Research Article

ROLE OF CURCUMIN IN THE PREVENTION OF OSTEOARTHRITIS

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ABSTRACT

Osteoarthritis is a chronic degenerative disorder characterized by loss of cartilage and its underlying bone as well as the formation of osteophytes. Obesity serves as one of the major risk factors for osteoarthritis. The present study was aimed to investigate the role of curcumin in preventing obesity which in turn prevents osteoarthritis. Female rats were divided into 4 groups each containing 6 animals. Group I was considered as a control in which animals were fed with a normal/standard diet. Group II animals were fed with high-fat diet (Monosodium glutamate 4mg/g). Group III animals were fed with normal/standard diet along with curcumin (200mg/Kg) and group IV animals were fed with high-fat diet (monosodium glutamate 4mg/g) along with curcumin (200mg/Kg) for 28 days. Parameters like body weight, serum High-density lipids (HDL), low-density lipids (LDL), very low-density lipids (VLDL), triglycerides and cholesterol were estimated. The data of our study shows that the animals which were fed with curcumin have less percentage of weight gain when compared to the animals which were fed with high-fat diet. Serum HDL was found to be higher in group II animals when compared to group I and higher in group IV when compared to group III. Other parameters like serum LDL, VLDL, cholesterol, triglycerides were higher in animals fed with high-fat diet group III when compared to all other groups. It demonstrates that curcumin, when included in diet, has a role in preventing obesity and thereby reduces the risk of osteoarthritis.

Keywords: Cholesterol, curcumin, obesity, osteoarthritis, the percentage of weight gain.

INTRODUCTION

Osteoarthritis is a pro-inflammatory degenerative disorder characterized by cartilage destruction, osteophytes formation, and bone remodeling. Multiple risk factors like age, sex, trauma, obesity and genetic predisposing factors are linked to osteoarthritis. Obesity, one of the risk factors for osteoarthritis is one of the major concerns today worldwide. According to the estimation of WHO 2.3 billion people are overweight and 700 billion are obese in the world in 2015. Overweight and obesity put people at a high risk of comorbidities like diabetes II, osteoarthritis, cancer, cardiovascular diseases increasing morbidity and mortality[1, 2].

Obese people are more prone to get affected by Osteoarthritis. The link between obesity and osteoarthritis is because of certain metabolic factors. These factors are termed as adipokines which are leptin, adiponectin, resistin, visfatin. These factors mediate lipid and glucose metabolism, insulin sensitivity, other physiological functions like reproductive functions, regulation of blood pressure, bone formation and angiogenesis.

Adipose tissue is considered as an endocrine gland which releases adipokines and cytokines which in turn are capable of promoting low-grade inflammation. Obesity is also related to altered lipid metabolism leading to low serum high-density lipid levels, high serum free fatty acids, triglycerides and oxidized low-density lipids.

Curcumin also called as a golden herb is an active chemical constituent of the rhizome *Curcuma longa.* Extensive research has been conducted on the anti-inflammatory, antioxidant and anti-cancer properties of curcumin. The present study is to investigate the role of curcumin in preventing overweight or obesity in rats in rats thereby helpful in preventing osteoarthritis.

MATERIALS AND METHODS

24 female Wistar rats weighing around 180-250 g were used for this study. The animals were accommodated in standard conditions of ventilation and temperature (25±2° C), humidity (60-70%) and light/dark condition (12/12). They were housed in pathogen-free conditions.

