Review Article

Reviewing Effects of Rosehip, Curcumin, Piperine and Chondroitin Sulfate on Collagen

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ABSTRACT

This article is an examination of the effects of rosehip, curcumin, piperine and chondroitin sulfate on collagen. The scientific development and subsequent use of rosehip, curcumin, piperine and chondroitin sulfate as a potential treatment for diseases such as osteoarthritis and rheumatoid arthritis, along with other therapeutical properties, continue to influence researchers all over the globe today. This article examines the research done and published by researchers and scientists. Consideration of current trends and data in scientific queries and demonstrates further aspects of rosehip, curcumin, piperine and chondroitin sulfate on collagen. Additionally, this article explores options for using these compounds as anti-inflammatory, anti-metastatic and antioxidant compounds. It also covers their chondroprotective and hepatoprotective activities.

Keywords: Osteoarthritis, Rheumatoid arthritis, Wound Healing, Anti-inflammatory Properties, Chondroprotective activity.

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INTRODUCTION

Rosehip is rich in polyphenols (mainly flavonoids including proanthocyanidins and catechins), triterpene acids, essential fatty acids, galactolipid, folate, vitamin A, C and E, mineral (Ca, Mg, K, S, Si, Se, Mn and Fe), among other bioactive components. Chondroitin sulfates (CS) are glycosaminoglycans (GAGs), which are practically nonimmunogenic and consist of sulfated, negatively charged, repeating disaccharide units. Piperine is an organic compound classed in the lipid family (a group consisting of fats and fatlike substances) and with the alkaloids, a family of nitrogenous compounds with marked physiological properties. Curcumin is a naturally-occurring chemical compound found in spice turmeric. Collagens constitute a major part of the extracellular matrix and play an important role in inflammation, wound healing, angiogenesis, liver injuries and diabetes. Osteoarthritis is a common joint disease which prevalent in more than 630 million individual throughout the world, and it occurs due to the disintegration of articular cartilage and synovial joints. Such disintegration of cartilage and synovium join related to inflammation and pain. Rheumatoid arthritis is an autoimmune disease that is known to primarily affect joints. Symptoms mostly include swollen and painful joints. Wrists and hands are most commonly involved. Complications may sometimes lead to low red blood cell count, inflammation around the heart and lungs. Sometimes it is characterized by synovial hyperplasia, angiogenesis and mononuclear infiltration. All of the above compounds help in the treatment of collagen-related diseases by exhibiting chondroprotective activity. In this review, it is shown how the multimeric effect of these compounds can be utilized to act together and be much more effective than plain anti-inflammatory drugs available in the market. Many of the commercially available synthetic drugs may cause gastrointestinal disorders, immunodeficiency as well as humoral disturbances. Hence these compounds can be used as an alternative as they have natural health benefits as well as confers anti-metastatic, antithyroid, antidepressant, hepatoprotective against CCl4-induced toxicity, anti-tumor and immune-stimulating, anti-inflammatory and arthritic activities. Even when paired with anti-angiogenic therapy, the effects of radiation and penetration capacity of chemotherapeutic drugs are enhanced with the use of these compounds.

Several studies conducted by various researchers prove that rosehip improves the osteoarthritic & rheumatoid condition. It has large amounts of antioxidant which has potential to treat osteoporosis by receding the damage which occurs due to an excess amount of ROS in bone tissue, also induces the formation of collagen matrix and osteoblast differentiation. Rosehip can regulate blood lipid and obesity. Rosehip also supports and improves cell age, skin wrinkles, elasticity and moisture content. Chondroitin sulfate is present in the cartilage and extracellular matrix

and is an essential component of cartilage and synovial fluid, which stimulates the anabolic process of cartilage metabolism. It was found to have had increased the type II collagen and proteoglycan synthesis. Piperine and its health benefits are known worldwide, and it ranges from acting as an anti-inflammatory to helping curb metastasis of cancer cells; it also plays a pivotal role in the treatment of chronic diseases such as arthritis, periodontitis, liver damage and transplantation. It is known to have a chondroprotective activity in joint disease and to lower lipid peroxidation, protect against oxidative stress. Piperine can also be used as a potential therapeutic agent for enhancing soft and mineralized tissue healing in addition to traditional treatments like mechanical debridement. Curcumin acted as a potent antioxidant and reduced crosslinking of collagen. Curcumin showed a significant effect on reducing collagen deposition, thereby reducing fibrosis and helped to restore proper functioning of the body. **The application of Curcumin and their interactions with collagen favored several phases of the wound healing process. The anti-inflammatory properties of curcumin also helped in reducing the pain of the wound. Thus owing to the varied applications of these compounds, extensive research has been performed to understand their mode of action, especially by studying their effects in collagen. This review covers in detail the properties of rosehip, curcumin, piperine and chondroitin sulfate on collagen.**

METHODS

This study was conducted using four databases: Google Scholar, SAGE, DOAJ and PubMed. The selection of papers was made based on keywords and themes relevant to this review. Further, the published papers from these databases were arranged in systemic order with respect to the year of publication.

RESULTS AND DISCUSSION

Rosehip on Collagen[1-6]

Role of rosehip extract in osteoarthritis prevention by involving doctor pharmacy[1]

Osteoarthritis is a common joint disease prevalent in more than 630 million individuals throughout the world; it occurs due to the disintegration of articular cartilage and synovial joints. Apart from the disintegration of articular cartilage, the entire joint organ included subchondral bone and synovium involve in OA. Such disintegration of cartilage and synovium join related to inflammation and pain. In this study, check the safety and efficacy of the combination of collagen peptide (10gm) with rosehip extract (500mg), vitamin C (22mg) and selenium (25mcg) sachets. OA patient is administered to new combination drug, within 3 months, it gives brilliant results. This combined drug improves the collagen between the bones; in this research, 90 patients are cured by this drug sachet in early osteoarthritis. In this 1 to 13-week study, the combination of Collagen peptide (10gm), Rosehip extract (500mg), Vitamin C (22mg) and Selenium (25mcg) drug test observed with 60% to 70% efficacy as compared to glucosamine, the Glucosamine (1500mg) shown 20% efficacy. The response range is 70-90% efficacy observed with Collagenpeptide (10gm), Rosehip extract(500mg), Vitamin C (22mg) and Selenium (25mcg) combined sachet treatment and 43%

Suppressed IL-1β- induced NF- F-κB Activation in Canine Articular Chondrocytes by botanical extract of Rosehip[2]

Joint disease osteoarthritis involves articular cartilage along with synovial membrane, subchondral bone and periarticular soft tissue. OA can cause traumatic injury to the joint, which results in infection and it occurs due to aging. The main character of OA is swelling, pain, stiffness and limited mobility. The extracellular matrix is aberrantly synthesis with a low cellular event, the disintegration of cartilage, decreased osteophytosis, subchondral bone density and synovial inflammation. The chondrocytes and matrix protein interaction are largely mediated by e β1-integrin receptors. An important signal transduction pathway activated by β1-integrin receptors is the MAP Kinase pathway. Inhibition of the MAP Kinase pathway shows that disruption of cell-matrix communication and such inhibition leads to caspase- 3 activation, cleavage of Poly(ADP) Ribose polymerase, and chondrocyte apoptosis. OA is characterized by loss of cartilage matrix component, mainly type II collagen and aggrecan at the molecular level. IL-1β and TNF-α show a proinflammatory effect which is regulated by transcription factor "nuclear transcription factor κB" (NF-κB). The main reason for the downregulation of the SOX-9 transcription factor is NF-κB, which involves in regulation of the gene for cartilage-specific extracellular matrix (ECM) proteins. Apart from Non-steroidal anti-inflammatory drugs (NSAIDs), natural botanical extractable to inhibit NF-κB mediated catabolic activity and proved as a therapeutic agent to treat OA. One of the best botanical extracts studied is rosehip (Rosa canina). Different antibodies use, such as (AB746), β1-integrin (MAB1977) for type II collagen and cartilage-specific proteoglycan antibody (MAB2015), and botanical extract from rosehip, primary canine articular chondrocytes were isolated from joint of client dog.

In vitro condition, the botanical extract(10 µg/mL) was used to treat chondrocytes and show no cytotoxicity. To check the effect of botanical extracts on the NF-κB activation pathway is IL-1β was used. The viability and proliferation of the chondrocytes cultivated only in the presence of IL-1β were significantly lower compared to those of chondrocytes treated with botanical extracts, and the results are positive by botanical extract about the cell viability and proliferation on inhibiting IL-1β-induced cytotoxicity on chondrocytes. The botanical extract shows positive results about cell viability and proliferation on inhibiting IL-1β-induced cytotoxicity on chondrocytes. The result of rosehip extract indicates that the antiapoptotic effects and counteract the IL-1βinduced apoptosis in chondrocytes. In contrast to chondrocytes stimulated with IL-1β alone, pre-treatment with all botanical extracts

resulted in a significant upregulation of synthesis of collagen type II, CSPG and β1-integrin. As compare to chondrocytes stimulated by IL-1β alone, pre-treatment with all botanical extracts and co-treatment with IL-1β led to a decrease in COX-2, MMP-9 and MMP-13 expression. The result of rosehip botanical extract represents that treatment with the three botanical extracts inhibited the IL-1β-induced decrease in Shc, ERK1/2 and SOX-9 expression. The botanical extracts inhibited IL-1β-induced NF-κB activation if NF-κB-subunit after pre-treatment with botanical extracts (10 µg/mL each). Cotreatment of chondrocytes with botanicals and IL-1β resulted in inhibition of nuclear transition of activated phosphor-p65 and decreased cytoplasmic staining for this protein and showed a decrease in activation of NF-κB. IL-1β could not induce IκBα degradation in chondrocytes when co-treated with botanical extracts Considering, IL-1β-induced IκBα degradation in untreated cultures is an indicator of NF-κB activation, and this suggests that the botanical extracts block IL-1β-induced IκBα degradation. The botanical extracts of rosehip able to inhibit the phosphorylation of IκBα induced by IL-1β in the presence or absence of the inhibitor. Every 10 µg/mL of botanical extract pre-treatment alone resulted in well-developed cartilage nodules with viable cells and organized organelles; the cells formed a dense and regular ECM.

