Fig 4: Angiogenesis pathways in Osteoarthritis

Patient education: The patient must be educated with the risk factors and preventive measures involved in osteoarthritis. Their weight should be assessed and different weight loss programs should be advised. Their diet should be reviewed and progress should be monitored with regular follow-ups.

Exercise: Exercise or physical activity is the best non pharmacological treatment for osteoarthritis.

Pharmacological treatment: Analgesics – NSAIDs, Anti depressants, Intra articular corticosteroid, Nutraceuticals- glucosamine/ chondroitin, Topical agents. Non-steroidal anti-inflammatory drugs (NSAIDs) are the

drug of choice for osteoarthritis, rheumatoid arthritis and gout. The most common form of arthritis is osteoarthritis and because of increasing joint pain, the quality of life of the patients is impaired. NSAIDs effectively relieve pain and increase mobility in osteoarthritic patient. Commonly used NSAIDs are: Acetaminophen, Ibuprofen, Naproxen and Diclofenac.

HERBS USED IN THE TREATMENT OF OSTEO ARTHRITIS:

The conventional drug therapy for osteo arthritis most commonly involves the use of Non steroidal anti inflammatory agents. These drugs sometimes become ineffective in

some patients and they often have serious adverse effects. Gastro intestinal toxicity and nephrotoxicity is of major concern. Therefore an alternate approach of using herbal medicines which are more effective with less adverse effects is the need of the hour in osteoarthritic patients. The herbs which can be used in alleviating the symptoms of Osteoarthritis are:

Boswellia: It possess anti inflammatory, anti arthritic, analgesic, hepatoprotective action due to the presence of boswellic acids. They inhibit the activity of LOX enzyme thereby inhibiting the formation of leukotrienes. Aflapin and 5- Loxin present in boswellia are said to have both chondroprotective and anti inflammatory action. They also inhibit MMP-3 activity. Because of these activities it can be used in the treatment of osteoarthritis [27].

Capsaicin: Capsaicin is a naturally occurring alkaloid which is the main chemical constituent of Capsicum genus (hot chilli pepper or cayenne pepper). It is used as an analgesic agent. It relieves pain in Osteoarthritis by depleting the levels of substance P by acting on transient receptor potential vanilloid 1 (TRPV1) receptor which is involved in sensing warmth, pain, heat etc [28].

Flax seed: *Linum usitatissimum* or flax seed contains high amount of omega -3 fatty acids such as linolenic acid, lignans such as matairesinol, pinosresinol, lariciresinol, and isolariciresinol. Lignans have estrogenic, antiestrogenic, anti inflammatory, anti carcinogenic properties. It reduces pain in osteoarthritis by triggering opioid receptors on cells by releasing serum beta-endorphin levels which are analgesic physiologically [29].

Ginger: Ginger (*Zingiber officinalis*) consists of complex of compounds like gingerols, shogaols and paradols which are responsible for anti inflammatory or pain relieving activity. They show this activity by inhibiting COX (COX-2 preferably), and LOX pathway. They inhibit the expression of Tumor necrosis factor- α in synoviocytes thereby can be used in treating Osteoarthritis [30].

Kalonji:

According to Islam, it can cure all diseases except death. It has antioxidant, anti inflammatory, anti cancer, anti bacterial, anti fungal, anti parasitic properties. The main constituents of these seeds are thymoquinone (TQ), dithymoquinone (DTQ),

thymohydroquinone (THQ), and thymol (THY). Thymoquinone is said to have anti inflammatory properties acting by inhibiting COX activity, thereby can be used to reduce the pain in osteoarthritis. It also suppresses the production of NO which is an added advantage in OA [31].

Aswagandha:

It contains alkaloids such as isopelletierine, anaferine, cuseohygrine, anhygrine etc; steroidal lactones such as withanolides and withaferins; and saponins. It is said to have anti stress, anti arthritic, anti helminthic and stimulant. It is used as astringent, aphrodisiac, narcotic, diuretic etc [32].

Cat's claw:

Cat's claw (*Uncaria tomentosa*) inhibits TNF activity and acts as anti inflammatory agent. It reduces the pain in physical activity but not the pain at rest. It causes headache, dizziness, vomiting and hypotension hence contraindicated in hypertensive patients [33].

Curcumin:

It is a yellow pigment obtained from the rhizomes of *Curcuma longa*. It has anti inflammatory and anti oxidant properties because of which it can be used in the treatment of osteoarthritis [34].