The animal procedures were conducted according to CPCSEA guidelines. Approval for animal studies was obtained from an animal ethical committee of TRR College of pharmacy with ethical clearance number: 2/IAEC/TRRCP/2016.
Female rats (n=24) were divided into four groups each group containing 6 animals. Group I was considered as control animals receiving standard chow or normal diet. Group II was fed with high-fat diet i.e. monosodium glutamate (4mg/g), group III animals were fed with standard diet along with curcumin (200mg/Kg) and group IV animals were fed with monosodium glutamate (4mg/g) and curcumin (200mg/Kg).
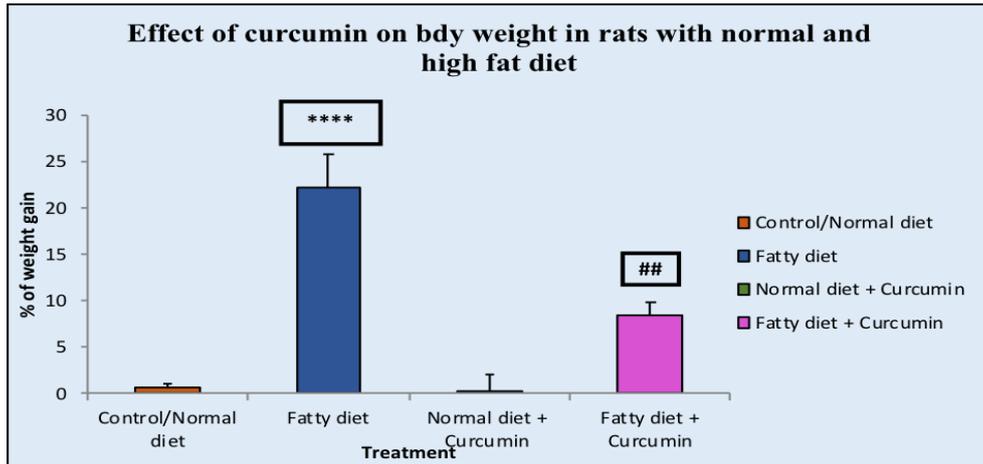
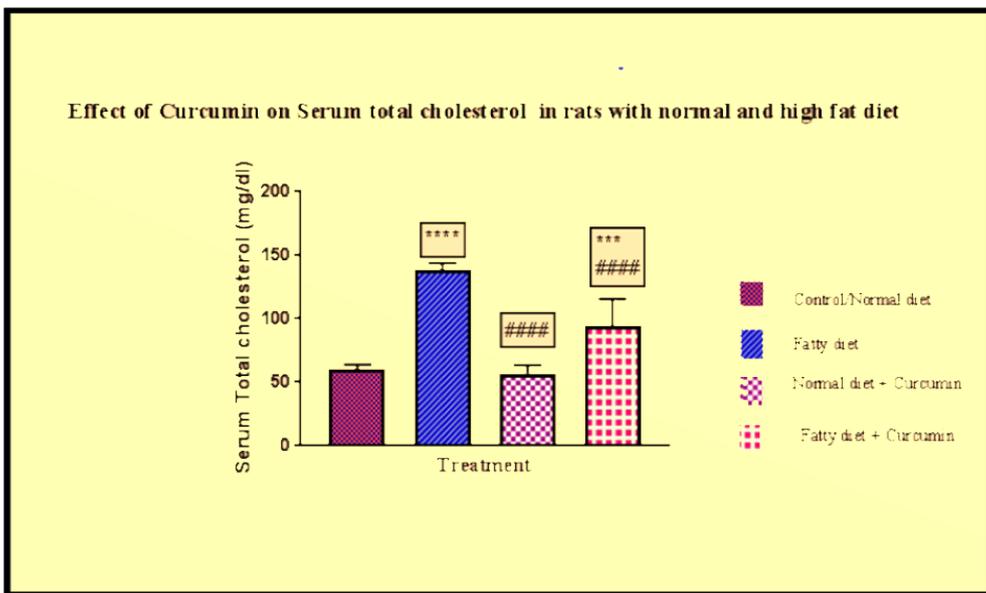**Fig 1: Effect of curcumin on body weight in rats with normal and high fat diet**