This experimental study characterizes the effect and mode of botanical extract from the rosehip plant. The systematic reviews of different clinical studies present evidence that botanical extract effective in the treatment of osteoarthritis. On the basis of this study that the botanical extract of rosehip can inhibit the IL-1β-induced inflammatory process upstream of the IκBα phosphorylation step. Enhanced not only the mitochondrial activity but also show a significant effect on chondrocyte viability, differentiation and function as well as having inhibitory effects on IL-1β-induced suppression of proliferation and viability.

Enhanced effect of Anti-Inflammatory and Chondroprotective by novel rosehip preparation[3]

The degradation and reduction of extracellular matrix (ECM) cause osteoarthritis condition. The activation of the enzymatic system in matrix metal-proteinase (MMP), aggrecanase in chondrocytes and synoviocytes cause a change in ECM structure. Natural substance suppresses such OA conditions, glucosamine and chondroitin appear as promising substances against OA. Rosehip effectively proves in clinical studies in the treatment of OA. In a study, two rosehip extract are prepare which mark RH-A (with seed) and RH-B (without seed), to know the effectiveness and enhance the effect on OA. RH-B(without seed) prepared sample is more potent anti-inflammatory effects as compare to RH-A(with seed). RH-B contain a higher amount of ursolic acid, betulinic acid, GLGPG, 3-omega PUFAs show anti-inflammatory effect but not by Vitamin C and E. As compare to RH-A, RH-B shows a stronger impact on the expression of inflammatory genes. RH-A reduced the MMP-1 and MMP-3 expression by 50% and 90% by a high dose of RH-A. RH-B produces a weak effect than RH-A. By performing principal component analyses (PCA), Rosehip induced changes in the OA biomarkers. The principal component is taken as meta- biomarker; the PCA has relied on the expression of 1 PBL protein, 10 PBL genes and 14 NHAC-kn genes. The data observed from the study indicate that the effect of RH on OA biomarker is beneficial, and RH-B produces a stronger effect than RH-A.

This compared study of rosehip powder with or without seed reveals that the cellular activity related to inflammatory response and cartilage destruction is altered by complex mixture substance which presents in RHP, The gene expression which degrades the ECM was reduced and show a chondroprotective effect of RHP on cartilage tissue. The effect of RHP is measured multiple times in different cells and compared by PCA; such analyses present that RH-A and RH-B robustly alter the pattern of biological response. Performance of PCAs revealed that RH-B gives a stronger effect on OA biomarker as compare to RH-A in clinical studies. The completed randomized active-controlled trial proved that taken at half the original dose of RH-B (enhanced rosehip powder) had similar effects in patients with symptomatic OA as the original (RH-A).

Rosehip effectiveness on cell life, skin wrinkles, moisture and elasticity[4]

The longevity of cells depend on genetics, nutrition and environment; such factor is also responsible for aging of the skin. Experiencing UV radiations produce the reactive oxygen species, which cause chronic inflammation and shattering of the cell membrane in photoaging of the skin, which leads to damage of collagen, elastin and skin moisture barrier. Such damage leads to wrinkles, sagging, toughening and dry skin. A pseudo fruit of the rose plant (Rosa canina) is known as rosehip, which holds great medicinal property, which has a rich amount of Vitamin-C, carotenoid, polyphenols, GOPO and another compound that show the antioxidant property. GOPO is a strong anti-inflammatory and antioxidant agent which stimulates the synthesis and recovery of Collage. In this study, check the effect of standard rosehip powder on skin aging, which compares with the well-known compound astaxanthin, which improves the skin condition of all skin layers. Along with this, the longevity of the erythrocyte membrane was examined. This study design was a double-blinded controlled clinical trial, compare the effect of rosehip and astaxanthin on skin wrinkles, measures the crow feet wrinkles, elasticity and moisture at the beginning of the study, after 4 and 8 weeks of supplementation, with 34 volunteers of both sexes. The longevity of red cells was open, which determine the difference in plasma hemoglobin leakage and hemolytic index in the sample of blood that was treated with rosehip and compared with untreated individuals, with 18 volunteers of both sexes.

Thirty-three volunteers completed the blind study of rosehip powder except one which takes botulinum toxin injection during the study. Rosehip-treated subjects

resulted in a visible reduction in the depth of crow's feet wrinkle as the initial visicoscan index decreased from 45.52±5.10 to 41.78, P<0.05, after 8 weeks of treatment. There is also a show effect of the astaxanthin treated group. The effect of Rosehip increases the moisture content. In the beginning, the level rose from 51.55±8.94 to 62.74±8.51, P<0.05 after 8 weeks of treatment. The same pattern was observed with no difference between the two groups was seen for astaxanthin. The elasticity of skin was improved by the intake of rosehip at the initial level of 54.65±15.28, which increased to 66.74±11.78 after 8 weeks of rosehip treatment, P<0.05. the same type of improved elasticity was observed for astaxanthin with no significant difference between the group. Cell longevity was improved by the intake of rosehip powder.

The oral intake of rosehip in a double-blind study gives evidence of improved skin wrinkles, moisture and elasticity, which is measured at the eighth week of assessment. There were no significant differences observed in comparing the effectiveness of rosehip and astaxanthin intake. In the earlier trial, after 4 weeks, astaxanthin appears as more powerful in crow feet wrinkles. Astaxanthin and rosehip powder both are a strong antioxidant that resists the formation MMP-1, which is responsible for the breakdown of collagen. Both of them protect collagen and elastin from ROS. Rosehip is also rich in Vitamin-C, and another polyphenol compound that is responsible for supporting the cell, and vitamin-C helps in the skin and collagen formation. Rosehip support and improve cell age, skin wrinkles, elasticity and moisture content.

Mitigate the inflammation and arthritis pain by Rosehip powder in animals and humans[5].

The pseudo fruit extract rosehip is reliable in its effectiveness in vitro study. The main effective ingredients are flavonoid and fatty acid, which show effectively in a medical condition such as osteoarthritis in vitro study, such ingredients only present in the seed of rosehip. Some of the known compound in rosehip effectively remove pain and inflammation, but some compound is not known which positively affect on such condition In this review study check the effects of rosehip preparation on inflammation and pain in animal and humans.

Study in horse and dog: A randomized and placebo-controlled study of rosehip powder in 44 horses for three months shows that the rosehip has a similar anti-inflammatory effect in horses as it previously describes in humans. The chemotaxis of neutrophils of horses treated with rosehip was reduced as compared to a placebo-treated horse. Also, such treated horses show improvement in speed, litheness and horse plasma vitamin C level. The dose of rosehip is less than 250mg daily, which decreases the liberation of oxidative anion and increase the blood level of vitamin C. Greyhound dog administered to the same rosehip powder for 3 months, which show some anti-inflammatory response and a total number of leucocytes decrease but such result not observed in the placebo group. The speed of the dog improved, P<0.027.

Human studies: The open study in the treatment of osteoarthritis with rosehip. In the first open study, 8 humans were administered to RHP, out of which 4 are healthy, and 4 are osteoarthritis patients. As a result, a reduction in CRP and polymorphonucleated leucocytes (PMNs) was observed. On the basis of comparison, Vitamin C did not affect PMNs which show anti-inflammatory and anti-oxidative capacities. In another clinical study, testing of rosehip on humans, in which 13 healthy volunteers are treated with 45g of rosehip powder daily for 4 weeks and followed by at least 1 month of withdrawal and then further treated with 10g of RHP daily for next 4 weeks. The result of such a test is positive, as a decline in CRP and chemotaxis of PMN by use of 45g of RHP. In another large open study was carried out to know the efficacy of RHP in reducing Arthritis patients. Total 152 patients, out of which 124 suffered severe back pain, 1 had pain in the hip, 9 had pain in knees, and 8 had pain in the lower back; they all took part in a pilot clinical study. Initially, 5g of rosehip seed and shell product administered for 6 weeks, but the dose was increased from 5 -10g due to severe pain, and their symptoms are tested every 6 weeks during 1 year trial period. 75 patients dropped out during the one-year study, and 42 of these patients did so due to insufficient pain release. Only 77 patients completed the test. The result of pain sore is reduced by 35% to 65% of baseline, and the positive responder rate was higher than 60%. 27 patients reported a total of 32 side effects that were possibly related to active treatment. In the one year study, there no side effect is shown as compared to a placebo-controlled study which ran for over 3 to 6 months in which the test group received 5g RHP per day. In rheumatoid arthritis condition, the efficacy of rosehip treatment was evaluated; a total of 89 patients randomly allotted the treatment with 5g of RHP with seed and shell daily., n=44, placebo=45. The test run for 6 months and patient are tested before a test and after 3 and 6 months. The result of the test is a significant improvement in the HAQ-DI score as compared to placebo after 3 and 6 months (P<0.014 and P<0.032, respectively). In RA patients the side effect was few but not confined to active treatment. It was found that combined seed and shell powder of rosehip is well tolerated at a 5g/ day dose in six months of study. In a study of osteoarthritis, patients were administered to 5g daily dose of RHP or either placebo, the bodyweight of the subject in a range of 50 to 122kg. In this study, lower body weight received double does as compare to higher body weight. But there was no correlation between body weight and the reduction in pain score in the group treated with RHP (correlation coefficient -0.41, P-value =0.014) after 3 months of treatment as similar observed were made in RA patient who was treated with 5g of either RHP or placebo for 6 months.