Resveratrol:

It is a stilbenoid, a natural phenol which is obtained from red wine. It is thought to be as an anti inflammatory agent as it inhibits the activation of NF-kB and reduces the levels of Nitric oxide (NO) induced by cytokines therefore acting as an anti arthritic agent [35].

Soya bean:

Soya bean or Glycine max is also called as golden bean. It is rich in healthy oil and proteins. Soy proteins contain genistin, isoflavones and diadzin. They have anti carcinogenic, anti oxidant and anti inflammatory properties. It reverses the process of bone degradation and stimulates bone formation helping in the treatment of osteoarthritis [36].

Olive oil:

Olive oil is obtained from olive seeds (*Olea europaea*). The main components in olive oil are monounsaturated fatty acids (mainly oleic acid) which are essential to maintain bone health. It is a potent COX inhibitor and also decreases the release of NO in the joints and hence can be used in

osteoarthritis. It also contains phenols like oleuropein, tyrosol and hydroxytyrosol which give olive oil its antioxidant, anti-inflammatory and clotting properties^[37].

CONCLUSION:

The present review focuses on the symptoms, risk factors, pathogenesis and treatment of Osteoarthritis which can be included in the research as the future therapeutic targets in effective treatment of osteoarthritis.

REFERENCES:

1. Aigner T: Osteoarthritis. *Curr Opin Rheumatol* 2007; 19:427-8
2. Wluka AE, Cicuttini FM, Spector TD: Menopause, oestrogens and arthritis. *Maturitas* 2000; 35(3):183-99
3. Srikanth VK, Fryer JL, Zhai G, Winzenberg TM, Hosmer D, Jones G: A meta-analysis of sex differences prevalence, incidence and severity of osteoarthritis. *Osteoarthritis Cartilage* 2005; 13(9):769-81
4. D'Ambrosia RD: Epidemiology of osteoarthritis. *Orthopedics* 2005; 28(2):201-205.
5. Kellgren JH, Moore R: Generalized osteoarthritis and heberden's nodes. *Br Med J* 1952; 1:181.
6. Historical criteria for Osteoarthritis in use at the department of Orthopaedic and Trauma Surgery, University of Cologne
7. McAlindon TE, Felson DT, Zhang Y, et al: Relation of dietary intake and serum levels of vitamin D to progression of osteoarthritis of the knee among participants in the Framingham Study. *Ann Intern Med* 1996; 125(5):353-9
8. Harris WH: Etiology of osteoarthritis of the hip. *Clin Orthop Relat Res.* 1986; 213:20-33.
9. Almquist EE: Evolution of the distal radioulnar joint. *Clin Orthop* 1992; 275:5-13
10. Alford JW, Cole BJ: Cartilage restoration, part I: basic science, historical perspective, patient evaluation and treatment options. *Am J Sports Med.* 2005; 33:295-306
11. Alice J. Sophia Fox, Asheesh Bedi, Scott. A. Rodeo: The Basic Science of Articular cartilage. *Sports Health* 2009; 1 (6):461-468
12. Hu K, Xu L, Cao L, Flahiff CM, Setton LA, Youn I, et al: Pathogenesis of Osteoarthritis-like Changes in Joints of Type IX Collagen-Deficient Mice. *Arthritis Rheum* 2006; 9:2891-900
13. Xu L, Polur I, Lim C, Servais JM, Dobeck J, Li Y, et al: Early-onset osteoarthritis of mouse temporomandibular joint induced by partial disectomy. *Osteoarth Cartil* 2009; 17:903-8
14. Liekens S, De Clercq E, Neyts J: Angiogenesis: regulators and clinical applications. *Biochem Pharmacol* 2001;61:253-70.
15. Bonnet CS, Walsh A: Osteoarthritis, angiogenesis and inflammation. *Rheumatology* 2005; 44:7-16
16. Redlitz A, Daum G, Sage EH: Angiostatin diminishes activation of the mitogen-activated protein kinases ERK-1 and ERK-2 in human dermal microvascular endothelial cells. *Journal of Vascular Research* 1999; 36 (1): 28-34
17. Lee TY, Muschal S, Pravda EA, Folkman J, Abdollahi A, Javaherian K: Angiostatin regulates the expression of antiangiogenic and proapoptotic pathways via targeted inhibition of mitochondrial proteins. *Blood* 2009; 114:1987-1998.
18. Folkman J: Antiangiogenesis in cancer therapy—endostatin and its mechanisms of action. *Exp Cell Res* 2006; 312:594-607
19. Abdollahi A, Hlatky L, Huber PE: Endostatin: the logic of antiangiogenic therapy. *Drug Resist Updat* 2005; 8:59-7
20. Yamauchi M, Imajoh-Ohmi S, Shibuya M: Novel antiangiogenic pathway of thrombospondin-1 mediated by suppression of the cell cycle. *Cancer Sci.* 2007; 98(9):1491-1497
21. Schutze N: Angiogenesis in Osteoarthritis. *Current Rheumatology Reviews* 2008; 4(3):1-4
22. Forsythe JA, Jiang BH, Iyer NV, et.al: Activation of vascular endothelial