Fig 2: Effect of curcumin on Serum total cholesterol in rats with normal and high fat diet
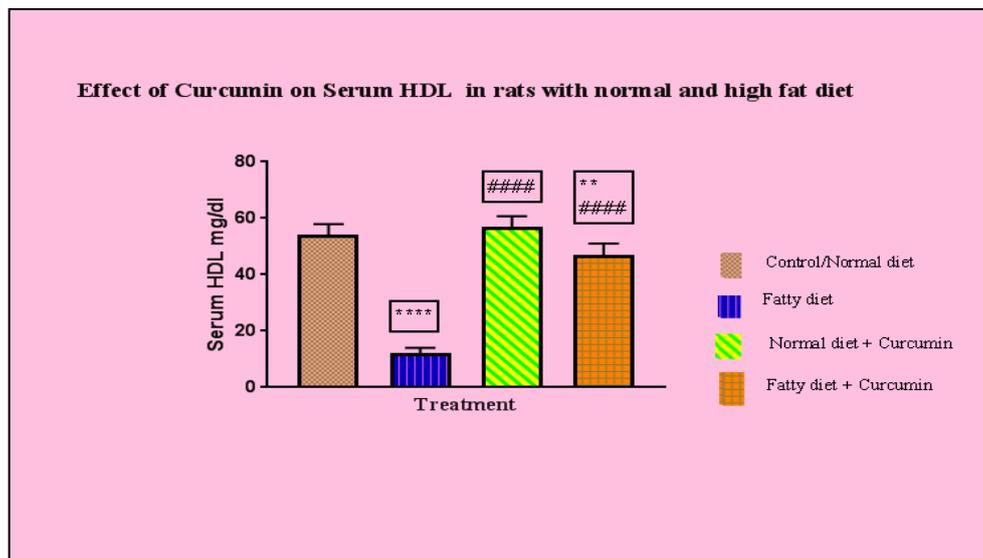

Fig 3: Effect of curcumin on Serum HDL in rats with normal and high fat diet
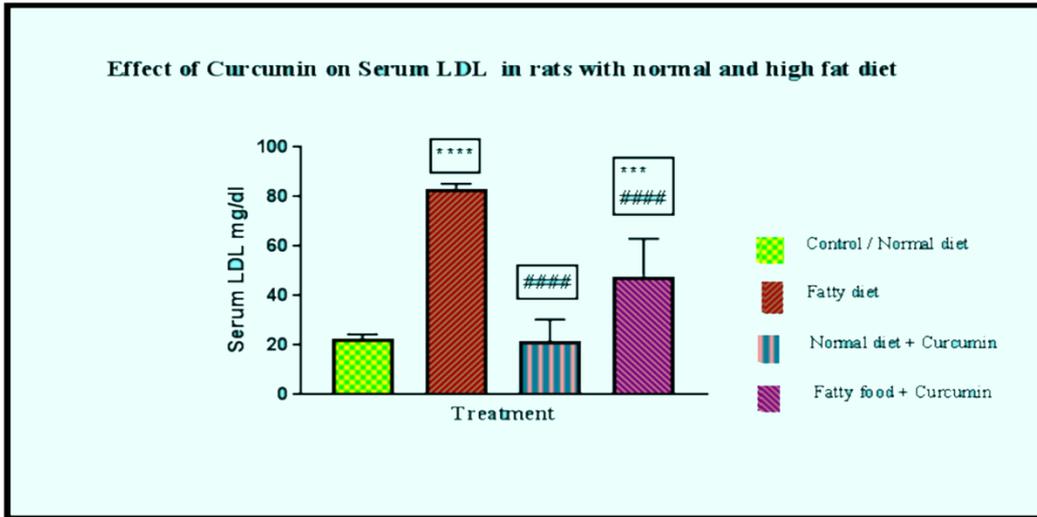
Fig 4: Effect of curcumin on serum LDL in rats with normal and high fat diet
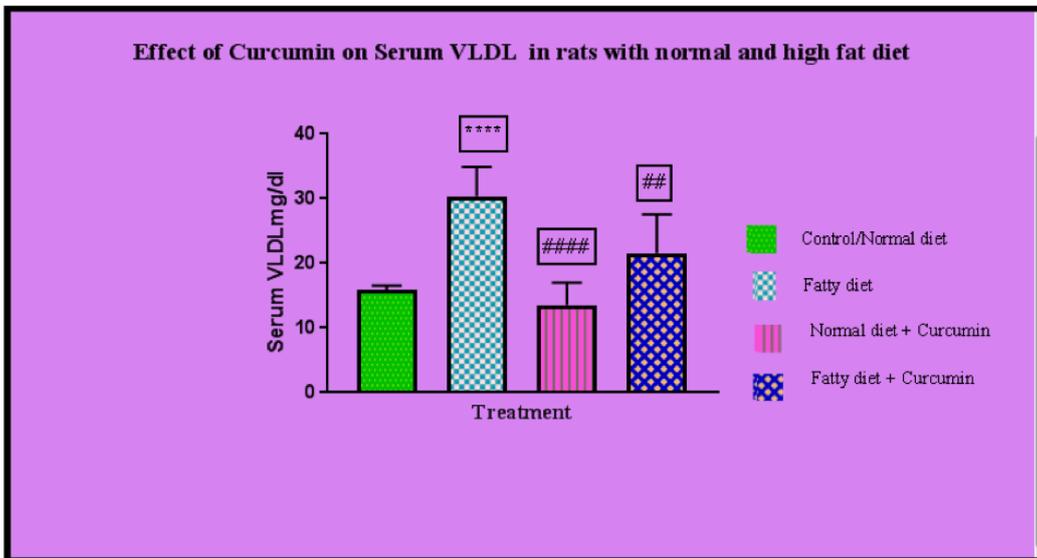