A systematic review of rosehip pharmacological ingredient and molecular mechanism to act on osteoarthritis[6]

One of the most common joint disorders though out worldwide is osteoarthritis. It occurs due to the degradation of articular cartilage and other parts of the joint, which leads to immobility of joints. Inflammation occurs in OA conditions; such inflammatory response causes overproduction of reactive oxygen species and nitrogen species (RONS). Chondrocytes produced RONS along with superoxide, hydrogen peroxide, nitric oxide and peroxynitrite, which involve in OA. RONS is an essential immune agent, which fights against the pathogen and its overproduction by abnormal chondrocytes leads to oxidative stress. Such excessive production damage the lipid, protein and extracellular matrix. The signaling of RONS and the cellular damage multiply the inflammatory response. Which includes NF-κB PI3K/Akt and ERK signaling, expression of inflammatory cytokines transcription factors, as well as matrix-degrading enzyme such process proceeds along with chondrocyte senescence and permanent cell cycle exit. The mitochondrial respiratory chain produced RONS for their protection. Healthy mitochondria conserve RONS homeostasis. With age, mitochondria not able to main the homeostasis of RONS and show imbalance. In this study, the selective literature database Medline used regarding Rosa canina or rosehip to know their relevance to the rosehip and OA.

A well known herbal antiphlogistic is Rosehip, has been used for its anti-inflammatory and pain-relieving property. In several clinical studies suggest their efficacy and safety of their use. In a double-blind placebo-controlled randomized study of 100 OA patients for 4 months, in which 5g RHP/day administered to the patients, as a result, show a decrease in joint pain and improve the mobility of joints as compared to placebo. In another study of double-blind placebo-controlled cross-over with 112 patients for 3 months, revel a reduction in joint pain in 66% of patients who were treated with 5g RHP per day as compared to other 36% of placebo-treated patients. And another similar double-blind placebo-controlled randomized cross-over study treated 47 OA patients treated with 5g RHP per day and other 47 patients with placebo; in this 3-month study, rosehip provides significant results in a reduction in WOMAC pain score and decline in the rescue medication. In this meta-analysis, three studies depict that if OA patient-administered to RHP as compared to placebo patient, respond to the therapy (odds ratio = 2.19; p = 0.0009).

In numerous publications regarding the pharmacological effect of Rosehip, at various levels to inhibition of OA. Specifically, rosehip reduces the inflammatory response, and the neutralization of RONS by the anti-oxidative compound is the major action mechanism by rosehip. Rosehip reduces the proinflammatory cytokines and chemokines, reduction of NF-kB signaling, inhibition of proinflammatory enzymes, including COX1/2, 5-LOX and iNOS, reduction of C-reactive protein levels, reduction of chemotaxis and chemoluminescence of PMNs, and inhibition of proinflammatory metalloproteases. Such multiple mechanisms act synergistically and target RONS. In a review of the Phytochemistry of Rosa canina, describe the 129 chemical compounds. Phenolic acids, Anthocyanins, Flavonoids, Phytosterols, Fruit acids, Carotenoids and Galactolipids are the promising and prominent health-promoting compounds found in Rosehip. Rosehip can regulate blood lipid and obesity, which show indirect beneficial effects regarding OA. Flavonoid suppresses the dysfunctional mitochondria by modulating the adenosine monophosphate-activated protein kinase/ sirtuin 1 signaling. Carotenoids from rosehip inhibit the COX-1 and COX-2. In human articular chondrocytes, cyanidin-3-Oglucoside was found to attenuate matrix metalloproteinase induction; also it inhibited the degradation of the NF-κB inhibitor α (IκBα), modulated the phosphorylation of the NF-κB subunit p65, and inhibited the ERK/ MAPK pathway.

A herbal remedy, Hyben Vital (stand. powder of a subspecies of Rosa canina fruits), reduces pain and improves general wellbeing in patients with osteoarthritis--a double-blind, placebo-controlled, randomized trial.

112 patients were treated with 5g/day Hyben vital for 3 months. The group mark A (placebo first) and then Hyben vital show improvement from p<0.0078 to <0.0025. Group B (Hyben vital first) shows the same order result as group A. Group A response rate 31/47(66%) compare to that of placebo group B 18/50 (36%), P<0.0185.

A powder made from seeds and shells of a rosehip subspecies (Rosa canina) reduces symptoms of knee and hip osteoarthritis: a randomized, double-blind, placebo-controlled clinical trial

94 patients were enrolled, 47 were given 5g of rosehip for 3 months. And remaining were treated with the same amount of placebo. Group initially treated with placebo and then rosehip. As a result, there is a significant decrease in WOMAC pain (p<0.014) as compared to placebo. The severity assessment of the disease was not altered by 3 weeks but reduce actively (p<0.018, p<0.038, p,0.035) after 3 months.

The rosehip herbal remedy in patients with rheumatoid arthritis – a randomized controlled trial

89 patients were treated with 5g daily for 6 months; in the rosehip group, the HAQ-DI improved by 0.105+/-0.346, while worsened in the placebo case by 0.039+/-0.253. The HAQ patient pain scale shows no significant difference in both groups.TheHAQ Global patient pain scale favour rosehip (p= 0.078).

Rosehip Powder for Knee Osteoarthritis. NCT01430481

150 participants, randomized allocated 3 different rosehip mark as Rosehip powder (RHP) A, B and C, A is standard with 6 capsules, B is modified RHP of 6 capsules, and C is

modified with a half dose (3 capsules). The trial is 12 weeks long with randomized control (1:1:1) into 3 groups.

Study to Assess the Efficacy and Safety of Reflex Plus™ in Osteoarthritis. NCT02655939.

258 participants of OA are enrolled for 12/24 weeks, double-blinded, randomized, placebo-controlled study, the Reflex plus allocated which is a mixture of collagen hydrolysate 5g and RH aqueous 0.55g. WOMAC score in the first 12 weeks is 27 with protocol A, which decreased from the baseline. After 24 weeks, the score is the same as 27 with protocol B

Chondrotin sulfate with collagen[7-12]

Effect of Chondroitin Sulphate-Protein on Collagen fibrogenesis (in vivo)[7]

Multiple pieces of evidence from publications had established that tropocollagen molecules were precursors of collagen fibers in vivo. At physiological pH and ionic strength, in vitro tropocollagen molecules were capable of "self-assembly" into "native-type" fibrils when solutions had been warmed to 37 degrees Celsius. It was well known that sulfated AMPS (acid mucopolysaccharide) occurred in the extracellular phase of connective tissues as complexes with protein. The study aimed to describe the "instantaneous precipitation" of a fraction of tropocollagen by chondroitin sulfate-protein (CS-protein) isolated from nasal cartilage". It was suggested that “interactions between AMPS-protein and tropocollagen took place in vivo at the surface of connective-tissue cells". Further, it was suggested there be a mechanism that enabled the cells to control the orientation and packing of fibrils into collagen fibers. "Based on the experiments in vitro, the authors had proposed a sequence of events for collagen fibrogenesis in vivo.”

It was found that the precipitation of collagen fibrils (at 37 degrees Celsius) from mixtures of chondroitin sulfate-protein and tropocollagen (at physiological ionic strength and pH) took place in two distinct phases. The first phase occurred immediately on mixing either at 4 degrees or 37 degrees Celsius, and the second phase occurred only at 37 degrees. The second stage of precipitation was inhibited by mixing the reactants at 4 degrees Celsius. The initial precipitate was found to contain 'native type' collagen fibrils and chondroitin sulfate-protein. Based on kinetic experiments, it was concluded that aggregates of chondroitin sulfate-protein and tropocollagen form instantaneously. It was also observed that they acted as "sites for the second stage of precipitation of fibrils". It was found that, if formed in the presence of the initial precipitate of chondroitin sulfate-protein and tropocollagen, the gels were fibrous in appearance (resulted after continued incubation at 37 degrees Celsius).

The tropocollagen solutions used in the study had been found to contain at least two fractions differing in their ability to react with CS-protein and to form fibrils at 37 degrees. It had been confirmed by prior studies that fibrogenesis occurred in two distinct processes, called 'nucleation phase' and 'growth phase'. During the lag phase, the 'nucleus forming fraction of tropocollagen was supposed to rise to small aggregates of 'nuclei', which were the sites for further accretion of the 'growth' tropocollagen at the time of precipitation phase. Hence, the occurrence of the later phase had been considered necessary. It was found that the number and shape of the 'nuclei' were influenced by protein-free CS. "It was found that the initial aggregation of tropocollagen and CS-protein affected the lag time, but not the subsequent precipitation rate". The lag phase had represented the slow accretion of a tropocollagen coat to the CS-protein-tropocollagen nuclei and had been followed by rapid accretion of further tropocollagen in the precipitation phase. Excess of CS-protein had been observed to have accelerated the process further. Based on the experiments in vitro, the authors proposed a sequence of events for collagen fibrogenesis in vivo. The sequences had been that the connective-tissue cell had aligned itself in the appropriate direction, then the cell had secreted tropocollagen and AMPS-protein into grooves or folds on the cell surface. This led to the formation of AMPS-protein complexes that reacted with tropocollagen. Further, the CS-protein in the matrix would have participated in interactions with polymerized forms of collagen, contributing to the tissue's mechanical and permeability properties. Overall, the study is in-depth, and the findings are essential for further investigations in the field.