- growth factor gene transcription by hypoxia- inducible factor-1. *Mol Cell Biol* 1996;16:4604-13
23. Russell T, Turner, Satya P, Kalra, Carmen P, Wong, Kenneth A, Philbrick, Laurence B, Lindenmaiera, Stephane Boghossian, and Urszula T, Iwaniec: Peripheral Leptin regulates bone formation. *J Bone Miner Res*. 2013. 28(1): 22–34
 24. Fanny Ng, Wijaya L, Tang BL: SIRT1 in the brain—connections with aging-associated disorders and lifespan. *Front cell NeuroSci* 2015; 9(64):1-13
 25. Takayama K, Ishida K, Matsushita T, Fujita N, Hayashi S, Sasaki K, Tei K, Kubo S, Matsumoto T, Fujioka H, Kurosaka M, Kuroda R: SIRT1 regulation of apoptosis of human chondrocytes. *Arthritis Rheum*. 2009; 60(9): 2731-40
 26. Brosseau L, Yonge KA, Welch V, Marchand S, Judd M, Wells GA, Tugwell P: Thermotherapy for treatment of osteoarthritis. *Cochrane Database of Systematic Reviews* 2003; 4. Art. No.: CD004522
 27. Kimmatkar N, Thawani V, Hingorani L, et al: Efficacy and tolerability of *Boswellia serrata* extract in treatment of osteoarthritis of knee - a randomized double blind placebo controlled trial. *Phytomedicine* 2003; 10(1):3-7
 28. McCarthy GM, Mc Carty DJ: Effect of topical capsaicin in the therapy of painful osteoarthritis of the hands. *J Rheumatol*. 1992; 19(4) 604-7
 29. Nagwa H, Mohamed, Eman El-gharoury, Hemat allam, Ghada A. Helmy and Emad Effect of dietary flaxseed on knee osteoarthritis. *Med. J. Cairo Univ*. 2015; 83(2).
 30. Bartels EM, Folmer VN, Bliddal H, Altman RD, Juhl C, Tarp S, Zhang W, Christensen R: Efficacy and safety of ginger in osteoarthritis patients: a meta-analysis of randomized placebo-controlled trials. *Osteoarthritis Research Society International* 2014; 23:13-21.
 31. Ansari R, Batra NG: Effects of *Nigella sativa* against osteoporosis. *Int. J. Pure App Biosci* 2013; 1(2):6-14
 32. Singh N, Bhalla M, De Jager P, Gilca M: An overview on Ashwagandha: A Rasayana (Rejuvenator) of Ayurveda. *Afr J Tradit Complement Altern Med*. 2011; 8(S):208-213
 33. Patel D, Kaur G, Sawant MG, Deshmukh P: Herbal Medicine-A Natural Care to osteoarthritis. *Indian Journal of Natural products and resources* 2013; 4(1):27-35.
 34. Henrotin Y, Priem F, Mobasher A: Curcumin: A New Paradigm and therapeutic opportunity for the treatment of osteoarthritis: Curcumin for osteoarthritis management. *Springerplus* 2013; 2(1):5
 35. Wang J, Gao JS, Chen JW, Li F, Tian J: Effect of Resveratrol on cartilage protection and apoptosis inhibition in experimental osteoarthritis of rabbit. *Rheumatol Int*. 2013; 32(6):1541
 36. Christiansen BA, Bhatti S, Goudarzi R, Emami S: Management of Osteoarthritis with avocado/Soyabean Unsaponifiables. *Cartilage* 2015; 6(1): 30-44
 37. Abdul-Majeed A, Saja H, Hashem AT, Mohammad J: The effect of topical application of extra virgin olive oil on alleviating knee pain in patients with knee osteoarthritis: A Pilot Study. *Indian Journal of Physiotherapy and Occupational therapy* 2013; 7(3):6-11