Fig 5: Effect of curcumin on Serum VLDL in rats with normal and high fat diet
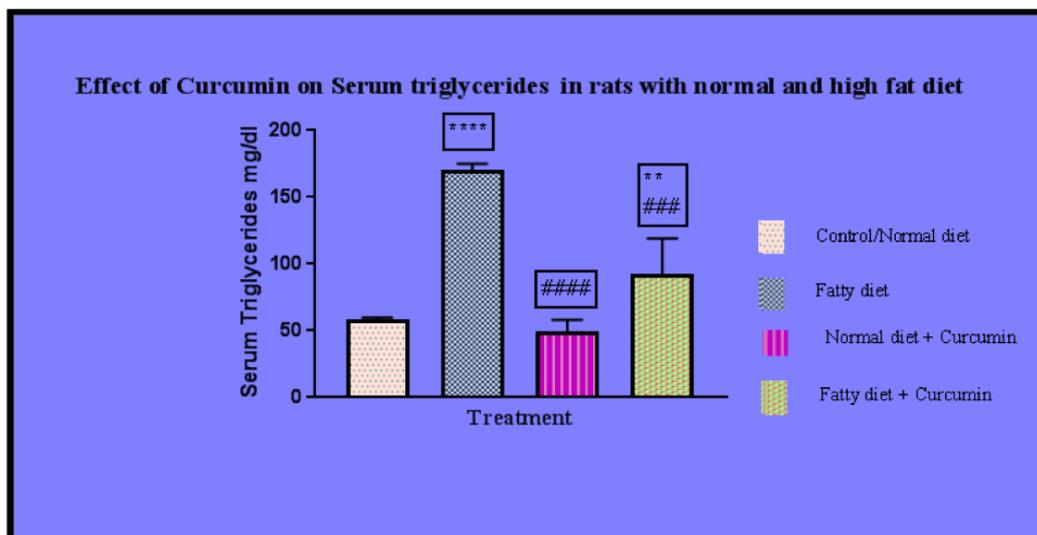