Effects of Proteoglycans on the organization of collagen fibrils[8]

It had been suggested that the precipitation of collagen fibrils from solutions (at 37°C) and physiological pH and ionic strength retarded distinctly in the presence of small amounts of proteoglycan monomer (PGS) and proteoglycan aggregate (PGC). The specific absorbance of the collagen gels directly related to specific retardation in the presence of PGS and PGC, when the ratio of proteoglycan to collagen had been less than 25 µg/mg. This suggested that the size and organization of the fibrils in the gels had been dependent on the presence of proteoglycans. It had been supported by previous studies that the organization of collagen fibrils in tissues might be related to the amount and kind of proteoglycans present in the tissues. In the paper, the authors studied the interactions of glycosaminoglycans and proteoglycans with collagen. According to publications, chondroitin-4-sulphate, chondroitin-6-sulphate, and keratan sulfate had very slightly accelerated fibril formation, whereas dermatan sulfate and hyaluronic acid had no effect. It had been suggested that precipitation occurred in two consecutive phases, a nucleation phase and a growth phase. The results showed that the rate of formation of fibrils in solutions of collagen had been markedly delayed in the presence of minimal amounts of proteoglycan monomers. Furthermore, about 60% of the collagen molecules reacted with the proteoglycan monomers at

4°C. It was also reported that, although monomeric forms of proteoglycans inhibited fibrillogenesis in solutions of collagen at 37" C, the aggregated forms of the same proteoglycans did not. The findings are significant and can be used for future studies in the field.

There was a lag or nucleation phase followed by a rapid phase of fibril formation and growth. The change in absorbance (AA) increased rapidly on the addition of small amounts of PGS until a maximum value was reached, after which it decreased. "It was reported that the absorbance of the collagen gels in the absence of added proteoglycan, AAO, was directly proportional to the concentration of collagen". In Method B, where the temperature change was used to initiate fibril formation instead of a pH change (Method A), the AA was also dependent on PGS concentration. The chemical and physical characteristics of this PGS were very similar to that of the PGS from bovine nasal septa, except that the chondrosarcoma PGS had no keratan sulfate and contained only chondroitin-4-sulfate. The results were not different from those obtained in the presence of the PGS from the bovine nasal septa. "The data also indicate that all of the PGS molecules were capable of binding to collagen, provided the PGS is present as the fibrils of collagen form".

The data presented in this report showed that collagen fibrillogenesis in solutions (at approximately physiological ionic strength and pH) was markedly altered in the presence of minimal amounts of PGS or PGC. As the proteoglycan concentrations increased to 50 µg/mg of collagen, the curves for AA exhibited the characteristic hyperbolic shape. "Throughout this range of proteoglycan: collagen ratios, all of the PGS molecules became tightly bound into the final fibril structure". An initial increment of absorbance at 400 nm was observed immediately after adding proteoglycan to collagen solutions at 4°C. "This increment in absorbance was caused by an interaction between the proteoglycan molecules and a proportional amount of collagen up to saturation that yielded complexes of a much smaller size than fibrils but still large enough to be removed from solution by centrifugation". At pH 7 and ionic strengths less than 0.17, intact PGS molecules were significantly retarded on the column. Chondroitin sulfate did not bind, whereas core molecules isolated from chondroitinase digests of PGS were significantly retarded under the same conditions. The size of the proteoglycan molecules or their derivatives appeared to have had a significant factor affecting fibrillogenesis. Further, when the PGS was added late in the nucleation phase, it was still bound, and it still altered the final organization of the fibrils. The results of the study suggested that the effect of PGS on collagen fibrillogenesis in vitro was related to the availability of a limited number of binding sites on collagen filaments as they were being organized into collagen fibrils and that the interaction of the PGS and collagen had been probably due to electrostatic forces.

Role of glycosaminoglycans in the development of collagen fibrils[9]

Extensive studies and incongruent results have made it difficult to assign individual glycosaminoglycan (GAG) the definitive role in collagen fibrillogenesis or fibril growth. The authors studied the relationship between collagen fibril diameter and GAG content of various mammalian tissues at various stages of development and have attempted to formulate a new hypothesis. It showed that tissues with the smallest diameter collagen fibrils (mass-average diameter < 60 nm) contain high concentrations of hyaluronic acid whereas, tissues with the largest diameter collagen fibrils (mass-average diameter -200 nm) had high concentrations of dermatan sulfate. Also, increased levels of chondroitin sulfate had been associated with fibrils of medium size (average mass diameter of 60-1 50 nm). Also, it suggested that the growth of fibrils beyond a diameter of about 60nm is inhibited by the presence of a surplus of hyaluronic acid which could be reversed by increasing the chondroitin sulfate and dermatan sulfate levels and again vice versa.

When correlations between the GAG compositions and the mass-average diameters of the collagen fibrils were studied, no simple linear relationship was observed. However, when the individual GAGS were expressed as "a fraction of the total glycosaminoglycan pool", the results were significant. It was found "that tissues containing the smallest fibrils frequently had the highest hyaluronic acid levels, those containing fibrils of intermediate size (mass-average diameter of 60-l 50 nm) had elevated chondroitin sulfate levels, and those with the largest diameter collagen fibrils contained the highest levels of dermatan sulfate. It was observed that during maturation, the hyaluronic acid concentrations of many connective tissues tend to go down rapidly whilst the chondroitin sulfate and dermatan sulfate contents tend to increase. It was proposed that during the second stage of fibril development, the inhibition of the lateral growth of fibrils imposed by the hyaluronic acid was removed by the proportionate increase of chondroitin sulfate. An increasing proportion of dermatan sulfate, at later stages, might remove the inhibition of fibril growth imposed at the earlier stages of development and hence, allow the collagen fibrils to grow laterally. This may be because of the strong ionic interaction between dermatan sulfate and collagen under physiological conditions. The authors further suggested that the process of fibrillogenesis was sequential.

Various data were used by the authors to support their proposed hypothesis. They included examples like the fact that cartilage and bone, which contained chondroitin sulfate predominantly, also had small to moderately sized fibrils with mass-average diameters -40-80 nm at maturity. The other evidence in support of the hypothesis came from the study of rabbit flexor digitorum profundus tendon (which curved around the back of the ankle) and showed markedly different chemical and structural features on the concave and convex sides. "On the concave (pressure)

side, the GAG content is -2.3-3.5%, of which 60% was chondroitin sulfate, whereas the associated collagen fibrils had a mass-average diameter of -150nm". In the tensional parts of the tendon, the GAG content is -0.2% (70% being dermatan sulfate), and the fibrils had a mass-average diameter of -200 nm. It had also been found that if the tendon was translocated forward so that it was subjected only to tensional forces, the cartilaginous pressure-bearing sesamoid region, usually containing small diameter collagen fibrils and high levels of chondroitin sulfate, was gradually replaced by normal tension-transmitting tendon (which had closely packed thick collagen fibrils associated with small amounts of GAG, of which a significant proportion was then dermatan sulfate). This process could have had been reversed by repositioning the tendon at an appropriate time after initial translocation. Thus, there was a "reversible and concomitant change" in fibril diameter and GAG composition when the physical environment of the cells was altered. It was further concluded that the growing collagen fibril could only sustain a particular diameter provided that the appropriate GAG levels were maintained. Though more could have been built upon the future scope of the hypothesis, the study is insightful.

Physical properties of the collagen matrix, which are significant for future research.

Comparison between the ability of the collagen types I and II to bind with preparations of the chondroitin sulfate types A-C (CS A, CS B, CS C).[10]

Collagen has been found recently to be used as a scaffold material for tissue engineering (TE). Collagen in fibrillar form has had been used to coat titanium surfaces, improving osteoblast spreading, attachment, proliferation, and differentiation in vitro. Collagens have known to be present in two types, Type I (present in the mineralized bone) and Type II (present in cartilage and developing bone). "Chondroitin sulfates (CS) are glycosaminoglycans (GAGs), which are practically nonimmunogenic and consist of sulfated, negatively charged, repeating disaccharide units". CS types are, CS A (chondroitin-4-sulfate), CS C (chondroitin-6-sulfate) and CS B (dermatan sulphate). The study aimed to compare collagen types I and II based on their ability to bind CS A-C during fibrillogenesis in vitro. Moreover, the effect of fibril-bound CS A-C on osteoblast adhesion and spreading has also been highlighted. "Collagen types I and II showed different affinities for the CS A-C preparations used, with the amount of CS bound/milligram fibrils decreasing in the order CS C > CS B > CS A." The presence of CS A and CS B in collagen fibril coatings on titanium surfaces appears to enhance the formation of focal adhesions by osteoblasts after 2-h incubation. These results could be crucial when deciding which collagen or CS type to use for the construction of scaffolds for TE purposes or implant coatings.

It was observed that collagen II bound more CS C and CS B than collagen I and that both collagen types bound different amounts of different CS types, with the amount of CS bound per unit fibril mass decreasing in the order CS C > CS B > CS A. The percentages of both collagen I and II incorporated into fibrils decreased with increasing CS A: collagen ratio and CS C: collagen ratios. However, no significant effect was observed when CS B: collagen ratio was increased. Further, all three CS types caused both collagen I and collagen II fibrils to become thinner. The most marked change was observed for collagen II fibrils formed in the presence of CS C. The smallest fibril identified was a collagen II fibril formed in the presence of CS C, which measured approximately 250 nm in length and 100 nm in diameter. After 2 h, cells cultured on collagen I-coated surfaces and collagen II-coated surfaces had a more flattened appearance and had spread better than those cultured on bare titanium. The formation of focal adhesions appeared to be influenced positively by all CS types except CS C. However, at 24 h, cells had adopted a spread shape and formed focal adhesions on surfaces containing CS C.