Fig 6: Effect of curcumin on serum triglycerides in rats with normal and high fat diet
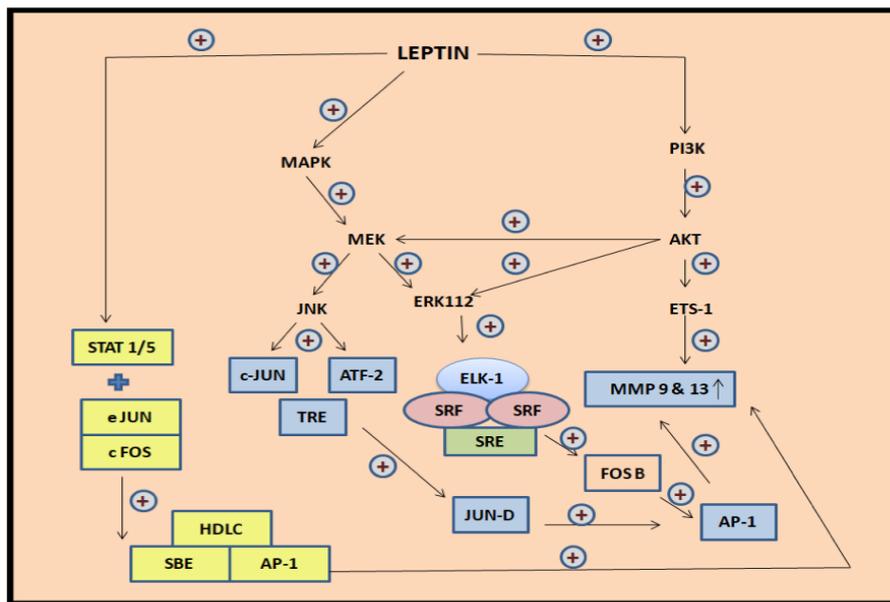
Fig 7: Role of leptin in the pathogenesis of Osteoarthritis

RESULTS

Fig 1: Effect of curcumin on body weight in rats with normal and high-fat diet. All the details are expressed in % of weight gain. Normal/standard diet group I animals have not shown a much % increase in body weight. Group II animals which were fed with high-fat diet (monosodium glutamate) has shown much increase in weight when compared to group I (p<0.0001). The body weight was normal in group III. Group IV animals fed with monosodium glutamate and curcumin has shown less increase in body weight when compared to group II but high increase when compared to group I and group III (p<0.01) significantly.

Fig 2: Effect of curcumin on Serum total cholesterol in rats with normal and high-fat diet. All the details are expressed in mean ± S.D. Group I animals have shown normal levels of cholesterol in serum. Group II animals which were fed with high-fat diet have shown increased levels of serum cholesterol (p<0.0001). Group III animals fed with normal diet along with curcumin has decreased levels of serum cholesterol when compared to group II (P<0.0001). The serum cholesterol increased in group IV animals when compared to group III and the group I (P<0.001) and III but is lower when compared to group II (P<0.0001).

Fig 3: Effect of curcumin on Serum HDL in rats with normal and high-fat diet. All the data are expressed in mean±SD, n=6. The serum HDL value has decreased significantly in group II (p<0.0001) which were fed with high fat diet when compared to group I. Serum HDL values were found to be normal in group III whereas it increased in group IV animals which were fed with high-fat food along with curcumin significantly when compared to group II (p<0.0001) and decreased when compared to group I (p<0.001).

Fig 4: Effect of curcumin on serum LDL in rats with normal and high-fat diet. All the data are expressed in mean ± S.D (n=6). The serum LDL value was found to increase in group II animals which were fed with high-fat diet when compared to group I significantly (p<0.0001). It was found to be normal in animals which were fed with normal diet and curcumin group III whereas it increases in group IV animals when compared to group I (p<0.001) and decreased when compared to group II (p<0.0001).

Fig 5: Effect of curcumin on Serum VLDL in rats with normal and high-fat diet. All the data are expressed in mean ± S.D. The serum VLDL levels were found to be high in group II animals fed with high-fat diet when compared to group I significantly (p<0.0001). Group III animals which were fed with normal diet and curcumin have shown normal values whereas group IV have shown increased levels when compared to group I non-significantly and decreased levels when compared to group II significantly (p<0.001).