In the study, both collagen I and collagen II were shown to bind in the order CS C > CS B > CS A. The interactions between CS and collagen are believed to be ionic. According to many publications, an increase in ionic strength weakens the CS binding. It was suggested that GAGs "bridge" basic, cationic regions in neighboring collagen molecules, causing a stabilizing effect. Since collagen II was found in tissues with a high GAG content, such as cartilage, it was suggested that "the ability to bind a larger amount of GAG might be physiologically useful". Further, it was found that the proportion of collagen I and II incorporated into fibrils decreased with increasing concentration of CS A and C but not CS B. Once bound to fibrils, CS might "sterically hinder" further fibril growth, resulting in less collagen being incorporated into fibrils. The most pronounced reduction in fibril thickness was observed for collagen II fibrils containing CS C. Finally, it was found that the formation of focal adhesions was being promoted by CS A and CS B and not by CS C at 2 h. But by all three CS Types at 24 h. This was because the more considerable amount of CS C bound might result in more "blocked" recognition sites for osteoblasts on the surface of collagen fibrils. But, by 24 h, there might be the secretion of matrix proteins (e.g., fibronectin, collagen) by the osteoblasts, which overlapped the sites blocked by CS C. Overall, the study is comprehensive. The results could be applied when choosing collagen or CS type for the construction of scaffolds for TE purposes or implant coatings. However, further work may include more extensive cell adhesion experiments to determine the optimal CS: collagen ratios for CS A-C. Also, CS preparations with more similar molecular weights should be obtained. This would help future investigation and scope of the effects of CS structure on affinity for collagen and osteoblast adhesion.

Effects of chondroitin sulfate (CS) in bone cement for Bone Remodelling in Sheep Tibia[11]

Previous publications had reported that the addition of chondroitin sulfate (CS) to bone cement with calcium phosphate led to an enhancement of bone remodeling. It was also known to have had increased the formation of new bone in small animals. "The goal of this study was to authenticate the effect of CS in bone cement in a large animal model. “The influence of adding CS to hydroxyapatite/collagen (HA/Col) composites on host response was also assessed in a standard sheep tibia model”. The defect in the sheep tibia wound had been filled with a HA/Col cement cylinder in seven animals and with a CS-modified hydroxyapatite/collagen (HA/Col/CS) cement cylinder in seven animals. This was a novel study that investigated the “effect of HA/Col composites modified with CS applications on bone-implant interaction and bone remodeling in a large animal model". The X-ray investigation showed a significantly earlier callus reaction around the HA/Col/CS implants compared to that of HA/Col implants. At the endpoint of the experiment, the amount of newly formed bone was significantly larger around HA/Col/CS cylinders. "The study concluded that addition of CS enhanced bone remodeling and new bone formation around HA/Col composites".

"During the entire course of the experiment, 2 out of 14 sheep suffered a complication," and their data were excluded. At the end of the experiment (3 months after implantation), all bone defects were treated and healed uneventfully. Radiographs at 1 and 4 weeks after implantation did not show any difference between both types of implants. Eventually, after 8 weeks of implantation, an initial callus reaction was seen around the HA/Col/CS implants. At the endpoint of the experiment (12 weeks after implantation), a bridge of callus was built across all HA/Col/CS implants. However, callus formation had just started around the HA/Col implants. “The CT scan analysis 12 weeks after implantation showed that most of the HA/Col/CS implants were surrounded by newly formed bone”. However, a newly formed bone was seen only at the resection area around the HA/Col implants. The number of osteopontin-positive osteoblasts around HA/Col/CS implants was significantly higher than around HA/Col implants. The number of TRAP-positive osteoclasts stained using enzyme-histochemistry was significantly lower around HA/Col/CS implants compared to HA/Col implants. Further, macrophage activity was small around HA/Col implants and absent around HA/Col/CS implants. The inflammatory cells (granulocytes, lymphocytes), which were still being seen around HA/ Col implants, were not detected around the HA/ Col/CS implants.

It had been suggested that a method to optimize the influence of HA/Col composites on bone remodeling was by adding components of the extracellular matrix (ECM) to "mimic the natural surroundings" of the cells. The study examined the influence of HA/Col composites modified with CS in a standard sheep tibia model. It was observed that there was an earlier appearance of callus, and there was an increased amount of direct bone contact at later stages of bone healing. These findings suggested an improved bone healing through the addition of CS to HA/Col composites. “Furthermore, the volume and amount of newly formed bone were also increased when compared to pure HA/Col composites”. And the absence of phagocytotic cells or multinucleated giant cells at the end of the observation period indicates good tissue acceptance. “With this investigation, the promising results of small animal models were further supported in case of a large animal model”. In summary, the addition of CS “enhanced the osteoconductive properties of HA/Col composites". New bone formation was increased significantly concerning total bone contact and bone volume around such implants after three months. "The possible role of chondroitin sulfate could be the mediation of the attachment of cytokines and growth factors to the ECM or the cell surface, as well as a direct interaction with cytokines and growth factors, which should be the subject of further investigations”.

Use of Chondroitin sulfate in the Treatment of Osteoarthritis- A mini-review[12]

Chondroitin sulfate (CS) had been known to be a natural glycosaminoglycan and be present in the cartilage and extracellular matrix. It is suggested that CS be an essential component of cartilage and synovial fluid, which stimulates the anabolic process of cartilage metabolism. CS was found to have had increased the type II collagen and proteoglycan synthesis. Loss of CS from the cartilage resulted in osteochondral angiogenesis, which might cause osteoarthritis (OA). The review article highlighted the benefits of CS in the treatment of osteoarthritis. CS showed clinical benefits in symptomatic osteoarthritis (OA) due to its anti-inflammatory activity. CS might help “by providing resistance to compression, maintaining the structural integrity, homeostasis, slowing breakdown and reduces pain in sore muscles”. CS was approved in the USA as a dietary supplement for OA, while it was used as a symptomatic slow-acting drug (SYSADOA) in Europe and some other countries. Further, CS is considered the most widely used slow-acting drug for OA (SADOA) with minimum side effects.

It was established that joint trauma or overuse and tissue damage resulted in the production of damage-associated molecular patterns (DAMPs), including cartilage extracellular matrix (ECM) along with fibronectin, hyaluronan, plasma DAMPs, and intracellular alarmins. These signals through pattern recognition receptors on synovial macrophages, fibroblast-like synoviocytes (FLS) and chondrocytes induce the local production of inflammatory mediators. This might lead to chondrolysis and the release of additional ECM breakdown products, e.g., Tenascin C and hyaluronic acid. The main reasons for CS to be used as a slow-acting drug for OA SYSADOA therapeutic class might be the anti-inflammatory activity of CS in OA and CS's role in the formation of new bones,

cartilage, and tendons, and maintains the structural integrity of tissues as well as repair damage. Furthermore, being a large molecule, CS could penetrate chondrocytes and internalize as oligosaccharides or disaccharides by engaging membrane receptors. Through much evidence, the therapeutic efficiency of CS was concluded. CS is most often used in combination with glucosamine to treat OA. Also, CS can be taken in the form of pills, tablets, capsules, powder, or liquid and also by injection. It is used in creams, eye drops, cosmetics, and medical applications. Clinical studies of commercial CS further show that it is well tolerated with no side effects of overdoses and without any drug-drug interactions. It has rare adverse reactions, which suggest its long-term safety. Overall, the review enlightens the benefits of CS in osteoarthritis. However, the research arena in the field of OA treatment is still unsatisfactory as it does not throw light on the quantitative values on the low CS levels, which may lead to osteoarthritis.

Piperine with collagen[13-18]

Rheumatoid Arthritis-Piperine[13]

Rheumatoid arthritis is an autoimmune disease that is known to primarily affect joints. Symptoms mostly include swollen and painful joints. Wrists and hands are most commonly involved. Complications may sometimes lead to low red blood cell count, inflammation around the heart and lungs. Sometimes it is characterized by synovial hyperplasia, angiogenesis and mononuclear infiltration. Pathological changes observed include abnormal immunity, inflammation, pannus formation and chronic synovitis. The treatment mostly includes non-steroidal anti-inflammatory drugs and immune-suppressants are used, but these may cause gastrointestinal disorder, immunodeficiency as well as humoral disturbances. Hence piperine can be used as it has natural health benefits as well as confers anti-metastatic, antithyroid, antidepressant, hepatoprotective against CCl4-induced toxicity, anti-tumor and immune-stimulating, anti-inflammatory and arthritic activity. The mechanism through which it acts as an anti-inflammatory molecule is by inhibiting the production of nitric oxide and several proinflammatory cytokines and MMP's. In this review, they had investigated the anti-inflammatory effects of piperine against adjuvant-induced rheumatoid arthritis rats.

An experimental model of rheumatoid arthritis was compared with the non-steroidal anti-inflammatory drug indomethacin. *Mycobacterium tuberculosis* (heat-killed) was intradermally injected in the right paw; this resulted in increased paw volume, the concentration of lysosomal enzymes (acid phosphatase, β-galactosidase, N-acetyl glucosaminidase and cathepsin D) also increased, glycoproteins (sialic acid and hexosamine) and tissue marker enzyme (alanine transaminase, aspartate transaminase and alkaline phosphatase) levels were also elevated. After piperine treatment, these were returned to normal levels. The body weight of the rats, however, decreased. After histopathological analysis, it was observed that synovial hyperplasia infiltration was eliminated due to the actions of piperine.

Lysosomal enzymes are known to provoke inflammation by synthesizing inflammatory mediators like thromboxane, prostaglandins and leukotrienes; these are involved in the degradation of macromolecules in connective tissue and cartilage proteoglycans. Reduction of acid phosphatase, β-galactosidase, N-acetyl glucosaminidase, and cathepsin D due to piperine suggests that there was a decline in total leukocyte migration along with lymphocytes and monocytes/macrophages migration from the blood into the synovial cavity. Because of this membrane gets stabilized, and anti-inflammatory effects are observed. Glycoproteins in the connective tissue are known to radiate antigenic property in tissue transplants, this metabolism is carried out due to increased secretion of lysosomal enzymes, but after piperine treatment, the level of glycoproteins decreased in the liver, spleen and serum. Reduction in alanine transaminase, aspartate transaminase and alkaline phosphatase after piperine treatment indicates decreased tissue damage.

Effect of piperine on collagen induced angiogenesis[14]

Angiogenesis is a process where new blood vessels are formed with the help of pre-existing vessels formed in the earlier stage of vasculogenesis. Angiogenesis play's an important role in the formation of cancer, as it provides the tumor with oxygen and nutrients, which are essential for its growth. This process involves cell proliferation, migration, and tubule formation. When in the tumor micro-environment there is a lack of oxygen and nutrition, angiogenesis-promoting factors are activated, such as vascular endothelial growth factor (VEGF). Because of this, there is the formation of new blood vessels with the help of nearby endothelium. Tumor progression can be stopped by cutting down its nutrient and oxygen supply which in this case is angiogenesis. Thus it is an important step to control the growth and progression of tumors. When paired with anti-angiogenic therapy, the effects of radiation and penetration capacity of chemotherapeutic drugs are enhanced. Here, we understood that piperine inhibits the angiogenic activity by phosphorylating ser 473 and the 308 residues of Akt (protein kinase B). This protein is an important key regulator of endothelial cell function. Human umbilical vein endothelial cells (HUVECs) and rat aorta were used to study the in-vitro tubule formation as well as ex vivo angiogenesis. It was observed that the Atk signaling pathway could inhibit HUVEC proliferation and collagen-induced angiogenesis.

Collagen solution covered the aorta segments, and cultured in RPMI-1640 medium were supplemented with 100 u/ml penicillin, 100 µg/ml streptomycin, 2 mM L-glutamine, DMSO was used as a control. After 7 days, tubule formation was compared, it was observed that there was a 55% reduction in the migration of piperine-treated aorta and 93% absence of tubule formation than the vehicle control, ie.DMSO. Phosphorylation of Atk is considered to be an important proangiogenic signaling

molecule. LY 294002 is a growth factor receptor that is present upstream of Atk and is used to confirm the importance of the PI3K/Atk pathway; it acts as an inhibitor of PI3K. HUVEC's with piperine showed a reduction in Atk phosphorylation which in turn inhibited its proliferation and inhibition of tubule development in the rat angiogenesis model. Piperine-treated HUVEC's increased the expression of VEGFR1 but had no significant effect on VEGFR2 expression.

Piperine, a natural phytochemical, is an excellent substitute that can be used in cancer therapy as it has the least amount of side effects, here we discussed how piperine inhibits the formation, proliferation and migration of endothelial tubules, which in turn acts on collagen-induced angiogenesis. Their findings are indicative that piperine can interfere with Atk activation in response to VEGF (angiogenesis-promoting growth factor). Atk is important for the formation and proliferation of endothelial cells; this was proved by demonstrating the inhibition of angiogenesis with the help of LY-294002 in HUVEC's and rat aorta. By inactivating Atk signaling, we may also block the cell cycle and cyclin D3 expression. In addition to these, Atk signaling also controls the VEGF expression as in the presence of piperine VEGFR1 expression is upregulated, but this does not affect angiogenesis as VEGFR1 acts as a decoy receptor. Along with inhibition of angiogenesis with the help of piperine, the population of HUVEC's did not seem to be affected; this suggests that piperine is adequate to inhibit certain cellular functions during collagen-mediated angiogenesis whilst maintaining cell survivability.

Inhibition of inflammatory mediators-piperine[15]

Osteoarthritis is a degenerative disease that slowly progresses and causes fibrillation and erosion of articular cartilage, osteophyte formation as well as bone sclerosis. Production of cytokines plays a pivotal role in the progression of this disease, one of the major cytokines present in humans chondrocyte includes IL-β. IL-β causes upregulation of matrix metalloproteinases (MMPs), especially those affecting collagenase and are sub-divided into two forms MMP-3 and -13; MMP causes a breakdown of cartilage matrix by digesting the type 2 collagen, which then results in a release of matrix proteoglycans which are present in the cartilage and causes destructive joint diseases. COX-2, NO, PGE2 (prostaglandin E2) is also induced in response to IL-β activation. These play a role in the progression of the disease, resorption of bone and joint pains. Piperine is known to have a chondroprotective activity in joint disease; it is known to lower lipid peroxidation, protect against oxidative stress in addition to its anti-inflammatory effects.

During the course of this study, human chondrocytes were first treated with piperine at 10, 50 or 100 µg/ml, after which they were stimulated with IL-1β (5 ng/ml) for 24 h. It was observed that due to piperine, the production of PGE2 and NO-induced by IL-1β significantly decreased. MMP-3, MMP-13, iNOS and COX-2 also showed decreased levels of production, NF-kB concentration also decreased; this was determined by gene reporter assay. This is because piperine blocks IL-1β-induced IκB-α degradation, which causes NF-kB p65 activation.

Anti-inflammatory drugs have long been used to treat chronic inflammatory disease, a few of which include osteoarthritis and rheumatoid arthritis. From the evidence provided in this research paper, we can say that piperine can be used for the treatment of human osteoarthritis. Overproduction of NO, PGE2, MMP-3, MMP-13, iNOS and COX-2 at mRNA and protein level is disastrous for humans, as it causes inflammation and joint pains. Through this study, we have proved that piperine can easily curb its production by inhibition of NF-κB activation via inhibiting IκB-α degradation. COX-1 and 2 cause gastric defects, and thus by targeting them with piperine, a protective contribution towards gastric defense is also observed. (Ying *et al.*, 2013)

Collagen-induced arthritis-piperine[16]

Piperine and its health benefits are known worldwide, and it ranges from acting as an anti-inflammatory to helping curb metastasis of cancer cells; it also plays a pivotal role in the treatment of chronic diseases such as arthritis, periodontitis, liver damage and transplantation. It has already been studied that piperine is able to inhibit nuclear translocation of p65, p50, c-Rel subunits of NF-kB and other transcription factors such as ATF-2, c-Fos and CREB. Here they investigated the action of piperine as an antioxidant by monitoring ROS and GSH levels, its anti-inflammatory effect by measuring levels of pro and anti-inflammatory cytokines and levels of elastase and myeloperoxidase as they are directly linked to the accumulation and activation of polymorphonuclear leukocytes in the damaged tissues.

Piperine when administered at a dose of 100 mg/kg along with indomethacin, an inflammatory drug, was also administered at a dose of 1 mg/kg. Bodyweight was recorded for 21 days and effects of piperine on articular elastase, MPO, LPO, GSH, Catalase, SOD and NO were also looked out for. IL-1ß, TNF- α, IL-10 and PGE2 were the inflammatory mediators which were looked out for. Levels of all parameters (articular elastase, MPO, LPO, GSH, Catalase, SOD and NO) significantly decreased after piperine treatment. Along with this, all the proinflammatory molecule (IL-1ß, TNF- α, IL-10 and PGE2) levels also decreased, but the level of IL-10 increases, which codes for protective effects against arthritis.

Here we showed the anti-oxidative and anti-arthritic activity of piperine in the collagen-induced arthritis model; maximum bioavailability of piperine was found at 2.5 hours after oral ingestion. Elastase is known to be directly related to the influx of large numbers of activated PMNs in the tissues, which leads to inflammation. Piperine was able to reduce the levels of elastase by inhibiting lipid peroxidation, which in turn leads to a reduction in the formation of chemotactic proteins, hence less influx of

PMN's. In conclusion, we can say that piperine helps in suppressing the accumulation of lipid peroxidation and nitric oxide while simultaneously activating antioxidating enzymes and eliminating the migration of PMN's into tissues.

EFFECT OF PIPERINE ON ALVEOLAR BONE LOSS AND COLLAGEN FIBRES[17]

Piperine is known for its anti-inflammatory effects; it is known to be effective against a popular inflammatory disease-periodontitis which eventually leads to bone loss and tooth exfoliation. As traditionally known, inflammation leads to activation of more inflammatory factors, such as hydrolytic enzymes and ROS species which contributes to tissue destruction and bone loss. These inflammatory factors may include (IL)-1ß, TNF-α and MMPs. Evasion from this inflammation is generally difficult to avoid; thus, some additional agents are required to help in the evasion of periodontitis. In this review, they used periodontal disease as a model to study piperine's anti-inflammatory effect.

32 Wistar rats were divided into 4 groups; each group consisted of 8 animals. The groups were divided as follows: (i) control group, (ii)periodontitis group, (iii)periodontitis plus 50 mg/kg piperine group (P50) and (iv)periodontitis plus 100 mg/kg piperine group (P100). The levels of (IL)-1ß, TNF-α and (MMPs) were determined using Western blotting. After the necessary observations, it was found that piperine was able to inhibit alveolar bone loss by 42% in the P100 group, whereas there was a 26% decrease in the P50 group. Along with this, it was able to reform trabecula microstructures. Histological staining proved that piperine could reduce infiltration and inflammation in soft tissues. P100 and P50 both could limit the areas which were degraded by collagen fibers (P50, 55.4%; P100, 73.7%). P100 was able to significantly downregulate (IL)-1ß, MMP-8 and MMP-13 expression but was unable to downregulate TNF-α.