Fig 6: Effect of curcumin on serum triglycerides in rats with normal and high-fat diet. All the data are expressed in mean ± S.D. The serum triglycerides were higher in group II animals fed with high-fat diet when compared to group I significantly (p< 0.0001). It was found to be normal in group III and was increased in group IV when compared to group I (p<0.01) and decreased when compared to group II (p<0.0001).

DISCUSSION

Different physiological processes in our body depend on the diet which we take. Nutrition and diet have a great influence on our daily lives. Presently a sedentary lifestyle and excessive consumption of fast food have occupied a great space in everyday life. Diet comprising of many harmful preservatives, animal's fat and poor dietary habits are predisposing factors to obesity. Obesity, in turn, is a major risk factor for Osteoarthritis.

Obesity is defined as a condition of abnormal fat accumulation in the adipose tissue to an extent that it may impair health condition[3]. Obese people are more prone to get different co-morbidities like osteoarthritis, diabetes mellitus II, cardiovascular diseases and cancers leading to increased morbidity and mortality[4]. Obesity causes osteoarthritis by altering mechanical loading and by altering the lipid profile.

Mechanical loading and osteoarthritis

Joint loading is important in the maintenance of articular cartilage. When it is abnormal like in obesity, it causes harmful effects. Basal metabolic index of an obese is 60% more than normal. When it increased, it causes strain in medial and lateral

parts of the knee leading to increased joint loading [5]. High joint loading leads to mechanical stress in the joints, especially in cartilage and bone. Abnormal loading also induces the expression of MMPs in chondrocytes. Usually, MMP 1, 3 and 9 upregulation take place leading to proteoglycan and cartilage matrix degradation[6, 7].

It also inhibits DNA, proteoglycan and collagen synthesis. Mechanical stress also induces expression of pro-inflammatory mediators like cytokines, IL-1 (β), TNF-α and COX-2[8]. Cartilage metabolism and chondrocytes inflammatory state is also altered leading to cartilage destruction and subchondral bone alteration.

Abnormal lipid profile and osteoarthritis

Dyslipidemia is a condition of abnormal lipid profile where the serum has increased triglycerides, decreased HDL, increased ox-LDL, cholesterol, and free fatty acids.

HDL also called as good lipids help in lowering cholesterol by transporting it from blood to liver. On the other hand, oxidized LDL (ox-LDL) is bad lipid where it increases reactive oxygen species.

Role of HDL

HDL is decreased in osteoarthritis patients. Recent research was conducted on HDL- knockout mice which have shown increased expression of MMP-2, 9 and 13. In addition, collagen II proteins levels also were reduced[9].

Role of LDL

Ox-LDL acts on ox-LDL receptor-1 (LOX-1) and activates them[10]. Upon activation, VEGF is released from articular chondrocytes. VEGF, in turn, increases the expression of IL-1β, IL-6, and TNF-α. It also induces expression of matrix-degrading proteins like MMP 1 and 3[11].

Adipose tissue releases a high amount of free fatty acids into the bloodstream. In osteoarthritis, FFAs clearance is compromised or altered[12,13].

FFAs acts on toll-like receptor 2/4 which causes down streaming of c JUN N terminal kinase signaling pathway which leads to activation of macrophages[14]. Macrophages secrete pro-inflammatory mediators such as TNF-α in the adipose tissue which finally causes inflammation. As macrophages are present in synovial lining, they induce inflammation in it.

Role of cytokines

Obesity is also characterized by adipose tissue inflammation. Lean adipose tissue contains anti-inflammatory macrophages M2. In obesity, adipose tissue is infiltrated by different macrophages and it consists of pro-inflammatory macrophages M1[15, 16].

In addition to M1 macrophages, they also contain T cells, B cells, mast cells, and neutrophils. These immune cells and adipocytes secrete cytokines leading to low-grade inflammation. Cytokines are also produced from the intra patellar fat pad present in the knee cavity causing joint inflammation. Majorly released cytokines are IL-6, TNF-α, and VEGF.

Role of leptin

In addition to cytokines, adipose tissue and intrapatellar fat pad also release adipokines[17, 18].