Piperine can display protective effects on inflammation, alveolar bone loss, collagen fiber degradation as well as on bone microstructures. These protective effects are ascribed to piperine as it is able to downregulate the expression of (IL)-1ß, MMP-8 and MMP-13. More research can be carried out to understand why there was no inhibitory effect observed on TNF-α.

OSTEOARTHRITIS-PIPERINE[18]

Collagen is responsible for making 95% of joint cartilage; as the number of collagen decreases, the wear and tear of the joints increases, which may sometimes lead to osteoarthritis. It is always better to look out for natural drugs for the treatment of any disease. Thus the use of non-steroidal anti-inflammatory drugs (NSAIDs) and analgesics is the current standard care for the treatment of osteoarthritis. Here we study how effective Piperine or *Piper nigrum* is along with curcumin. Piperine is known to increase the bioavailability of curcumin 20-fold. A fixed-dose combination of piperine and curcumin, along with its efficiency and tolerability, was determined.

44 osteoarthritic patients (16 men, 28 women, mean age: 55.5 years) were given a combination of fixed doses of piperine and curcumin. Informed consent was taken, patients were given doses of 500mg curcumin and 5mg piperine twice a day over a period of 12 weeks. The symptoms of patients were evaluated at weeks 4,8, and 12. The assessment was done on the basis of the WOMAC score in the 12th week. Along with piperine and curcumin, NSAIDs were also given as rescue medication. After the 12th week, there was a significant improvement in the patient's condition; their joint pain, as well as the stiffness, was observed to decreased ($P<0.001$). Along with this, the need for NSAID pill consumption also decreased (54.25%) and was minimum after week 12 ($P<0.012$). The only side effect observed was mild gastrointestinal effects in 3 patients.

Through this study, we can say that using a combination of curcumin and piperine has a great advantage for the treatment of osteoarthritis. Curcumin has anti-inflammatory activity; it also leads to the suppression of many inflammatory molecules like JNK, MAPK and PI3K/Akt; its antioxidants are known to modulate the oxidative stress and formation of ROS. Co-administration of curcumin along with piperine increases its bioavailability through inhibition of curcumin glucuronidation within the intestine and liver; it also increased blood supply to the intestinal tissue and enhances the membrane dynamics leading to increased permeability of brush border. Thus we can conclude that using a combination of curcumin and piperine has a significant effect on improving the care for the osteoarthritic patient.

Curcumin with collagen [19-25]

Consequences of curcumin on the progress of glycation and collagen crosslinking in diabetic rats[19]

Collagens constitute a major part of the extracellular matrix, and these proteins are extremely vulnerable during diabetes. In diabetes, several Advanced Glycation End Products (AGE) had found to modify the morphology of Collagens and resulted in several complications. They had been found to increase crosslinking within collagens. Large amounts of free oxygen radicals were also formed during the oxidation of glucose which induces the further formation of more AGEs and induces crosslinking of collagen. Curcumin acted as a potent antioxidant and inhibited such AGE formation and therefore reduced crosslinking of collagen. They also helped to maintain the normal level of nonenzymatic antioxidants in diabetic rats. Curcumin reduced oxidative stress on collagen and thereby preventing the complications of diabetes. The effect of curcumin on the AGEs was estimated using ELISA immunoassay, which helped to determine the amount of AGE and crosslinking of collagen in different diabetic rats.

After inducing diabetes to the healthy rats, competitive ELISA was performed, and the amount of AGE was found to be lower in the curcumin-treated rats. Fractionation was done using the Miller and Rhodes method, and the degree of crosslinking was found higher in the curcumin-treated group. Antioxidants such as vitamin C, vitamin E etc. found to be higher in the curcumin-treated group by several biochemical estimations.

Curcumin showed significant effectivity on the crosslinking of collagen proteins by reducing the oxidative stress in the tissues. Therefore, curcumin can be used as an effective antioxidant to increase the crosslinking of collagen and protect it from various oxidative degradations. It can be used as a potent therapeutic to reduce the complications that arise from diabetes on the tissue level.

Obstruction in collagen synthesis and hepatic stellate cell stimulation in-vivo and in-vitro by curcumin[20]

It had been found that curcumin application inhibited collagen accumulation, the mRNA quantity of type I collagen in the hepatic stellate cells and the smooth muscle alpha-actin proteins. As the liver is considered one of the most important detoxification sites in our body, any injury to the liver causes adverse effects on the body. Therefore, a proper repairing mechanism in the liver is considered essential for the proper functioning of our entire body. While repairing, the liver can form a large number of scar tissue which may cause alterations to the normal liver functions and leads to cirrhosis. Staining, immunochemistry and immunoblotting methods had found that curcumin treatment helped to prevent the activation of stellate cells and inhibited collagen formation in order to prevent liver fibrosis.

Masson's trichrome method and streptavidin-biotin-peroxidase complex immunohistochemistry techniques were used to measure the amount of collagen and α SMA. It was found that curcumin treatment helped to reduce collagen accumulation and also alpha SMA protein levels indicating a reduced amount of stellate cell activation. In vitro, the ELISA and immunoblotting techniques had found a reduced amount of DNA and collagen type I and α SMA proteins in curcumin-treated rats. Chronic liver diseases are very dangerous to health as it affects the main detoxifying organ of the body. It reduces life expectancy, and no cure for chronic liver injuries has been found yet. Curcumin showed a significant effect on reducing collagen deposition, thereby reducing fibrosis and helped to restore the proper functioning of the liver. In-vitro experiments found that a cytokine called PDGF-BB played immense importance in the proliferation of stellate cells. Agents that block this cytokine can be used as potential therapeutics against fibrosis. Curcumin had been found to inhibit stellate cell activation even in vitro. Therefore, curcumins and curcumin derivatives can be used effectively for drug design against chronic liver injuries.

Enhancement of wound healing by collagen modulation and reduction of reactive oxygen species[21]

Wound healing is a process found in living organisms where damaged tissue is replaced by newly synthesized one. This process is very important as wounds can be life-threatening to an organism as they are the most susceptible entry points for various pathogens and may cause severe infections. Collagen plays an important role in wound healing. They deposit in the wound site and help in new tissue formation. Curcumin interacted with type III collagen and increased their synthesis and proliferation at the wound site. Curcumin mainly accelerated wound healing by speeding up the rate of movement of epithelial cells to the wound side, contracting the wound and increasing their elastic strength. Curcumin increased the levels of superoxide dismutase, catalase, glutathione peroxidase etc., which were mainly responsible for inhibiting oxidation in tissues and sped up wound healing. Curcumin also increased the crosslinking of collagen molecules by increasing their stability, shrinkage temperature, elastic strength etc. and all these helped to the process of wound healing. For the quantification of collagen method of Woessnor was used. For the fractionation and determining the subunit composition of collagen, the Piez method and interrupted SDS PAGE were used. For assessing the Superoxide dismutase, catalase and glutathione, several biochemical methods such as the method of Misra and Ivan Fridovich, Aebi and Rotruck were used. All these found that the curcumin-treated rats show a higher amount of DNA and proteins, a higher amount of collagen synthesis and an elevated Level of enzymes responsible for antioxidant properties.

Wound healing is a very complicated process involving several stages, and it takes different amounts of time depending on the type of tissue, depth of wound etc. Selecting certain therapeutic agents for the accelerated recovery of the wound is very beneficial. The application of Curcumin and their interactions with collagen favored several phases of the wound healing process. The anti-inflammatory properties of curcumin also helped in reducing the pain of the wound. Curcumin also served as a natural antiseptic and attracted a large number of phagocytic cells such as neutrophils, macrophages etc., to the open wound site. Therefore, curcumin and its derivatives can be effective in drug development for fast wound healing processes.

A psycho-chemical approach of analyzing collagen-curcumin interaction[22]

Curcumin affected the secondary helical conformation of collagen to some extent. The viscosity and thermal stability of collagen increased on interaction with curcumin. Curcumin treatment also increased the surface tension of collagen. Some methodologies and instruments had been used to examine these molecular changes, such as Circular Dichroism measurement, denaturation temperature measurement, Ostwald viscometer, Dynamic Surface Tensiometer etc. As the curcumin interacted with Collagen

by hydrogen bond formation and electrostatic interaction, it helped in additional crosslinking of Collagen molecules, thereby made the wound healing process fast.

Changes in helices of Collagen had been determined by measurement of circular dichroism. A solution of curcumin-treated Collagen was taken, and their viscosity measured using Ostwald viscometer. The viscosities of curcumin-treated collagen solutions were found higher than the native ones. The thermal stability of collagen had been determined using a micro-shrinkage tester. Shrinkage temperature, at which the collagen fiber shrinks to one-third, was found higher in curcumin-treated Collagen than native collagen fibers. The surface tension had been determined using a Surface Tensiometer by immersing the instrument into the sample solution. Here the surface tension of curcumin-treated collagen was found higher.

The interaction of curcumin with collagen brought about some significant changes which can be used for curative purposes for several diseases. Mainly curcumin increased crosslinking of collagen molecules and interacted by hydrogen bonds and electrostatic bonds with the collagen. These interactions helped to increase the viscosity, thermal stability and other such properties, which play a pivotal role in the wound healing mechanism of collagen. Therefore, the application of Curcumin can be proved to be a potent therapeutic agent against diseases that had been already proven as fatal due to compromised wound healing processes.

Curcumin fights against Arthritis induced by collagen through the inhibition of BAFF production.[23]

The development of rheumatoid arthritis had been found mostly characterized by the presence of an excessive amount of TNF family protein called B Cell Activation factor (BAFF). In collagen-induced rheumatoid arthritis of mice, curcumin showed a significant effect in reducing the amount of BAFF. In this disease, several types of interleukins were produced in an elevated amount like interleukin 6, interferon γ etc. Measuring the amounts of these interleukins using several techniques like western blot, luciferase assay etc., the amount of these interleukins found reduced. For doing so, curcumin mainly interfered with the STAT 1 signaling pathway and reduced the phosphorylation of the STAT 1 protein and nuclear translocation, which further reduces BAFF production. Therefore, BAFF can be used as a potential drug target for rheumatoid arthritis, and the interaction of curcumin proved its efficacy as a potential drug material.

To determine the effectiveness of curcumin, at first, the mice were immunized with type II collagen to induce arthritis. It was found that the arthritis index was much lower in the curcumin-treated mice. ELISA test was done, and the result showed that the serum level of BAFF, IL-6 and INF γ were much reduced in the curcumin-treated mice. In the transfection assay where the cells were transfected with luciferase and then treated with curcumin, it showed that curcumin inhibits the phosphorylation and nuclear translocation of STAT 1 protein, thereby reducing BAFF production. As there is no cure for rheumatoid arthritis, the only way out is to control the progression of the disease and to reduce pain and swelling at the joints. For this purpose, curcumin raised hope as it had already proven to be effective in clinical trials. They had also shown very few side-effects and thereby became more acceptable to a large number of patients. Curcumin not only reduced the pain by its anti-inflammatory effects but also interfered with the STAT 1 signaling pathway at the molecular level. Where rheumatoid arthritis had been mainly characterized by over-activation of B lymphocytes and excessive production of INF gamma, curcumin downregulated this pathway. Therefore, in medicinal biology, BAFF can be used as an effective drug target for treating collagen-induced rheumatoid arthritis.

Curcumin treatment reduces specific biomarkers of collagen, Coll2-1 in osteoarthritis patients.[24]

Osteoarthritis is a degenerative type of complex disease that mainly results in dysfunction of the joints of knees, hips, spines etc. The complication of this disease is mainly caused by the degradation of Type II collagen in the cartilages at the joint. The treatment of the disease is still challenging. It is generally recommended to control the symptoms as early as possible. For the early diagnosis of the disease and treatment, the role of precise biomarkers can be very important. Curcumin had been considered to be one of the most promising therapeutic agents here. It had been found that the regular administration of curcumin in osteoarthritis patients resulted in a significant reduction in the amount of Coll2-1 collagen biomarkers. Generally, the reduction of these markers was found to be very important for the evaluation of the status of the disease in patients. The anti-inflammatory properties of curcumin were also responsible for reducing the pain associated with this disease.

The quantification of biomarkers was done using ELISA immunoassay techniques. For Coll 2-1 and CTX II competitive ELISA and for Coll 2-1 NO2, Fib 3-1 and Fib 3-2 specific ELISA were used. For CRP, a highly sensitive immunophelometric method was used. It had been found that mainly the amount of Coll 2-1 and, to some extent, the amount of CRP decreased in the serum of the patients who had taken curcumin regularly. The Coll 2-1 biomarker was only found when the triple helix structure of collagen unwinds. As curcumin treatment reduced these markers, then it could be possible that curcumin might help to prevent collagen molecules from unwinding and thereby preventing their degradation. From the study, it can be said that curcumin helped to modulate the properties of collagen in various ways and well against osteoarthritis disease. The anti-inflammatory property of curcumin also helped in reducing the pain. Besides, curcumin had very few adverse effects, which could make it more acceptable as a drug material. Therefore, the application of Curcumin

at a bio-optimized level can work as a potential drug against osteoarthritis.

Consequences of application of curcumin caged silver nanoparticle on the stabilization of collagen[25]

Curcumin caged silver particles had shown to increase the stability of the collagen. The elastic strength increased as the particles mainly increased the crosslinking between the collagen molecules. It enhanced the thermal degradation temperature and hydrothermal stability. It helped in accelerated wound healing mechanism as they had resulted in increased cell division and prevention of microbial growth. They also increased the life expectancy of collagen and could be used in several therapeutic approaches. Several experimental techniques had been used to detect the changes in collagen while interacting with these nanoparticles, such as spectrometry, fibrillation assay, electron microscopy etc. The increased ability to crosslinking and wound healing could be used for medicinal purposes for accelerated recovery. The size and kinetics of curcumin caged silver particles had been determined using scanning electron microscopy, X-ray diffraction etc. To determine the stability of collagen, a fibrillation assay had been performed using a spectrophotometer. The stability was found to be higher in the post curcumin treatment of collagen. Brookfield Rheometer had been used to determine the viscosity, and it was found that the viscosity increased after the application of nanoparticles. The antimicrobial properties of the nanoparticle-treated collagen were by broth dilution method and agar diffusion method against Escherichia coli and Bacillus subtitles culture. In both cases, they showed an inhibition zone. Curcumin caged silver particles not only modulated the physicochemical properties of collagen but also provided the Collagens with antimicrobial properties. The increased crosslinking and fibril formation capabilities helped in the increased wound healing mechanism. The increased life expectancy of these molecules also favors the repairing process. The antimicrobial properties of silver and the antioxidant properties of curcumin also had some advantages over the normal wound healing mechanism. These can be used as a potential therapeutic agent in repairing external as well as internal damages.

Curcumin on Rheumatoid Arthritis: This study has been done by the University of California on 40 patients to check the effectiveness of curcumin in rheumatoid arthritis. Here the patients were divided into two groups, and one of the groups was given curcumin, and the other group was given a placebo for the first four months and vice versa for the next four months. The study has not been completed yet.

Exploratory Non-Comparative Study to Evaluate the Efficacy of Highly Bioavailable Curcumin (Flexofytol) in Patients with Knee Osteoarthritis: The study was done by Gilman S.A on 22 patients of knee arthritis to determine if regular curcumin ingestion has any role on the level of biomarkers of osteoarthritis in the serum. The patients were given a regular dose of curcumin twice a day for 3 months. But the results were not available on the website.

The Efficacy and Safety of Curcuma Domestica Extracts and Ibuprofen in Knee Osteoarthritis: The study was done by the Mahidol University of Thailand on 367 patients of Knee osteoarthritis to check the effectiveness of curcumin against the pain associated with the disease. The patients were given a regular dose of bio-optimized curcumin for a regular period of 28 days. The study has been completed, but the result has not been published yet.

Curcuma Longa L in Rheumatoid Arthritis (CLaRA): The study was initiated by the University of Arizona to find if regular intake of curcumin or turmeric had any effect on the patients of rheumatoid arthritis. But the study had been terminated due to insufficient participants.

Effectiveness of Curcumin-based Food Supplement in Reducing Pain and Inflammatory Component in Osteoarthritis (FENOXI-1900): This trial was planned by Istituto di Riabilitazione Santo Stefano to determine if curcumin as a dietary supplement had any effect on the patients of osteoarthritis. The study has not started yet.

Curcumin to Prevent Complications After Elective Abdominal Aortic Aneurysm (AAA) Repair: This study has been started by Lawson Health Research Institute on 606 participants to check the efficiency of curcumin against wound healing in case of acute kidney injuries. Here the patients were divided into two groups and one group was given curcumin regularly, and the other group was given a placebo. The trial is in phase 3 now, and no result was published by the Institute.

Oral Curcumin for Radiation Dermatitis: This study was done by the University of Rochester to determine the efficiency of curcumin as a dietary supplement to heal the wounds in Dermatitis caused by radiation induction on 686 patients for 6 weeks. It was found that the group treated with curcumin showed a higher rate of recovery than the group treated with placebo.

Curcumin for the Prevention of Radiation-induced Dermatitis in Breast Cancer Patients: This study was done by the University of Rochester on 30 breast cancer patients to find if regular intake of curcumin has any effect on wound healing in Dermatitis. The study found that the patients given curcumin for approximately 4-7 weeks showed a lower rate of Dermatitis than the patients not treated with curcumin.

Prophylactic Topical Agents in Reducing Radiation-Induced Dermatitis in Patients with Non-inflammatory Breast Cancer (Curcumin-II): This study was done by Gray Morrow to check the efficiency of regular curcumin ingestion against Dermatitis on 191 breast cancer patients for approximately one week. The results found that the group treated with curcumin showed higher efficiency of wound healing properties in Dermatitis.

CONCLUSION

This research review's purpose is to help the reader understand different aspects posed by the research on the effects of rosehip, curcumin piperine and chondroitin sulfate on collagen. This is significant because it gives insights into the anti-inflammatory, anti-metastatic, antioxidant, chondroprotective and hepatoprotective activities of the above compounds. There has been much research and discussion conducted on these opinions of their application in the treatment of osteoarthritis, rheumatoid arthritis, wound healing, angiogenesis, cancer metastasis and liver damage. Most of the research found was on how these compounds affect the nucleation, fibril formation and crosslinking in collagen. Another application in lipid metabolism and its effect on diseases such as diabetes was elaborated. More research and testing are required to gain a better understanding of the effects of rosehip, curcumin piperine and chondroitin sulfate on collagen.

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No Animals/Humans were used for studies that are base on this research.

AVAILABILITY OF DATA AND MATERIALS

The author confirms that the data supporting the findings of this research are available within the article.

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The authors whose names are listed immediately above certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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