Adipokines are the metabolic factors which mediate lipid and glucose metabolism, insulin sensitivity, other physiological functions like reproductive functions, regulation of blood pressure, bone formation and angiogenesis.

Leptin, adiponectin, resistin, visfatin are few of the adipokines. These factors mediate lipid and glucose metabolism, insulin sensitivity, other physiological functions like reproductive functions, regulation of blood pressure, bone formation and angiogenesis.

Important adipokine which is involved between obesity and osteoarthritis is leptin. Abnormal / altered articular cartilage and obese expresses more leptin than normal tissues. Leptin influences the chondrocyte catabolism and anabolism through activation of STAT-1 and STAT-5. Upregulation of leptin decreases the anabolic processes in the extracellular matrix in the joint contributing to the pathogenesis of OA. It is also associated with the release of pro-inflammatory cytokines such as IL-1, resulting in increased NO which in turn causes apoptosis induction, matrix metalloproteinase (MMP) activation and type II collagen synthesis inhibition. Leptin is an important hormone that regulates the amount of fat storage in our body. When there is an increase in food intake, leptin signals the hypothalamus present in the brain and brain, in turn, decreases the appetite and the fat storage is decreased.

If the leptin levels increase in the body, the body develops leptin resistance. Leptin levels will be more but it will not be able to signal the hypothalamus. Appetite continuously increases, food intake and fat storage increases leading to weight gain. This phenomenon is called leptin resistance. Therefore, leptin resistance causes obesity and is also associated with other metabolic disorders, infertility, insulin resistance and cardiovascular disorders. Therefore, there is a need to increase the leptin sensitivity by lifestyle changes and diet modification. Leptin when present in higher levels increases the secretion or release of MMP 9 and 13 which are responsible for cartilage destruction or proteolysis. Leptin activates 3 pathways called MAPK pathway [19], PI3 pathway [20] and JAK-STAT [21] pathway. It activates MAPK which stimulates MEK mediated JNK and ERK112. JNK activates CJUN, ATF-2 and bind to TRE in the nucleus. This complex now up-regulates the expression of JUND. This, in addition, activates AP-1 which is the promoter of MMP-9 and MMP-13 enzyme expressions.

ERK112 again stimulates ELK-1 transcription factor which binds to SRE, then activates FOSB which in turn activates AP-1 which is the promoter of MMP-1 and 13 expressions. The PI3K pathway involves activation of AKT, ETS-1 which again leads to the upregulation of MMP-9 and MMP-13 expression.

Leptin activates the JAK/STAT pathway which involves activation of STAT-1 and STAT-5 which on phosphorylation forms complex with e JUN and CFOS. They, in turn, activate HDLC which phosphorylates and activates AP-1 which is the promoter of MMP 9 and MMP-13. Curcumin is known to inhibit the JAK/STAT pathway, MAPK pathway, and PI3k pathway thereby inhibiting the expression of MMP 9 and MMP13, showing chondrocyte protective action.

Leptin is also known to regulate the metabolism of lipids. In obesity and in osteoarthritis there is a dysregulation of lipid metabolism causing dyslipidemia. There is a decrease in HDL-C, increase in LDL-C, Free fatty acids (FFA), Triglycerides (TG) in obesity as well as in osteoarthritis. Curcumin activates AMPK pathway, down regulates Hepatic Sterol Regulating Element Binding Proteins (SREBP) – targeted genes which are involved

in the fatty acid synthesis and cholesterol synthesis like Fatty acid synthase (FAS) and hydroxymethyl glutaryl co-A (HMG-CoA) reductase enzymes and maintains the homeostasis of lipid metabolism.

CONCLUSION

In this study, it is demonstrated that curcumin helps in maintaining homeostasis of lipid metabolism and also it decreases the leptin resistance which play a key role in obesity. As it helps in preventing obesity, which is the predisposing factor for osteoarthritis, it can be included in diet so as to reduce the risk of osteoarthritis.

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